Glycoconj J (2015) 32:575–613
DOI 10.1007/s10719-015-9606-6

ORIGINAL ARTICLE

Exploring the role and diversity of mucins in health and disease with special insight into non-communicable diseases

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Received: 18 May 2015 / Accepted: 18 June 2015 / Published online: 4 August 2015

Abstract Mucins are major glycoprotein components of the mucus that coats the surfaces of cells lining the respiratory, digestive, gastrointestinal and urogenital tracts. They function to protect epithelial cells from infection, dehydration and physical or chemical injury, as well as to aid the passage of materials through a tract *i.e.*, lubrication. They are also implicated in the pathogenesis of benign and malignant diseases of secretory epithelial cells. In Human there are two types of mucins, membrane-bound and secreted that are originated from mucous producing goblet cells localized in the epithelial cell layer or in mucous producing glands and encoded by *MUC* gene. Mucins belong to a heterogeneous family of high molecular weight proteins composed of a long peptidic chain with a large number of tandem repeats that form the so-called mucin domain. The molecular weight is generally high, ranging between 0.2 and 10 million Dalton and all mucins contain one or more domains which are highly glycosylated. The size and number of repeats vary between mucins and the genetic polymorphism represents number of repeats (VNTR polymorphisms), which means the size of individual mucins can differ substantially between individuals which can be used as markers. In human it is only *MUC1* and *MUC7* that have mucin domains with less than 40 % serine and threonine which in turn could reduce number of PTS domains. Mucins can be considered as powerful two-edged sword, as its normal function protects from unwanted substances and organisms at an arm's length while, malfunction of mucus may be an important factor in human diseases. In this review we have unearthed the current status of different mucin proteins in understanding its role and function in various non-communicable diseases in human with special reference to its organ specific locations. The findings described in this review may be of direct relevance to the major research area in biomedicine with reference to mucin and mucin associated diseases.

Keywords Human · Membrane proteins · Glycoproteins · Goblet cells · Mucus · Mucins · Polymorphism

Abbreviations

MUC	Mucin
VNTR	Variable number of tandem repeats
PMP	Pseudomyxoma peritonei
CRC	Colorectal cancer
DFS	Disease free survival
OMT	Ovarian mucinous tumours
HER2	Human epidermal growth factor receptor 2
TNBC	Triple negative breast cancer
CA125	Cancer antigen 125
MS	Minisatellite
CaP	Prostate cancer
pfu	Plaque-forming units
PMP	Pseudomyxoma peritonei
PDA	Pancreatic ductal adenocarcinoma
PC	Pancreatic cancer
PDA	Pancreatic ductal adenocarcinoma
IPMN	Intraductal papillary–mucinous neoplasm
PanIN	Pancreatic intraepithelial neoplasia
ECM	Extracellular matrix components
VEGF	Vascular endothelial growth factor

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IDC	Invasive ductal carcinoma
MCN	Mucinous cystic neoplasm
IPMT	Intraductal papillary-mucinous tumour
CagA	Cytotoxin-associated gene A
H. Pylori	Helicobacter pylori
SCLC	Small-cell lung carcinoma
NSCLC	Non-small-cell lung carcinoma
SRCC	Signet-ring cell carcinoma
IPF	Idiopathic pulmonary fibrosis
SSc	Systemic sclerosis
ILD	Interstitial lung disease
CF	Cystic fibrosis
CFTR	CF transmembrane conductance regulator
DPB	Diffuse panbronchiolitis
HSCR	Hirschsprung disease
CP	Cap polyposis
RCC	Renal cell carcinoma
MCKD1	Medullary cystic kidney disease1
ESRD	End-stage renal disease
GBC	Gallbladder cancer
MUPCDH	Mucin and cadherin-like protein
TRs	Tandem repeats
HMEECs	Human middle ear epithelial cell lines
RA	Rheumatoid arthritis

Visiting mucins

Mucins are gel like secretions that belongs to a broad family of polydisperse, with high molecular mass and heavily glycosylated, molecules which are synthesized by epithelial goblet cells or submucosal gland [1]. They possess varied functions of lubrication, signal transduction in forming chemical and pathogen barriers. Currently, 22 human mucin (*MUC*) genes have been reported [2] which are categorised into two major types, membrane-bound and secretory. In human, nine membrane-bound (*MUC1*, *MUC3A*, *MUC3B*, *MUC4*, *MUC12*, *MUC13*, *MUC16 MUC17* and *MUC22*) [3–9] and seven secreted mucins (*MUC2*, *MUC5B*, *MUC5AC*, *MUC6*, *MUC7*, *MUC19 and MUC20*) [10–16] that are further subdivided as gel-forming (*MUC2*, *MUC5B*, *MUC5AC*, *MUC6* and *MUC19*) and non-gel forming (*MUC7*and *MUC20*), respectively (Table 1, Fig. **1**).

Expression profile of mucins varies between tissues with the gastrointestinal tract showing the highest and most diverse expression. The protein structure of mucins have non-glycosylated amino and carboxyl terminal with a heavily glycosylated central region having multiple tandem repeats rich in serine or threonine. The size and number of repeats vary between mucins, and the genetic polymorphism represents number of repeats (VNTR polymorphisms), which means the size of individual mucins can differ substantially between individuals.

Secretory mucins are glycoproteins constituting the major macromolecular component of mucus, which plays a role in cell-cell and cell-matrix interactions and cytoprotection of epithelial surfaces. secretory mucins are further divided into three distinct subfamilies: (a) secreted gel-forming mucins, (b) cell-surface mucins and (c) secreted non-gel-forming mucins. Its biochemical and cellular functions have not been definitively assigned; on the other hand, membrane bound have been reported to function as cell surface receptors for pathogens and for activating intracellular signaling pathways [17]. Mucins combine with inorganic salts suspended in water to form mucus. Mucus, secreted by goblet cells, adheres to many epithelial surfaces like that of respiratory, gastrointestinal, urinary and genital tracts. Mucus is also an abundant and important component of saliva and is also present on eye surface. Mucus is said to serve as a substrate for the growth, adhesion and protection of the trillions of microbial cells that are present in the lumen in the gastrointestinal (GI) tract.

Phlegum, sputum and pus are different constituents of Mucus that are found in various human diseases [18]. Phlegm is from a Greek term for inflammation which is said to be a purulent secretion that is produced from airway inflammation. Phlegm consists of breakdown products of inflammatory cells and epithelial cells, including copolymers of DNA and filamentous (F-) actin, bacteria, cell debris and variable amounts of mucin [19, 20]. The expectorated phlegm is called sputum. The pus component of mucus is derived from neutrophil degradation that includes viscous material such as polymerized DNA and filamentous (F-) actin [21].

Malfunction of mucus is an important factor in human diseases, both in the etiology of certain pathological conditions or in the exacerbation of functional disturbances that have their mechanistic origin elsewhere. It is said that the deregulation of mucins/mucus production can have serious health consequences [22]. Human mucins are associated with diseases like adenocarcinomas of various tissues and are overexpressed in lung diseases like Chronic Obstructive Pulmonary Disease (COPD) and cystic fibrosis (CF) [17, 18]. It forms a major part of gastrointestinal tract and is involved in its health and disease [23–31]. Mucins play a major role in accommodating the resident commensal flora and limiting infectious disease by creating a mucosal barrier between external environment and tissues [32]. Mucins have also being considered as drug targets for some diseases like asthma, breast cancer, gastric cancer, pancreatic cancer etc. [33–40]. It is also being used as disease diagnosis [41–45, 23, 26] and prognosis [46] especially for certain carcinomas like breast cancer, colorectal cancer, pancreatic cancer, gastric carcinoma. In this review we explored the role of mucin mainly in non-communicable diseases of various organ systems of the human body like Carcinomas, Gastric carcinoma of stomach, Renal clear cell carcinoma, Medullary Cystic Kidney Disease Type 1 kidney, Inflammatory bowel disease (IBD), Hirschsprung's Disease,

Table 1 Human Mucins associated various diseases and genetic disorders

Mucin	Common (alternate names)	Chromosome	Distribution (Organ)	Disease	Entrez gene	Ensembl ID	MIM ID
Membrane bound mucins							
Mucin 1 (MUC 1)	CA15-3, Episialin, PEM; CA19-9	1q21	Colon, lung, ovary, Stomach, breast, gallbladder,cervix,pancreas,respiratory tract, duodenum, colon, kidney, eye, B cells, T cells, dendritic cells, middle ear epithelium	Medullary Cystic Kidney Disease Type 1, breastcancer, ovariancancer, cysticfibrosis, colorectalcancer, Pancreatic cancer, gastric carcinoma, Ulcerative Colitis	4582	ENSG00000185499	158340
Mucin 3 (MUC 3A)	Intestinal mucin-3A	7q22	Small intestine, colon, gall bladder, ovary, duodenum, middle ear epithelium	colorectal cancer,Ulcerative colitis, Crohn's disease (Inflammatory bowel disease(IBD)), cap polyposis,Renal clear cell carcinoma(von hippel-lindau disease and adenoma), Breast Cancer, cystic fibrosis,Adenocarcinoma,lung cancer, stomach cancer	4584	ENSG00000169894	158371
(MUC3B)	Intestinal mucin-3B	7q22	Small intestine, colon, gall bladder, ovary, duodenum, middle ear epithelium	Cystic fibrosis	57876	NA	605633
Mucin 4 (MUC4)	(a) Membrane anchored; sialomucin, ASGP-1, (b) secreted mucin, ASGP-2 (Ascites sialoglycoprotein 2)	3q29	Respiratory tract, colon, stomach, testis, esophagus, seminal vesicle, endocervix, ascites fluid, pancreas, cervix, eye, middle ear epithelium	Ovarian cancer, Gastric Carcinoma, Inflammatory bowel disease(IBD), epithelial ovarian tumours, Hirschsprung's Disease, Breast Cancer, Invasive ductal carcinoma, Lung cancer,pancreatic cancer	4585	ENSG00000145113	158372
Mucin 12 (MUC12)	Rectal-colon Mucin	7q22	Colon, small intestine, stomach, pancreas, lung, kidney, prostate, uterus	colorectal cancer, inflammatory bowel disease, adenocarcinomas,	10071	ENSG00000205277	604609
Mucin 13 (MUC13)	Hematopoietic Mucin Down-regulated in colon cancer 1	3q21	Colon, small intestine, trachea, kidney, appendix, stomach, middle ear epithelium	colon cancer, intestinal-type gastric cancer,ovarian cancer,Cancer Pathogenesis,pancreatic tumorigenesis,metastatic colon cancer,	56667	ENSG00000173702	612181
Mucin 14 (MUC14)	Endothelium, endomucin, Endomucin-2 Gastric cancer antigen Ga34	4q 24	Stomach, endothelium, Ovary	Angiolipoma	51705	ENSG00000164035	608350
Mucin 15 (MUC15)	Membraneassociated mucin	11p14.3	spleen, thymus, prostate, testis, ovary, small intestine, colon, peripheral blood leukocyte, bone marrow, lymph node, tonsil, breast, fetal liver, lungs, middle ear epithelium	Papillary thyroid cancer, Asthma, papillary thyroid carcinoma,colon cancer	143662	ENSG00000169550	608566
Mucin 16 (MUC16)	CA 125, epitope, ovarian tumor marker	19p13	Peritoneal mesothelium, reproductive tract, respiratory tract, eye, middle ear epithelium,	pseudo-meigs syndrome, meigs syndrome, Ovarian cancer, atopic keratocon junctivitis,	94025	ENSG00000181143	606154

Table 1 (continued)

Mucin	Common (alternate names)	Chromosome	Distribution (Organ)	Disease	Entrez gene	Ensembl ID	MIM ID
Mucin 17 (MUC17)	Small intestinal mucin-3	7q22	Ovary, Small intestine, colon, duodenum, stomach, middle ear epithelium	Biliary papillomatosis, cholangiocarcinoma, adenocarcinoma, inflammatory and neoplastic diseases of the colon,	140453	ENSG00000169876	608424
Mucin 18 (MUC18)	Melonoma associated mucin, Cell surface glycoprotein P1H12, Melanoma cell adhesion molecule, Melanoma-associated antigen A32, Melanoma-associated antigen MUC18, S-endo 1 endothelial-associated antigen, CD_antigen: CD146	11q23	Melanoma, neural crest cells, Melanocytes the melanin-producing cells located in the bottom layer (the stratum basale) of the skin's epidermis, the middle layer of the eye (the uvea), the inner ear, meninges, bones and heart.	placental site trophoblastic tumor, epithelioid trophoblastic tumor, prostate cancer cell, lung inflammation, metastatic melanoma, prostate cancer LNCaP, tumorigenicity of human breast cancer, uveal melanoma, Rheumatoid Arthritis, pulmonary metastasis, tumor vascularization, Inflammatory Skin Disease, bone marrow fibroblasts	4162	ENSG00000076706	155735
Mucin 21 (MUC21)	Epiglycanin	6p21.32	Cervix, bronchus, lung, breast, thymus, testes, large intestine, Expressed in normal and malignant bronchial epithelial cells	lung carcinomas, Graves' disease, Diffuse panbronchiolitis,	394263	ENSG00000204544	
Mucin 22 (MUC-22)	Panbronchiolitis-related mucin-like protein 1(PBMUCL, MUC1-like)	6p21.33	Expressed in lung by serous cells of the submucosal gland (at protein level). Detected in the placenta, lung and testis	diffuse panbronchiolitis	100507679	ENSG00000261272	613917
Secreted (Gel forming)							
Mucin 2 (MUC2)	Intestinal mucin-2; gel forming secretory mucin	11p15	Small intestine, colon, respiratory tract, eye, middle ear epithelium Trachea, bronchus,	Ovarian cancer,Gastric Carcinoma, Inflammatory bowel disease(IBD), epithelial ovarian tumours, Hirschsprung's Disease, Breast Cancer	4583	ENSG00000198788	158370
Mucin 5 (MUC5AC)	Gastric mucin Lewis B blood group antigen	11p15	Respiratory tract, stomach, cervix, eye, middle ear epithelium	Ovarian cancer, Colorectal cancer, breast cancer, human fetal gastrointestinal tract, Gastric Cancer, Pancreatic Ductal Adenocarcinoma, cork-handlers' disease, dry eye disease, uterine cervix, stomach cancer	4586	ENSG00000215182	158373
Mucin 5	Cervical mucin	11p15	Respiratory tract, salivary glands,		727897	ENSG00000117983	600770

Table 1 (continued)

Mucin	Common (alternate names)	Chromosome	Distribution (Organ)	Disease	Entrez gene	Ensembl ID	MIM ID
(MUC5B)	High molecular weight salivary mucin MG1 Mucin-5 subtype B, tracheobronchial Sublingual gland mucin		cervix, gallbladder, seminal fluid, middle ear epithelium	colorectal cancer, idiopathic pulmonary fibrosis (Lung disease), diffuse panbronchiolitis, cystic fibrosis, asthma, Bladder cancer, Gallstone formation, Mucoepidermoid carcinomas of salivary glands, Middle ear with chronic otitis media			
Mucin 6 (MUC 6)	Gastric Mucin; associates with MUC2	11p15.5	Stomach, duodenum, gallbladder, pancreas, seminal fluid, cervix, middle ear epithelium	Pancreatic ductal carcinoma, epstein-barr virus-associated gastric carcinoma, rectal carcinoma, stomach cancer,prostrate cancer, adenoma, pseudomyxoma peritonei, Breast Cancer, colorectal cancer, Gallbladder Inflammation, glandular hyperplasia,	4588	ENSG00000184956	158374
Mucin 8 (MUC 8)	Nasal mucin	12q24.33	Detected in endothelial cells in vascular tissue throughout the body. May appear at the surface of neural crest cells during their embryonic migration. Trachea; bronchus; mid-ear Eustachian tube, nose	Endometrial and ervical, chronic rhinosinusitis,	100129528	ENSG00000269676	601932
Mucin 9 (MUC 9)	Estrogen-dependent oviduct protein, Oviductal glycoprotein Oviductin	11p15	oviductin epithelial cells, Trachea; bronchus, ovary	Ulcerative Colitis, ovarian cancer,	5016	ENSG00000085465	603578
Mucin 11 (MUC 11)	Rectal-colon Mucin	7q22	Colon, small intestine, stomach, pancreas, lung, kidney, prostate, uterus, Lung, thymus,Rectum, colon, larynx, pharynx	Associated with inflammatory bowel disease, and adhesion modulation	10071	ENSG00000205277	604609
Mucin 19 (MUC 19)	variant-12,	12q12	Sublingual gland, submandibular gland, respiratory tract, eye, middle ear epithelium	Sjögren syndrome, mucoepidermoid carcinoma, inflammatory cytokines	283463	ENSG00000205592	612170
Secreted (Non-Gel forming)							
Mcin 7 (MUC 7)	Salivary mucin-1; APO-MG2, secreted form	4q13	Salivary glands, respiratory tract, middle ear epithelium, pancreas, sublingual	Asthma, ethmoid sinusitis, chronic periodontitis,	4589	ENSG00000171195	158375
Mucin 20 (MUC20)	MET regulator, MUC 20S, MUC 20 L	3q29	Kidney,s placenta, colon, lung, prostate, liver, middle ear epithelium, male UG tract, GI-tract	Injured Kidney, colorectal cancer, immunoglobulin A nephropathy,	200958	ENSG00000176945	610360

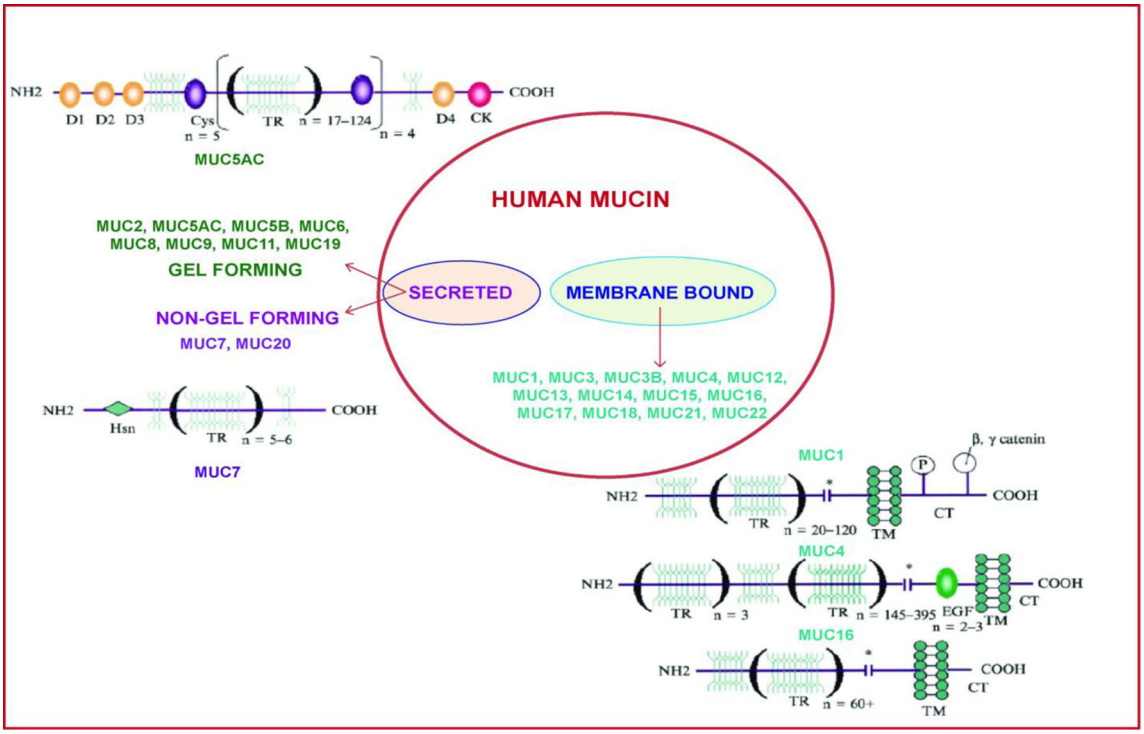

Fig. 1 The most commonly studied mucins are depicted. Cysteine-rich domains (D1, D2, D3 and D4) similar to the D domains that flank the tandem repeat region (TR) and provide sites for disulfide cross-linking. Additional cysteines (Cys) and a cysteine knot (CK) flank the TR. transmembrane (TM), cytoplasmic tail (CT), histatin-like domain (Hsn), epidermal growth factor (EGF). Drawn based on [371]

Cap polyposis of intestine, Lung cancer, Idiopathic pulmonary fibrosis of Lung and Dry Eye Disease of eye etc.

Human cancers

Epithelial tissues are widely distributed, lining the external and internal surfaces of our bodies and playing a number of specialized roles in human body with reference to various carcinomas that originate in epithelial tissues. These epithelia are covered by Mucus glycoproteins or mucins and provide an important role in their protection and lubrication. Mucins are present at the surface of most epithelial cells and play a role in their protection and lubrication. Both secretory and membrane bound mucins are closely involved in inflammation and cancer. Mucin protects the epithelial cells from the adverse effect of inflammatory response. Therefore, in cancer transformations, during progression and even in drug response mucin molecule plays an important role [47] thus considered as diagnostic marker [33] and drug target for cancer detection and therapies [48]. Functional analysis of drug resistant cancer cells revealed the differential expression of mucin potentially involved in angiogenesis, metastasis, differentiation and proliferation [49, 50]. Abnormal expression of the mucins are said to be reported in various cancers [51, 52], such as pancreatic adenocarcinomas, colon carcinomas [53], Breast cancer [48, 54] and cancers associated with other organs (Fig. 2).

Several animal models of mucin depleted foci or mucin therapy have demonstrated the role of mucin in onset and progression of carcinogenesis indicating importance of mucin in cancers [55, 56].

Breast cancer

Breast cancer (BC) is the most common cancer in women worldwide and is the second leading cause of cancer related mortality in women worldwide after lung cancer [48, 54]. It was reported that between 50 and 75 % of breast cancers begin in the ducts, 10–15 % begin in the lobules and a few begin in other breast tissues [57]. *MUC1* is over-expressed compared with other mucins in breast cancer [58] and therefore is mostly studied mucin for BC. It was demonstrated that other mucins, including *MUC2*, *MUC3*, *MUC4*, *MUC5AC*, *MUC5B*, *MUC6* and *MUC7* are also differentially expressed in BC cells. Over-expression and altered glycosylation allows *MUC1* to be used as a cancer marker [59] as a result it is the most widely targeted mucin for the therapy of BC. Histopathologically breast cancer is of three types: Invasive ductal carcinoma found in 55 %, ductal carcinoma *in situ* found in 13 % and invasive lobular carcinoma found in 5 % of breast cancers. BCs with reference to mucins are of two types mucinous and ductal carcinoma, the major form is ductal carcinoma. Kim *et al.* [60] has classified 4 subtypes of Breast tumors: luminal

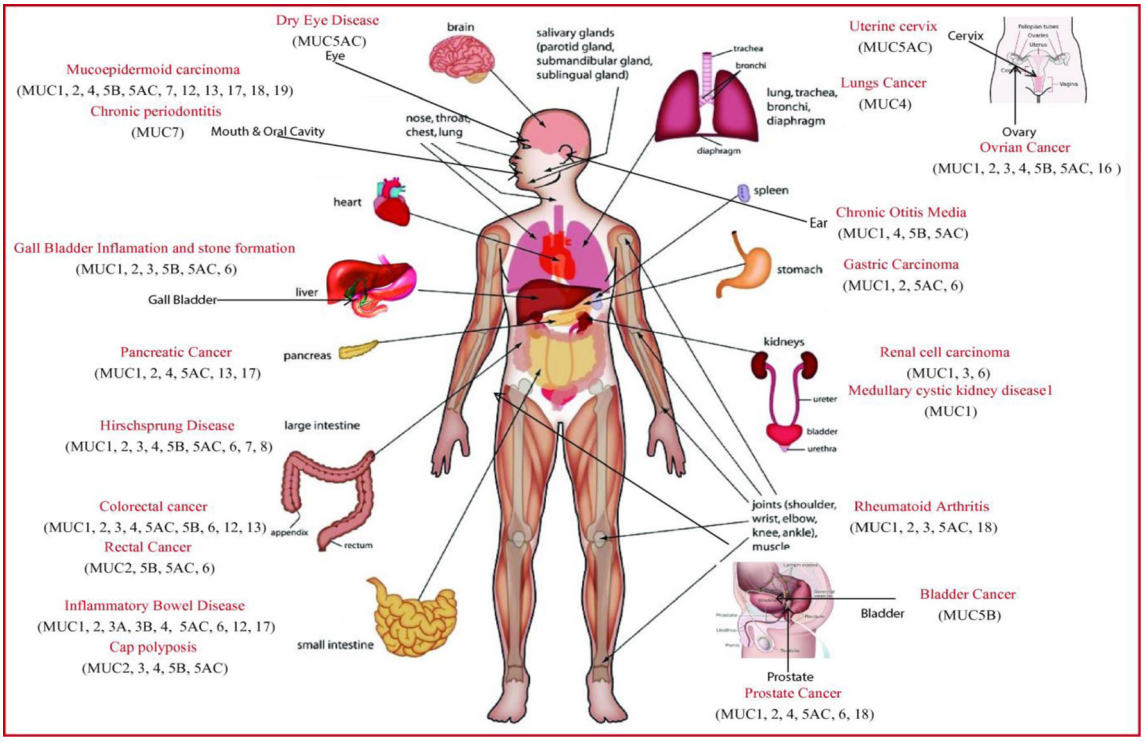

Fig. 2 Wide spectrum of mucins associated with various diseases along with their distribution in different organs in human.

A, luminal B, human epidermal growth factor receptor 2 (HER2) and triple negative breast cancer (TNBC). Mucinous carcinoma of the breast usually shows less frequent lymph node metastasis and more favourable outcome compared with invasive ductal carcinoma of the breast [61–64, 28]. Comparison of selected mucin expression in mucinous and ductal carcinomas revealed that *MUC2* and *MUC6* expression is significantly more common in mucinous carcinomas (94 and 71 %, respectively) than in ductal carcinomas (15 and 15 %, respectively). Unlike *MUC2* and *MUC6*; *MUC1*, is highly expressed in both types of BC (65–100 % in mucinous and 92–100 % in ductal carcinoma) and *MUC5AC*, is rarely expressed (12 and 4 % in mucinous and ductal cancer respectively) [28]. The high level of the aberrant *MUC1* expression in breast cancer and other cancers results in antigenically recognizable epitopes on the *MUC1* molecule leading to stimulation of the immune response and making *MUC1* a potential immunotherapeutic target. [65]. Based on differential expression of mucins, investigations were carried for potential diagnostic and prognostic relevance in BC and other malignancies and reviewed that the potential mucins can be used as diagnostic and prognostic markers in malignancies [66–70].

Ovarian cancer

Ovarian cancer accounts for approximately 3 % of all cancers in women and is the fifth leading cause of death for women in developing countries [71, 72] that causes more deaths than any other cancer of the female reproductive system, with more than 15,000 deaths expected in 2013 in the United States alone [73]. Mucins may be attractive candidates for the detection of early stage ovarian cancer as 90 % of ovarian cancers are of epithelial origin, [71, 72, 74].

Dong *et al*. [75] have described the detailed expression of *MUC1* and *MUC2* in epithelial ovarian tumours and suggested that *MUC1* influences metastasis with the support of experimental evidence. Wang and Bahrawy [76] has compared the expression of four *MUCs* (*MUC1*, *MUC2*, *MUC5AC* and *MUC6*) in ovarian mucinous tumours (OMT) with statistical analysis and reported the change in the expressions of *MUC2* and *MUC6* with the progression of benign to malignant tumours via borderline and suggested that these changes may contribute to malignant transformation.

Mucins can serve as tumour markers based on the properties of aberrant O-linked glycosylation, which has been termed ‘glycodynamics’ that form a linkage between the carbohydrate and mucins. In malignant conditions, these heterogeneously O-glycosylated mucins aberrantly enter the bloodstream and therefore, could be the diagnostic biomarkers for detection and monitoring of cancer [77, 78].

MUC1, *MUC2* and *MUC16* (Cancer Antigen 125) [68, 79, 80] are the series of mucin molecules (*MUCs*) that were identified aberrantly and secreted by ovarian cancer cells. An ovarian cancer antigen, CA125, was later identified as a mucin molecule and was designated as MUC16 [81, 82]. MUC16

is routinely used for diagnosis of ovarian cancer and to monitor the recurrence after therapy [83, 84]. Rump *et al.* [85] have reported mesothelin to be a novel CA125-binding protein that contributes to the metastasis of ovarian cancer to the peritoneum by initiating cell attachment to the mesothelial epithelium via binding to mesothelin.

Several mucins including *MUC1*, *2*, *4*, and *5 AC* are expressed by epithelial ovarian cancers including *MUC3* and *MUC5B*, which are expressed rarely. *MUCl* and *MUC5AC* are expressed only in transformed non-malignant ovarian epithelial cell lines [86].

An overexpression of *MUC4* mRNA has also been reported in OC [86, 87] and in an earlier study, it has been shown that *MUC4* is aberrantly expressed in >90 % of malignant ovarian tumors with very low to an undetectable expression in the normal ovary [88, 89] this suggested *MUC4* to have a major role in the pathogenesis of OC. It has been reported that malignant ovarian tumors often express more mucins than benign and borderline ovarian tumors. *MUC1* and *MUC16* have also been found to have implications in the treatment of ovarian cancer [90–92].

Ponnusamy *et al.* [93] studied the evaluating potential involvement of *MUC4* in the metastasis of OC cells by inducing epithelial-to-mesenchymal transition (EMT) and reported a novel role for MUC4 in inducing EMT through the upregulation of N-cadherin and promoting metastasis of OC cells. Chauhan *et al.* [94] reported the expression profile, functions and potential role of *MUC13* in ovarian cancer diagnosis and pathogenesis that altered the cellular characteristics of SKOV3 cells.

Colon and rectal

Colorectal cancer (CRC) is the third most common cancer and fourth most commonly diagnosed malignant disease worldwide, with over 1 million new cases each year [95]. It is the second most frequent cause of cancer death in the world [96, 97]. CRC is also known as colon cancer, rectal cancer or bowel cancer that is developed in the colon or rectum [98]. Tumours were classified as mucinous carcinoma, when more than 50 % of tumour volume consisted of mucin [99]. *MUC1* is a membrane bound glycoprotein, which has been demonstrated to be predictive of tumour progression and worsening prognosis in both gastric [100–102] and colorectal cancer [103, 104]. *MUC3* is also a trans-membrane glycoprotein which is seen in both colorectal cancers and normal colon. Duncan *et al.* [105] demonstrated the role for *MUC1* in the progression of colorectal cancer and reported the presence of *MUC1* in colorectal cancer development possibly through its effects on cell adhesion.

Expression level of *MUC2* and 3 was found to be reduced (down regulated) compared with the levels in normal tissue [106]. A study on transcriptomic assay of colorectal cancer (CRC) suggested higher *MUC1* mRNA levels in CRCs compared with normal mucosa, whereas *MUC4*, *MUC12*, and *MUC13* expression was found to decrease with malignant transformation and *MUC3* mRNA levels in CRCs remain roughly comparable to those found in normal mucosa [107]. In addition, another study by Duncan *et al.* [105] has assessed the prognostic value of *MUC1* expression in a large cohort of colorectal cancer patients using high throughput tissue microarray technology and proposed that tumours lacking expression of *MUC1* will be more likely to metastasise, which is due to previously observed loss of cell-cell adhesion that lead to more aggressive cancers with poorer prognosis. This immunohistochemical analysis of *MUC1* and *MUC3* expression [105] reported that *MUC1* expression in colorectal cancer is an independent marker of poor prognosis, which supported the previous studies [108] suggesting the role for *MUC1* in colorectal cancer development, possibly through its effects on cell adhesion. *MUC12*, a novel membrane-associated mucin gene on chromosome 7q22 [5] is also known to be down-regulated in CRC, [5, 107]. Takatoshi *et al.* [109] studied the clinical, pathological and prognostic significance of *MUC12* in CRC and reported the expression of *MUC12* as a novel independent prognostic variable in patients with Stages II and III CRC. Patients with low *MUC12* expression showed significantly poorer disease-free survival (DFS) than those with high *MUC12* expression.

Xiao *et al.* [110] have reported *MUC20* to be one of the up-regulated genes in CRC patients with poor prognosis that can be a newly identified biomarker. It may serve as an important predictor of recurrence and poor outcome for CRC patients. *MUC20* overexpression could enhance migration and invasion abilities of CRC cells. Walsh *et al.* [111] has reported *MUC2*, *MUC5AC*, *MUC5B* and *MUC6* in a large series of colorectal carcinomas and provided the first comprehensive immune histochemical assessment of *MUC5B* expression in colorectal tumors.

Rectal cancer

Unlike colorectal cancer, which occurs in the colon or rectum, rectal cancer occurs specifically in the tissues of the rectum. The specific expression pattern of *MUC6*, *MUC2*, *MUC5AC* and *MUC5B* during the different steps of tumor progression toward adenocarcinoma suggested that they play significant roles in tumorigenesis [112, 113]. Among these, gastric mucin *MUC6* has a role in gastric cancer development [52] and is aberrantly expressed during the progression of some colorectal cancers [114]. *MUC6* has five novel tandem repeats (TR) (*MUC6*-(minisatellite, MS) MS1, -MS2, -MS3, -MS4, -MS5) in intronic regions [115]. Aberrant MUC6 expression was often found in gastrointestinal diseases, in relation to

MUC6-MS5 and susceptibility to rectal cancers [116]. *MUC6*-MS5 sequences with different sizes were found to contain several putative transcription factors binding sites for Hnf4, Maz, E2f1, Pbx, Tal, Bach2 and Krox [115]. Ahn *et al*. [116] suggested that loci of *MUC6* MSs may function as a useful predisposition marker of rectal cancer risk particularly to the male gender.

The prognostic value of different mucin component proportions in patients with stage III rectal cancer was studied by Wang *et al*. [29] and reported Histological subtype and lymphovascular invasion to be independent prognostic factors in multivariate analysis for disease free survival (DFS), and histological subtype (tumor with different mucin component) was the only independent prognostic factor for overall survival (OS). Survival curves showed the survival time of mucinous adenocarcinoma (*MUC*) was shorter than non-*MUC*.

Prostate cancer

Prostate cancer (CaP) is developed in the prostate gland in the male reproductive system [117]. Prostate cancer is now the most commonly diagnosed malignancy and the second leading cause of death in American males [118, 119].

Epithelial cancers like such as prostate and breast are found with the expression of *MUC1,* which is aberrantly glycosylated providing unique targets for imaging and therapy [120]. Andrén *et al*. [121] have tested the hypothesis that altered expression of *MUC1* is associated with prostate cancer progression. Based on their studies they reported *MUC1* to be an independent prognostic marker for prostate cancer death. Strawbridge *et al*. [122] has reported the genetic differences in *MUC1* between blood and prostatic cancer tissue that proved the principle of association studies focussed on blood DNA rather than on the tumor DNA. The discriminate antibodies between the variants and standardized methods would help to clarify the role for *MUC1* as a prognostic marker.

Cozzi *et al*. [123] examined the expressions of *MUC1*, *MUC2*, *MUC4*, *MUC5AC* and *MUC6* in CaP tissues using microarrays (TMAs) to look for tumor-associated antigens (TAAs) for targeted therapy and examined a large series by investigating mucin expression in normal prostate, benign prostate and CaP. It was reported that *MUC1* is over-expressed in primary CaP (Gleason score 7 or higher) and 90 % lymph node metastases but not in normal prostate, benign prostatic hyperplasia (BPH) or prostatic intraepithelial neoplasia (PIN) and this over-expression is correlated with CaP progression. The expression of *MUC2*, *MUC4*, *MUC5AC* and *MUC6* was not found either in normal or in CaP tissues. *MUC1* antigen could be an ideal target for targeted therapy, especially for CaP in late stage, post-surgical minimal residual disease (MRD) or for micrometastatic lesions with moderate to strong *MUC1* over-expression.

In addition, increase in the expression of *MUC18* during prostate cancer initiation (high grade PIN) and progression to carcinoma and in metastatic cell lines and metastatic carcinoma was reported by Wu *et al*. [124].

Pantuck *et al*. [125] conducted phase 1 clinical trial of 5×10(5), 5×10(6), and 5×10(7) plaque-forming units (pfu) of vaccinia viruses in the dose-escalating study to determine the maximum tolerated dose, safety of a multiple-dose regimen and the immunologic effect of vaccinia virus expressing *MUC1* and IL-2 genes (VV/MUC-1/IL-2) in patients with advanced prostate cancer. It was suggested that 5×10(7) pfu is safe and well tolerated maximum dose of VV/MUC-1/IL-2 gene therapy.

Pseudomyxoma peritonei

Pseudomyxoma peritonei (PMP) is a rare malignant growth, characterized by the progressive accumulation of mucus-secreting (mucinous) tumor cells within the abdomen and pelvis. The disorder develops after a small growth (polyp) located within the appendix bursts through the wall of the appendix and spreads mucus-producing tumor cells throughout the surrounding surfaces (*e.g*., the membrane that lines the abdominal cavity [peritoneum]). Therefore, mucin plays a key role in the biology of the PMP tumor.

A case of synchronous tumors in appendix and ovaries with pseudomyxoma peritonei was reported by Ciriza *et al*. [126]. Through histopathological analysis they have demonstrated a well-differentiated mucinous adenocarcinoma of appendiceal origin with metastasis in ovaries and peritoneum (pseudomyxoma peritonei).

The primary tumor appears to arise from the *MUC2* expressing goblet cells in the appendix. In case of PMP, mucin is ectopically secreted and gets deposited in the peritoneal cavity where it is unable to degrade or drain away and causes a major part of the morbidity in PMP. Amini *et al*. [127] reported the presence of *MUC2*, *MUC5AC* and *MUC5B* in PMP secretions of which the intestinal mucin *MUC2* is known as the PMP-specific mucin.

O'Connell *et al*. [128] reported the essential expression of *MUC5AC* in primary ovarian mucinous tumors and expression of MUC2 along with MUC5AC in solitary appendiceal mucinous tumors and different categories of PMP, which supports the notion that PMP is a neoplasm of appendiceal origin. *MUC2* is more voluminous than *MUC5AC* as it is more extensively glycosylated; hence formation of abundant mucinous collections is more than 10 times of a cell. PMP was concluded to be a disease of the *MUC2*-secreting goblet cells by investigators therefore, based on the conclusion; *MUC2* could serve as a molecular marker for PMP [128, 129]. The

prognostic significance of *MUC2* is reported to be controversial, as the expression level of *MUC2* in PMP is independent of the degree of the malignant transformation [130]. The presence of *MUC5B*, in addition to *MUC2* and *MUC5AC* was reported in case studies of PMP subjects [131, 132], investigations by Sheehan *et al.* implicated a low-charge glycoform of *MUC5B* in the production of a tenacious respiratory mucus plug [133, 134], it may be *MUC5B* as speculated by Mall *et al.* that is responsible for the semisolid material found in some PMP patients. The development of mucin-targeted therapies was suggested by Amini *et al.* [127] which could be a promising avenue for future research based on the relevance of *MUC2*, *MUC5AC* and *MUC5B* in PMP.

Pancreatic cancer

Pancreatic cancer (PC) is one of the most aggressive forms of cancer that has the worst prognosis of all cancers and is the fourth leading cause of deaths [135]. There are different types of pancreatic cancer, but the most common is pancreatic adenocarcinoma or Pancreatic Ductal Adenocarcinoma (PDAC), that accounts about 85 % of the cases, [136] to which the term "pancreatic cancer" is often referred. Invasive ductal carcinoma (IDC) of the pancreas is said to be the fifth cause of carcinoma related death in men and the sixth cause of carcinoma related death in women in Japan that still has a relatively poor prognosis [137]. These adenocarcinomas start within the pancreatic glands which make digestive enzymes. Jonckheere *et al.* [138] focussed on the altered expression pattern of mucins in pancreatic cancer, from the early neoplastic lesion Pancreatic Intraepithelial Neoplasia (PanIN) to invasive pancreatic carcinomas, its molecular mechanisms (including genetic and epigenetic regulation) and signaling pathways known to control their expression. They discussed the recent advances about the biology of both secreted and membrane-bound mucins and their key roles in pancreatic carcinogenesis, resistance to therapy and exciting opportunities that mucins offer as potential therapeutic targets in pancreatic cancer. Relationship between mucin and pancreatic cancer were described in many reports [139–141].

Levi *et al.* [142], reported *MUC1* as a membrane tethered glycoprotein expressed on the apical surfaces of normal glandular epithelia that is over-expressed and aberrantly glycosylated in>60 % of human pancreatic ductal adenocarcinoma (PDA). Focussing on the role of *MUC1* in PC, Curry *et al.* [143] have determined the sensitivity and specificity of the anti-MUC1 antibody, TAB 004 and assessed the Cancer Stem Cells (CSCs) in Pancreatic Cancer (PC) enzyme immunoassay (EIA) that detected circulating MUC1 using TAB 004-FITC on *in vitro* PC cell lines. They reported TAB 004 antibody may be explored as a therapeutic targeting agent for CSCs in PC and may be explored as a PC stage diagnostic biomarker.

Nagata *et al.* [27] demonstrated the expression profile of different mucins like *MUC1*, *MUC2*, *MUC5AC*, *MUC6* in various types of pancreatic cancer like invasive ductal carcinoma (IDC), two subtypes of intraductal papillary—mucinous neoplasm (IPMN dark cell type and IPMN clear cell type), pancreatic intraepithelial neoplasia (PanIN), and mucinous cystic neoplasm (MCN) of the pancreas including normal tissue. Changes in mucin expression or glycosylation accompany the development of cancer and influence cellular growth, differentiation, transformation, adhesion, invasion and immune surveillance [27, 112].

Statistically significant associations are reported between expression of *MUC5AC* and shorter survival time in patients with pancreatic cancer [141]. It was studied that expression of *MUC5AC* in human pancreatic cancer cell lines has a role in the progression of pancreatic cancer by inducing adhesiveness and invasiveness in extracellular matrix components (ECM) via (vascular endothelial growth factor) VEGF overexpression, and indicated *MUC5AC* to be a potential target in the treatment of pancreatic cancer [144]. Expression of *MUC4* has been detected in IDC [145–148]. MUC4 was expressed in 89 or 79 %, of IDCs and the expression increases progressively in pancreatic intraepithelial neoplasia (PanIN) [149, 150]. Although the combined evaluation of *MUC4* and *MUC1* expression did not show any significant difference in survival for patients with IDC [151], the importance of *MUC4* expression as a useful indicator to predict the outcome of patients with surgically resected IDC [151] was observed. *MUC4* has potential as a prognostic marker for clinical management of patients with IDC and its expression in IDC is a new independent factor for poor prognosis and disease outcome. Expressions of *MUC5AC* and *MUC6* were observed in the cytoplasm of the IDC tumor cells. *MUC5AC*-positive patients showed significant better survival than those *MUC5AC*-negatives, whereas, MUC6 expression was significantly related to tumor location but not with patient survival [152].

The expression of various mucins in pancreatic ductal adenocarcinoma (PDAC) and intraductal papillary mucinous neoplasms (IPMNs) have demonstrated by Yokoyama *et al.* [44] through immunohistochemical (IHC) studies. Kaur *et al.* [153] studied the expression pattern of various mucins in the pancreas under various conditions along with contribution of the tumor microenvironment in pancreatic cancer development its progression, diagnostic / prognostic efficacy of mucins and mucin-based therapeutic strategies. This information could explore family of mucins that play key role in pancreatic cancer, through various mechanisms in both tumor cells and the microenvironment and worsen disease outcome. A direct association of *MUC13* with pancreatic cancer and its influence on pancreatic tumorigenesis was reported [154]. Over expression of *MUC13* in pancreatic cancer and the exogenous

expression of *MUC13* augments tumorigenic features in pancreatic cancer cells, such as enhanced cell proliferation, cell motility, cell invasion, and *in vivo* tumor growth was reported. Conversely, the suppression of *MUC13* expression by short hairpin RNA (shRNA) in human pancreatic adenocarcinoma cell (HPAFII) shows the opposite effect. The expression of *MUC13* correlates with the expression/activation of HER2, PAK1, ERK, Akt, and S100A4 and the decreased expression of p53 [154]. The regulatory mechanism of *MUC17* was reported by Kitamoto *et al*. [155] under hypoxia, as an essential feature of the tumor microenvironment and a driving force of cancer progression. Role of mucins in Intraductal papillary-mucinous tumor (IPMT) of the pancreas, a rare disease characterized by a proliferation of the epithelium lining the pancreatic ducts was also reported [156–159]. The altered expression of mucin, characteristic of IPMT of adenoma type and of colloid carcinomas that may contribute to the better clinical outcome of these neoplasms, compared to conventional pancreatic ductal adenocarcinomas has been demonstrated by Terris *et al*. [160].

Stomach

Gastric carcinoma

Stomach cancer or Gastric cancer develops from the lining of the stomach [161] that remains the fourth most common cancer and the second leading cause of cancer-related mortality worldwide [162]. Although, Pan *et al*. [163] have reported the exact etiology (describe the etiology in brief) of gastric cancer that remains to be identified, accumulating studies have reported gastric carcinogenesis as a complex, multistep and multifactorial process that involves genetic factors and environmental triggers. The cancer is said to be spread from the stomach to other parts of the body, particularly the liver, lungs, bones, lining of the abdomen and lymph nodes [164]. Mucinous gastric carcinoma (MGC) constitutes only 2 to 6 % of all stomach cancers [165] and defined as a gastric adenocarcinoma by the World Health Organization (WHO) with a substantial amount of extracellular mucin (≥50 % of tumor volume) within tumors [166]. Choi *et al*. [167] analyzed the clinicopathologic and molecular characteristics of MGCs and Non MGCs and reported that the molecular characteristics of MGCs differed from those of NMGCs. Gastric cancer is mostly caused by the infection of a bacterium, *Helicobacter pylori* (*H. pylori*), that accounts for more than 60 % of cases [168]. Certain type of *H. pylori* has greater risks than others. The mechanism by which *H. pylori* induces stomach cancer potentially involves chronic inflammation or the action of *H. pylori* virulence factors such as cytotoxin-associated gene A (CagA) [169].

Emerging evidence states that *MUC1* acts as an oncoprotein when overexpressed [170]. The cytoplasmic tail of *MUC1* interacts with the *H. pylori* virulence factor cagA and is a major effector of the wnt-β catenin intracellular signalling cascade. It is reported that two single nucleotide polymorphisms (rs4072037 and rs2070803) in the *MUC1* gene has been identified in gastric cancer patients and may have a prospective role in the stratification of high-risk subjects [171]. The overexpression of *MUC1* and *MUC4* also mediates resistance to the trastuzumab, a monoclonal antibody against HER-2/neu [172, 173] siRNA to *MUC1* was tested in trastuzumab drug resistance cells and a better response to the drug was seen in siRNA treated drug resistant cell when compared to control or junk siRNA treatment [174].

In gastric cancer, expression of *MUC5AC* and *MUC1* is reduced and *de novo* expression of *MUC2* occurs. All the three mucins expression decreases with progressive loss of tumor differentiation and increased tumor stage [170]. Cardia and non-cardia are the subtypes of gastric cancer. It is now generally accepted that *Helicobacter pylori* (*H. pylori*) infection is the single most important risk factor in the development of non-cardia gastric cancer [175, 176]. Several published investigations have strongly suggested that *MUC5AC* forms the major receptor for H. pylori in the human stomach [177, 178], and the infection of H. pylori can alter the expression of *MUC5AC* [179]. Some studies have shown that *MUC5AC* is aberrantly expressed in gastric cancer [180–182].

Zhou *et al*. [183] has highlighted the importance of *MUC5AC* gene in gastric cancer risk and reported the common genetic variations in *MUC5AC* gene (rs3793964 and rs11040869) that might be associated with a decreased risk of non-cardia gastric cancer in north-western Chinese Han population. Accumulating evidence implicates potential roles of *MUC1*, *MUC5AC*, and *MUC6* genetic variation in the development of stomach cancer. During the process of gastric carcinogenesis the expression of these genes are altered [184–189]. Reports shows the relationship between a variable number tandem repeat (VNTR) polymorphism of *MUC1* [190], *MUC6* [191] gene and the risk of stomach cancer associated with *H. pylori* infection and an excess risk of stomach cancer [192].

Using the tagSNP approach based on the HapMap data Jia *et al*. [193] provided the evidence for association of an increased risk of stomach cancer with some common genetic variations in *MUC1* and *MUC5AC* genes that could lead to a better understanding of gastric carcinogenesis by further evaluation of the functional relevance of identified variants.

Epstein-Barr virus (EBV)-associated gastric carcinoma (GC) is a distinct subset of GC, accounting for 10 % or less of total GC [194]. Rita *et al*. [195] has reported that the phenotype analysis may be also useful in EBV-negative GC to identify a specific subgroup, such as a mixed phenotype based on the studies of EBV-associated GC that showed a

characteristic expression pattern of *MUC5AC*, *MUC6*, *MUC2* and cluster of differentiation 10 (CD10), namely null and gastric phenotypes.

It is distinctive that common gastritis frequently caused by *H. pylori* initiates in the antrum. On the other hand, in the case of EBV-associated GC, tumors are frequently located near the mucosal atrophic border, where mild to moderate atrophy is common [196]. Iizasa *et al*. [197] have reported the epidemiology and clinical features Of EBV-associated gastric carcinoma and presented the role of viral genes in infection and its carcinogenicity. The possibility of therapies targeting EBV-associated gastric carcinoma was proposed. Nishikawa *et al*. [198] detected both EBV and *H. pylori* in the mucosa of patients with moderate to chronic atrophic gastritis and have clearly proved the direct infection of human gastric epithelial cells by EBV.

Lung

Lung cancer

Lung cancer is the most common cancer in the world and accounted for 13 % (1.6 million) of total cases and 18 % (1.4 million) of cancer deaths [135]. Most cancers that start in the lung, known as primary lung cancers, are carcinomas that are derived from epithelial cells. The main primary types are small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC) [199]. Their resistance to environmental injuries, exposure to pathogens, particles and toxic chemicals in inhaled air depends on a highly effective defence provided by airway mucus, an extracellular gel in which water and mucins (heavily glycosylated proteins) are the most important components. The excessive production of airway mucus is a feature of chronic inflammatory lung diseases such as bronchial asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis and cystic fibrosis (CF). Hypersecretion of mucus results from hyperplasia and metaplasia of mucous cells, which lead to greater numbers of these cells being found throughout the airways, including the distal airways, where they are normally absent [200]. The mechanisms involved in the upregulation of secreted mucins in lung cancer was studied by Hauber *et al*. [201] and they discussed the induction of mucin by neutrophil elastase, bacteria, cytokines, growth factors, smoke and cystic fibrosis transmembrane conductance regulator malfunction. Fahy *et al*. [202] examined the normal formation and clearance of airway mucus, the formation of pathologic mucus, the failure of mucus clearance that results in symptoms and abnormal lung function and the therapy of mucus dysfunction.

Abnormal *MUC4* expression has been reported in various cancers, as well as in other lung and airway inflammatory diseases including cystic fibrosis and chronic obstructive pulmonary disease [203–205]. *MUC4* also plays a critical role in regulating diverse processes in lung stromal/parenchymal cells, including apoptosis and metastasis. *MUC4* acts as an intramembrane ligand for ErbB2/HER2/neu and potentiates its autophosphorylation [206]. *MUC4* may possess a tumor-promotion function, in part by regulating *HER2* gene expression.

Chen *et al*. [207] reported that glucocorticoid receptor (GR) and histone deacetylase-2 (HDAC2) are recruited to two glucocorticoid response elements, GRE3 and GRE5 cis-sites in the *MUC5AC* promoter and mediate the Dexamethasone-induced cis-repression of *MUC5AC* gene expression. These mechanisms help in better understanding that glucocorticoids repress *MUC5AC* gene expression may be useful in formulating therapeutic interventions in chronic lung diseases.

Zhang *et al*. [208] provided evidence that *MUC4* polymorphisms (rs3096337, rs859769, rs842461, rs863582, rs842226, rs2550236, rs842225 and rs2688515) and their interactions with smoking status may contribute to lung cancer etiology. Immunohistochemical staining for *MUC1* and *MUC2* glycoproteins can distinguish between primary lung signet-ring cell carcinoma (SRCC) and metastatic lung SRCC originating in the gastrointestinal tract. Lung SRCC was positive for *MUC1* but negative for *MUC2*, whereas it was vice-versa for metastatic lung SRCC [209]. De Pas *et al*. lung cancer was studied by Hauber[210] reviewed the key points for effective active immunotherapies and combination therapies of most promising vaccines, anti-*MUC1* vaccine (belagenpumatucel) and anti-TGF-β(2) vaccine (BPL-25), developed for Non-small cell lung cancer (NSCLC).

Idiopathic pulmonary fibrosis (Lung disease)

Idiopathic pulmonary fibrosis (IPF) is a chronic and ultimately fatal disease characterized by a progressive decline in lung function [211]. Fibrosis is usually associated with a poor prognosis [211, 212]. The term ‘idiopathic’ is used because the cause of pulmonary fibrosis is still unknown [211]. Reports have mentioned the genetic mutations that are associated with familial pulmonary fibrosis. Genetic associations include mutations in pulmonary surfactant proteins A1, A2, C (SFTPA1, SFTPA2B) and mucin (*MUC5B*) ((OMIM) 178500). A remarkable aspect of the *MUC5B* variant is its high frequency of detection, as it is found in approximately 20 % of patients with Northern and Western European ancestry and in 19 % of the Framingham Heart Study population [213]. It was reported that Idiopathic pulmonary fibrosis is etiologically heterogeneous, biologically dynamic and sequence and trascriptional changes in *MUC5B*, in the fibrotic lung [214, 215] and serum biomarkers, including chemokine ligand 18, KL6, SFTPA, SFTPD, matrix metalloproteinase7 (MMP-7), intercellular

adhesion molecule 1 and interleukin 8, are potential predictors of disease activity and outcome in patients with IPF [216–219].

A common polymorphism in the promoter of a mucin gene (*MUC5B*) has been found to be associated with an increase in risk of developing both familial and sporadic IPF in an allele dose-dependent manner [220, 221]. Linkage and fine mapping resulted in identification of *MUC5B* in pathogenecity of IPF. It was found that dysregulation of *MUC5B* expression in the lung is involved in the pathogenesis of pulmonary fibrosis. A minor-allele of the SNP rs35705950 upstream of the gene was found to be highly associated with IPF ($P=2.5\times10^{-37}$) (219). Peljto *et al*. [222] have reported a common risk polymorphism (rs35705950) in *MUC5B* that can be used in improved survival among the patients with IPF.

Stock *et al*. [223] have confirmed an association of *MUC5B* rs35705950 variant with IPF in UK population and no association with lung fibrosis in the context of systemic sclerosis (SSc) or sarcoidosis, potentially highlighting fundamental differences in genetic susceptibility. Borie *et al*. [224] have confirmed a strong association between the *MUC5B* rs35705950 variant and IPF in Caucasian population whereas this association was absent in SSc related interstitial lung disease (ILD) from the European data and meta-analysis.

Cystic fibrosis

Cystic fibrosis (CF), which is also known as mucoviscidosis is a common inherited autosomal recessive genetic disorder that not only affects the lungs but also the pancreas, liver and intestine. CF is a multisystem disorder caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR) [225, 226]. This protein is required to regulate the components of sweat, digestive fluids and mucus. The mutations in this cyclic AMP-regulated chloride ion channel lead to either mis-localization of CFTR or loss of function, resulting in defective chloride ion transport across epithelial cell surfaces and the build-up of a dehydrated mucus layer in the lung [226]. This result in malfunction of these CFTR protein blocks the flow of these ions out of the cell due to blockage in ion channels. Individuals with identical CFTR polymorphism also demonstrated wide range in the severity of CF, with some individuals facing lung transplantation or death early in life and others demonstrate mild lung disease till adulthood. Therefore, necessity for finding additional modifier genes was felt. There is now growing evidence that polymorphic variants in genes besides CFTR also play an important role in determining severity of CF lung disease [227]. To analyze the correlation between the expression of CFTR and NF KappaB or *MUC1*, in the endometrium of infertile women with and without hydrosalpinx (a pathogenesis of fallopian tube blockage with cause related to CF). Song *et al*. [228] investigated the expression of CFTR, nuclear factor kappa B (NF KappaB) and mucin-1 (*MUC1*). From the study they reported an increased NF KappaB expression and decreased CFTR and *MUC1* expression in the endometrium of infertile patients with hydrosalpinx.

In pulmonary CF the airway can become susceptible to subsequent infections with *Pseudomonas aeruginosa* [229] because mucus constitutes a favourable niche for bacterial growth [230]. The dense nature of thickened mucosal secretions traps microorganisms and other opportunistic pathogens and allows these organisms to establish successful lung infections [231, 232]. Mucin glycoprotein overproduction and hypersecretion are common features of chronic inflammatory airway disease. David *et al*. [233] discussed the roles of multifunctional O-linked glycoproteins and polymeric mucins in human health and chronic airways disease (*e.g*., asthma, cystic fibrosis, and chronic obstructive pulmonary disease).

Fahy *et al*. [202] examined the normal formation and clearance of airway mucus, the formation of pathologic mucus, the failure of mucus clearance that results in symptoms and abnormal lung function and the therapy of mucus dysfunction.

Henke and Ratjen [234] reported the accumulation of Mucus in the lower airways to be a key feature of cystic fibrosis (CF) lung disease that contains pus that includes viscous material such as polymerized DNA derived from degraded neutrophils but not mucin. However, other studies suggested that the drugs that are mucokinetic and preserve viscoelasticity, rather than mucolytic may prove to be beneficial for CF lung disease in the future. Airway mucins are produced mainly by goblet cells in the surface epithelium and by glands in the submucosal tissue. This suggested that mucins play a key role in the pathogenesis of CF lung disease [235]. The monomeric mucins, such as *MUC1*, play an important role in the pathogenesis of CF [236]. It was suggested that the primary effect of CFTR malfunction is the overexpression of mucins in the airways. Out of the seven gel forming secretory mucins, *MUC5AC* and *MUC5B* have been identified as major gel-forming macromolecules in respiratory secretions, whereas *MUC2* contributes only to a lesser extend to the matrix [237, 238]. A novel link between the *MUC5AC* 6.4 kb VNTR allele and severity of CF lung disease was established [235]. In presence of inflammatory cytokines like IL-1beta and IL-17A there is an upregulation of *MUC5AC* in the airway epithelium [239]. The transcription of the mucin gene *MUC 2* in epithelial cells is profoundly upregulated by *P. aeruginosa* lipopolysaccharide [240]. Alterations in antibacterial peptide function, as well as the increased mucin expression and secretion (*MUC 5 AC and MUC 5B*), are important biochemical factors responsible for the propensity for infection in CF airways. Alterations in mucin and lipid composition induce an increased viscosity and adhesiveness to the airways that can affect the mucociliary and cough transport. The increased content of pro-inflammation cytokines such as interleukin-8 (IL-

8) suggest that, before infection, airway inflammation occurs very early in CF. The development of non-invasive techniques and humanised animal models (xenografts) represents a major opportunity to identify early abnormalities in CF airway mucus [241]. Destruction of the lungs as a consequence of recurrent infections with microorganisms such as *Pseudomonas aeruginosa* remains the underlying cause of most morbidity and mortality in cystic fibrosis (CF). It is hypothesized that changes in the glycosylation of key tracheal mucins such as *MUC5B* and *MUC7* might increase the risk of pulmonary disease in CF patients [242]. While the main high-molecular mass proteins in the sputum from all subjects were the mucins *MUC5B* and *MUC5AC*, which appeared degraded in CF adults with an exacerbation. The glycosylation of these mucins also showed reduced sulfation, increased sialylation and reduced fucosylation in CF adults compared with controls [243–248, 204]. However, some studies [249], conducted on the length polymorphisms in the central repetitive regions of *MUC1*, *MUC2* and *MUC5AC* as these are excellent candidates for contributing to the presence of meconium ileus (MI) (blockage in the baby' ileum) in cystic fibrosis (CF) reported nil association of genetic length variants of three *MUC* genes with MI in subjects with CF. This indicates that epigenetic factors involved in regulation of *MUC* genes might be involved in CF and its associated pathogenesis.

Diffuse panbronchiolitis

Diffuse panbronchiolitis (DPB) is an idiopathic inflammatory disease that is characterized by progressive suppurative and obstructive airway disease which, if left untreated gives rise to bronchiectasis, respiratory failure and death [250]. DPB is believed to occur when there is susceptibility or a lack of immune system resistance to DPB causing bacteria or viruses, caused by several genes that are found predominantly in individuals of East Asian descent.

This disease was established as a new clinicopathologic entity distinct from chronic obstructive pulmonary disease (COPD) [251], which is considered to be a complex genetic disease mostly affecting East Asians [252]. Based on evidence from retrospective and non-randomised studies, Macrolides, a class of antibiotics, have been used as the main treatment for DPB. Ginori *et al.* [253] from their studies confirmed the correlation between a status of immunodeficiency and the development of DPB that provided more information on the accumulation of nodules of foamy macrophages in DPB.

Mucous hypersecretion is often observed in various chronic respiratory disorders, such as chronic bronchitis, bronchial asthma and bronchiectasis. Especially in DPB, patients always suffer from a large amount of sputum. Kamio *et al.* [254] detected the promoter polymorphisms in the regulatory region of six mucin genes *MUC1*, *MUC2*, *MUC4*, *MUC5AC*, *MUC5B* and *MUC7* and reported that polymorphism identified in the *MUC5B* gene was significantly associated with DPB disease. *MUC5AC* is predominant and *MUC5B* expression is generally scarce in the normal lung. Kamio *et al.* [254] reported that the level of mucus secretion might be modified by single variation or haplotypes in the promoter region of the *MUC5B* gene. These findings suggested that polymorphisms located in the *MUC5B* promoter region influences the levels of mucin gene expression, although of little consequence in the healthy airways, may be relevant in a disease context in which microbial and host inflammatory factors stimulate mucin gene expression [255].

The polymorphisms located in the *MUC5B* promoter was focused and identified with differential allelic expression of this mucin *in vitro* [255]. This was followed in further studies of *MUC5B* alleles that demonstrated low relative expression alleles, with a lower frequency in individuals with diffuse panbronchiolitis [254]. Thornton *et al.* [233] reported influence of polymorphisms in the regulatory regions that affects the levels of mucin gene expression in DPB.

Asthma

Asthma is a complex, prevalent and multifactorial disease [256] reflecting genetic and environmental components characterized by variable airflow limitation, airway hyperresponsiveness (AHR) and chronic airway inflammation [257]. It is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction and bronchospasm. Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic) [258] where atopy refers to a predisposition toward developing type 1 hypersensitivity reactions [259]. It is known to be caused by a combination of genetic and environmental factors [260]. Its diagnosis is usually based on the pattern of symptoms, response to therapy over time and spirometry [261]. The development of asthma and exacerbation including allergens, air pollution and other environmental chemicals are associated with many environmental factors [262].

Some genetic variants may only cause asthma when they are combined with specific environmental exposures [260]. An example is a specific single nucleotide polymorphism in the CD14 region and exposure to endotoxin (a bacterial product). Mucins are overproduced in asthma, as well as other lung diseases, and contribute to airway pathophysiology and thus to disease morbidity and mortality [263–266]. Genetic analyses of some *MUC* genes have been carried out in patients with atopy or asthma. A longer VNTR length in the *MUC2* gene is associated with a cohort of atopic, non-asthmatic patients, but no associated differences with asthma and VNTR domains of *MUC1*, *MUC4*, *MUC5AC* or *MUC5B* genes have been found [187].

The Li *et al.* [267] studied and demonstrated the levels of *MUC2* in guinea pig model of allergic asthma in lungs of

ovalbumin sensitized animals that increased significantly shortly after acute allergen exposure and suggested that *MUC2* likely plays an important role in airway inflammation and mucin overproduction, both hallmark pathophysiologic features of asthma.

Watson *et al*. [268] have reported the presence of *MUC7* mucin in the airway secretions of asthmatic but not in the control and pediatric patients suggesting that *MUC7* mucin may have a role in the pathophysiology of asthma.

Watson *et al*. [269] studied *MUC7* gene, that exhibits a high degree of polymorphism that generates a variable number of tandem repeat (VNTR) domains, typically encodes for 6 VNTR, each with 23 amino acids in different cohort. They reported a decreased risk of asthma with presence of a novel *MUC7**4-VNTR polymorphism, in an African-American subjects. Future studies will be needed to determine mechanisms by which polymorphisms in the *MUC7* gene alter the host innate immune response of *MUC7* mucin and its relevance to asthma.

Dizier *et al*. [270] has reported eczema as an allergic manifestation that is strongly associated with asthma and allergic rhinitis with reference to *MUC15* and genetic variants of eczema. Based on the studies *MUC15* was suggested to be a strong candidate for eczema.

Morcillo and Cortijo [33] have reviewed the contributions to the field of therapeutic avenues that control mucus hypersecretion and reported the targets such as epidermal growth factor receptor (EGFR) cascade to be crucial in excessive and abnormal mucus secretion,. Delineating cross-talk between EGFR and other receptor systems towards the activity of acetylcholine was suggested may provide new clues to the mechanism of mucin secretion. Success of these studies may lead to the rational design of new antihypersecretory drugs that may enhance future asthma treatment.

Lai and Rogers [271] have studied identification of potential drug targets for treatment of hypersecretion in asthma and COPD. They reported the underlying factors for upregulation of mucin synthesis and development of goblet cell hyperplasia to be the best drug targets. Keeping in view the side effects they suggested for translation of the promising preclinical studies to the clinic, which depends on development of drug moieties with low off-target activity.

Intestine

Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) results from a complex and abnormal mucosal immune response to commensal microorganisms primed by infection with a specific pathogen or an impaired mucosal barrier, which arises as a result of the interaction of environmental and genetic factors. [272, 273]. IBD is a group of inflammatory conditions of the colon and small intestine comprises diseases that are characterized by chronic or relapsing inflammation in the gastrointestinal tract. Ulcerative colitis (UC) and Crohn's disease (CD) are the major forms of inflammatory bowel diseases (IBDs) that are of multifactorial disorders of unknown etiology. These two diseases share many clinical and epidemiological characteristics, suggesting a potentially mutual causation [274]. Intestinal mucosal cells secrete key components of mucus, including phospholipids, secretory dimeric immunoglobulin A (IgA) and mucins, which are highly glycosylated, filamentous proteins present at the interface between many epithelia and their extracellular environments adhesion with microorganisms, which is increasingly thought that alterations to enteral bacteria can contribute to inflammatory gut diseases [275, 276]. Aroniadis and Brandt [277] reported that the IBD affected individuals were prescribed antibiotics in the 2–5 years period before their diagnosis compared to unaffected individuals. This shows the role of gut flora for the cause of inflammatory bowel disease.

Ou *et al*. [278] reported intestinal lining in humans with large surface area, estimated to approximately 100 m^2 that is continuously exposed to innocuous, mostly beneficial antigens from the diet and the commensal microflora, also to potential pathogens, gut microbes that are either harmless or of benefit to the host. The most abundant microflora is present in the distal parts of the gut; the majority of the intestinal bacteria are Gram-negative anaerobes. The gut microbiota protects against enteropathogens extracts nutrients and energy from our diets and contributes to normal immune function. Disruptions to the normal balance between the gut microbiota and the host have been associated with obesity, malnutrition, inflammatory bowel disease (IBD) [279, 280] neurological disorders and cancer.

Nishida *et al*. [281] investigated the role of *MUC1* in development of colitis in mice by considering T helper (Th) 17 cells as they produce the effector cytokine interleukin (IL)-17, along with IL-22, which stimulates colonic epithelial cells to produce a membrane-bound mucin, Muc1 associated with susceptibility to inflammatory bowel disease because of Disruption of this negative feedback pathway by variants in *MUC1*.

Lee, *et al*. [282] studied the effects of *Gymnophalloides seoi* antigen on the host's intestinal epithelial cells, to determine expression of Toll-like receptors (TLRs) and mucin-related (*MUC*) genes on a human intestinal epithelial cell line (HT29 cells) induced by *Gymnophalloides* (G) *seoi*. They reported that TLR2 and *MUC2* expression on human intestinal epithelial cells were up regulated by *G. seoi* antigen. These effects reflect a helminth-induced, IFN-gamma-dependent, and innate mucosal immune mechanism in this human intestinal cell line. Senapati *et al*. [283] investigated cellular location and expression of *MUC17* in specimens of normal,

inflamed and neoplastic colon. These studies indicated that the potential protective effects of this membrane-bound mucin are primarily or secondarily diminished in inflammatory and neoplastic conditions.

Lozupone *et al.* [284] reported the underlying factors, such as hypoxia induced factors, that changes the composition and function of gut microbiota under disease condition. They emphasized the need of comprehensively reviewing the gut microflora in human intestine and their underlying factors that alter their composition and function at different states *i.e.*, normal and diseased conditions and their variance between individuals in order to understand these factors to aid in the design of therapies. Gomes *et al.* [285] suggested that altered intestinal microbiota leads to increased intestinal permeability and mucosal immune response, which in turn contributes to various diseases. This mucosal immune system has developed specialised regulatory, anti-inflammatory mechanisms for eliminating or tolerating non-dangerous, food and airborne antigens and commensal micro-organisms (oral, mucosal tolerance) at the same time the mucosal immune system provides local defence mechanisms against environmental threats (*e.g.*, invading pathogens). Regulation of microflora composition (*e.g.*, by probiotics and prebiotics) offers the possibility to influence the development of mucosal and systemic immunity but it can play a role also in prevention and treatment of some diseases. Disruption of this negative feedback pathway, perhaps by variants in *MUC1*, might contribute to inflammatory bowel disease in patients [286, 281, 282]

Jostins *et al.* [287] expanded on the knowledge of relevant pathways by undertaking a meta-analysis of Crohn's disease and ulcerative colitis genome-wide association scans and observed considerable overlap between susceptibility loci for IBD and mycobacterial infection. Gene co-expression network analysis emphasized this relationship, with pathways shared between host responses to mycobacteria and those predisposing to IBD.

Crohn's disease

Crohn's disease (CD) is a chronic relapsing inflammatory bowel disease of unknown origin that not only affects the small intestine and large intestine, but it can also affect the mouth, oesophagus, stomach and anus [288–290]. It is characterised by chronic mucosal ulcerations, which affect any part of the intestine but most commonly are found in the ileum and proximal colon [291]. The intestinal epithelium is covered by a continuous layer of mucus that provides a physical barrier between the underlying epithelium and aggressive agents present in the gastrointestinal tract lumen [292, 293].

Buisine *et al.* [293] studied cell specific expression of mucin genes in the ileum of patients with CD and suggested that gel forming mucins particularly *MUC5AC* and *MUC6* may have a role in epithelial wound healing after mucosal injury in inflammatory bowel diseases in addition to mucosal protection. Pullan *et al.* [294] identified altered mucus composition has been in IBD but could not detect any change in the number of goblet cells and alteration in mucosal thickness in CD.

Kyo *et al.* [295] reported a possible association of rare variable number of tandem repeat (VNTR) alleles of the *MUC3* gene with a susceptibility to UC. They described and analyzed the single nucleotide polymorphisms (SNPs) in the exonic sequences of the 39 portions of these two genes *MUC3A* and *MUC3B* in order to find the sequence variance in these regions that can cause person-to-person differences in the susceptibility to IBDs. They reported that non-synonymous SNPs of *MUC3A*, involving a tyrosine residue with a proposed role in cell signaling, may confer genetic predisposition to CD.

The genome-wide association studies have reported several risk factors for Crohn's disease. Based on these studies Barrett *et al.* [296] carried out replication in 3,664 independent cases with a mixture of population-based and family-based controls, which could be helpful in advanced gene discovery. They strongly confirmed 11 previously reported loci and provide genome-wide significant evidence for 21 additional loci, including the regions containing STAT3, JAK2, ICOSLG, CDKAL1 and ITLN1, this could promise for informed therapeutic development based on the concerned disease. The genetic loci (rs11175593) implicated in association with CD also bears *MUC19* gene thereby, indicating its role in CD.

Ulcerative colitis

Ulcerative colitis, in contrast, is restricted to the colon and the rectum. Anemia is the most prevalent extra intestinal complication of inflammatory bowel disease [297, 298]. Associated complaints or diseases include arthritis, pyoderma gangrenosum, primary sclerosing cholangitis and non-thyroidal illness syndrome (NTIS) [299].

Deregulated mucin production has been associated with various types of cancer and inflammatory disorders. Microscopically, ulcerative colitis is restricted to the mucosa (epithelial lining of the gut), while Crohn's disease affects the full thickness of the bowel wall. Inflammatory bowel disease (IBD) affects the quantity and quality of mucins due to the reduction in the number of goblet cells. Alteration in different types of mucins and aberrant location may contribute to the underlying pathology by affecting the mucus barrier function or may instead be a response to inflammation [300].

Lapensee *et al.* [301] reported Mucin 9 (*MUC9* as oviductin, which is expressed in epithelial cells. Furusho *et al.* [302] has studied the expression of *MUC9* gene in patients with UC and reported decreased expression of *MUC9* mRNA in colonic mucosa from patients with active and remission UC compared to the healthy control group (P ¼ 0.003 and P ¼

0.007, respectively). Major mucins present in the colorectum are *MUC1*, *MUC2*, *MUC3*, and *MUC4*. *MUC2* synthesis, secretion and sulfation are all reduced in active ulcerative colitis, which would make the colonic mucosa more accessible to toxic agents and pathogens.

Shirazi *et al.* [300] reported trefoils to be a group of small cysteine rich peptides that have an important role in the mucus layer [303] that referred to as trefoil factor family (TFF) and seem to play a part in mucosal protection and in mucosal repair. In humans, the region of the membrane-bound mucin gene cluster (*MUC3A*/*B*, *MUC12* and *MUC17*) has been implicated in genetic susceptibility to IBD [304, 305]. The rare variable number of tandem repeat (VNTR) allele of the *MUC3A* mucin gene was more common in patients with ulcerative colitis compared with controls. This mutated *MUC3* gene may result in a defective protein that would increase susceptibility to IBD [295]. Genotying of variable number of tandem repeat (VNTR) in the "*MUC3*" gene implied that rare alleles of "*MUC3*" with 51-bp repeat units are associated with the risk of UC [306]

Kyo *et al.* [295] has reported a possible association of rare variable number of tandem repeat (VNTR) alleles of the "*MUC3*" gene with a susceptibility to UC and demonstrated that distinct variants of *MUC3A* may be involved in the occurrence of UC and CD. SNPs in coding regions (cSNPs) and mutations that alter amino acid sequences of the 39 region of *MUC3A* could probably influence the function of this mucin protein, which would, in turn, cause increased susceptibility to CD. Moehle *et al.* [307] showed an aberrant mucin mRNA expression in the intestinal epithelium of IBD patients, especially for *MUC2* and *MUC12*. These mucins are located within IBD candidate loci and we were able to associate single SNPs in these genes with IBD with a significant downregulation in the colon obtained for *MUC2* in CD and *MUC12* in CD and UC.

Buisine *et al.* [293] have shown an abnormal mucin expression pattern in patients with CD involved in ileal mucosa adjacent to ulcerations with appearance of *MUC5AC*, *MUC6* and *MUC5B* and disappearance of *MUC2*. This suggested that gel forming mucins (more particularly *MUC5AC* and *MUC6*) may have a role in epithelial wound healing after mucosal injury in inflammatory bowel diseases in addition to mucosal protection and may contribute with trefoil factors to epithelium restitution.

Senapati *et al.* [283] has reported the loss of expression of *MUC17* in both inflammatory and early and late neoplastic conditions of the colon.

Hirschsprung's disease

Hirschsprung disease (HSCR) is a congenital disorder of the intestinal tract. In Hirschsprung's disease, the migration is not complete and part of the colon lacks these nerve bodies that regulate the activity of the colon. The affected segment of the colon cannot relax and pass stool through the colon, creating an obstruction [308]. In most affected people, the disorder affects the part of the colon that is nearest the anus.

Studies of the mucus layer in HSCR have shown changes in both mucins and secreted immunoglobulin in patients with HAEC [309–311]. A study of mucin turnover in HSCR patients showed that development of enterocolitis was specifically related to an increase in the ratio of intracellular to secreted mucins [312]. As the major mucus proteins are produced in goblet cells within the gut epithelium [313], Thiagarajah *et al.* [314] studied these cells and reported that aganglionosis is associated with increased goblet cell proliferation and differentiation resulting in altered surface mucus properties, prior to the development of inflammation in the distal colon epithelium. Restoration of normal goblet cell function and mucus layer properties in the colonic epithelium may represent a therapeutic strategy for prevention of Hirschsprung-associated enterocolitis.

Although, the study on mucin genes expression did not show a marked expression difference in *MUC* in patients and controls of HSCR. *MUC2* and 4 were found to be strongly expressed, *MUC1*, *MUC3*, and *MUC5B* had moderate to weak expression and *MUC5AB*, *MUC6*, *MUC7*, and *MUC8* had baseline expression. Therefore, expression of mucin genes and the quality of mucins is similar to normal controls [311]. However, another study by Mattar *et al.* [315] has reported that *MUC2* protein levels are significantly decreased in patients with Hirschsprung's disease and not detectable in those patients with Hirschsprung's-associated enterocolitis. Further studies are required to prove whether the decline in *MUC2* is caused by the aganglionic process as *MUC2* levels were significantly lower in Hirschsprung's disease in children with no clinical evidence of enterocolitis, therefore, the decline in *MUC2* was suggested to be caused by the aganglionic process itself.

Cap polyposis

Cap polyposis (CP) is a rare disease described by Williams *et al.* [316]. It is characterized by mucoid, bloody diarrhoea associated with erythematous, inflammatory colonic polyps covered by a cap of fibrinopurulent mucous. Its clinical symptoms are similar to inflammatory bowel disease or irritable bowel syndrome. The etiology is not well understood, some consider it as a form of inflammatory condition others suggests it to be of infectious origin. A possible association with mucosal prolapse syndrome (MPS) is suggested based on similar histologic features. In mucosal prolapse syndrome, mucosal prolapse occurs adjacent to tumors, diverticula and prolapsed colostomies. Similarly, abnormal colonic motility may result in mucosal prolapse at redundant transverse folds resulting in local ischemia, recurrent mucosal trauma and the

development of cap polyposis [317]. It is a rare disease with very few cases reported [316, 318–320].

Buisine *et al.* [321] had made a systematic study of the mucus of the characteristic polyps by histochemical and electron microscopic examination and looked at the expression of five mucin genes, *MUC2*, *MUC3*, *MUC4*, *MUC5AC*, and *MUC5B*, using *in situ* hybridisation, in a patient with recurrence of cap polyposis. The abnormality is observed in the ultrastructure of mucus in the goblet cells, prevalence of non-sulfated mucins, and abnormal expression of the *MUC4*, *MUC3*, and *MUC5AC* genes. However, it was reported that these abnormalities observed are probably secondary phenomena rather than primary. However, the mucin abnormalities detected were, deregulation of the expression of three apomucin genes (*MUC4*, *MUC3*, and *MUC5AC*), abnormal glycosylation and abnormalities of the secretion process, to be probably involved in clinical manifestations of cap polyposis.

Suzuki *et al.* [322] suggested betamethasone enema to be the second choice of treatment for cap polyposis patients after *H. pylori* eradication, metronidazole or levofloxacin therapy as Metronidazole, *H. pylori* eradication and levofloxacin therapies were not effective treatment.

Kidney

Renal clear cell carcinoma (von hippel-lindau disease and adenoma)

Renal cell carcinoma (RCC) is also known as hypernephroma, Grawitz tumor or renal adenocarcinoma. It is a kidney cancer that originates in the lining of the proximal convoluted tubule. RCC is the most common type of kidney cancer in adults, responsible for approximately 90-95 % of cases [323]. Initial treatment is most commonly either partial or complete removal of the affected kidney(s) and remains the mainstay of curative treatment [324]. It is relatively resistant to radiation therapy and chemotherapy [325], associated with a number of paraneoplastic syndromes (PNS), which are conditions caused by either the hormones produced by the tumor or by the body's attack on the tumor and are present in about 20 % of those with RCC [323].

In pathological situations, dysregulations of human mucin genes have been described with over-expression, loss of expression or aberrant expression affecting one or several mucin genes [326–328]. To date, little is known about the expression of human mucin genes in the normal kidney and in renal neoplasms. In the kidney, MUC1 is expressed in normal distal convoluted tubules, collecting ducts and clear renal cell carcinoma (cRCC) [329]. Leroy *et al.* [330] have investigated the expression pattern of *MUC1*, *MUC2*, *MUC3*,*4*,*5 AC*, *5B*, *MUC6* and *MUC7* in normal kidney and renal cell carcinoma by using *in-situ* hybridization, immunohistochemistry and reverse transcriptase polymerase chain reaction (RT-PCR) techniques. They found a difference in the expression of *MUC1*, *MUC3* and *MUC6* between normal and tumor kidney with the over-expression of *MUC3* in renal cell carcinomas favouring renal tumorigenesis.

The expression of *MUC1* was correlated inversely with the prognosis for RCC [331, 332]. *MUC1* is frequently up-regulated and abnormally glycosylated in carcinoma [333, 334]. The overexpression of *MUC1* is associated with a loss of polarity and circumferential distribution in tumor cells [335]. This abnormal overexpression is suspected to destabilize cell-cell adhesion and cell–extracellular matrix adhesion and to protect tumor cells from immune recognition and then to favour metastases.

The expression of *MUC3* could support this histogenetic hypothesis, but it was observed that *MUC1* is also expressed in clear renal cell carcinoma and in normal distal tubules, but not in proximal tubules. These findings strengthen the hypothesis stated by Hughson *et al.* [336] that multipotential metanephric differentiation exist in renal proximal and distal tubular type of neoplasm. In the tubulopapillary carcinomas, *MUC1* and *MUC3* mRNAs were both detected as in clear renal cell carcinoma, but the signals obtained were lower and not correlated with the nuclear grade.

Leroy *et al.* [330] have demonstrated *MUC1*, *MUC3* and *MUC6* expression in both normal and neoplastic kidney. The expression of *MUC1* and *MUC3* in clear renal cell carcinoma suggested that mucin genes may be implicated in the tumorigenesis of the kidney. The weak expression of *MUC6* was also detected by RT-PCR in renal cell carcinoma (clear and papillary carcinomas). Leroy *et al.* [331] has reported the high-level expression of *MUC1* with circumferential membrane staining is associated with high-grade tumors and with an increased risk of visceral dissemination in pT1 cRCC. They suggested that further large investigations of *MUC1* may be needed as a prognostic marker and potential therapeutic target of RCC. It has been shown that patients with advanced malignancies when given immunotherapy using autologous dendritic cells pulsed with *MUC1* derived peptides induced immunological and clinical responses [337].

Medullary cystic kidney disease type 1

Medullary cystic kidney disease1 (MCKD1) is an autosomal dominant rare kidney disorder characterized by cysts in both kidneys and tubule-interstitial sclerosis leading to end-stage renal disease (ESRD) [338]. Hypertension was reported [339] to be a sequel of the disease, occurring after the onset of kidney failure. Medullary cystic kidney disease1 (MCKD1) is confirmed by identification of sequence variants/mutations in *MUC1*, hence the potential kidney donors should be tested for the family-specific *MUC1* without any mutation so that he can be assessed as eligible kidney donors.

Kirby *et al.* [340] described the illustrative case of the simple Mendelian disorder medullary cystic kidney disease type 1 (MCKD1), mapped more than a decade ago to a 2-Mb region on chromosome and suggested that mutations in the variable tandem repeats (VNTRs) of the human mucin *MUC1* are associated with MCKD1. MCKD type 1 has a median onset of ESRD at age 62 years and is caused by defects in the *MUC1* gene that encodes mucin1 [340]. Mutation in *MUC1* has been shown to result in progressive chronic kidney failure and the age of onset of end stage kidney disease is highly variable, suggesting that gene-gene or gene-environment interactions contribute to phenotypic variability. *MUC1* gene encoding mucin 1 comprise of the extremely long (1.5–5 kb), GC-rich (>80 %) coding variable-number tandem repeat (VNTR) sequence. This leads to difficulty in identifying the genes and its mutation responsible for Mendelian, disorders like MCKD1 [340–342]. As *MUC1* over-expression in renal clear-cell carcinoma (RCC) is associated with poor prognosis, phase II clinical trial based on *MUC1* and interleukin-2 clones have been tested and preliminary results demonstrated feasibility and tolerability in patients with metastatic RCC [343].

MUC1 protein possesses a heavily glycosylated extracellular domain containing the VNTR and an SEA module with a cleavage site for release of the extracellular domain, which then binds non-covalently to the transmembrane domain [344–346].

Gallbladder

Gallbladder inflammation and stone formation

The most common malignancy of biliary tract is gallbladder cancer (GBC), which is the third most common cancer in gastrointestinal tract [347]. Gall bladder cancer (GBC) is said to be a principal reason of cancer-related mortality in the northern parts of the Indian subcontinent as reported by Shukla *et al.* [348]. Cholecystitis is known as inflammation of the gallbladder that occurs most commonly due to blockage of the cystic duct with gallstones (cholelithiasis) [349, 350]. This blockage causes a build up of bile in the gallbladder and increased pressure within the gallbladder, leading to right upper abdominal pain [350]. Inflammation and swelling of the gallbladder can reduce normal blood flow to areas of the gallbladder, which can lead to cell death due to inadequate oxygen supply [350].

Mucin plays an important role in protecting the gallbladder epithelium from the detergent effect of bile that also participates in gallstone formation. Gallbladder mucin polypeptide binds biliary lipids and may promote biliary cholesterol crystallization [351]. The interaction of gallbladder mucin with calcium-binding protein may have an effect on calcium phosphate precipitation and the formation of calcium-containing gallstones [352]. Hydrophobic domains on the mucin protein core may contribute to the pathogenesis of cholesterol stone formation.

Baeckström *et al.* [353], Vandenhaute *et al.* [354] have reported the expression of one or more of the nine mucin genes *MUC1*, *MUC2*, *MUC3A*, *MUC3B*, *MUC4*, *MUC5AC*, *MUC5B*, *MUC6* and mucin-like protocadherin protein (MUPCDH) in Gallbladder and its associated diseases along with many polymorphisms (rs3758650, rs7932167, rs34362213, rs2740375, rs7108757 and rs2740379) in mucin family as a risk factor for gallstone disease [355–357].

Maurya *et al.* [358] investigated and evaluated the secretory/gel forming mucins namely *MUC1*, *MUC5AC*, *MUC5B*, *MUC6*, *MUC7*, *MUC9* and *MUC11* in gallstone formation through western blotting and semi-quantitative PCR and reported that *MUC5B* protein are crucially involved in nucleation process during gallstone formation

Expression of *MUC1*, *MUC2*, *MUC3*, *MUC5AC*, *MUC5B* and *MUC6* gene was detected in the gallbladder wall [359]. Van Klinken *et al.* [360] investigated *MUC5B* to be the predominant mucin in human gallbladder mucosa [361]. In another study, Ho *et al.* [362] examined membrane as well as secretory mucins (*MUC1*, *MUC3*, *MUC4* and *MUC2*, *MUC5AC*, *MUC5B*, *MUC6* respectively) in cholecytitis. *MUC3*, *MUC5AC*, *MUC5B*, and *MUC6* mRNA were present in all gallbladder specimens and cell lines examined. In 86–100 % normal gallbladders prominent immunoreactivity to *MUC3*, *MUC5AC*, *MUC5B*, and *MUC6* was present. A significantly decreased expression of *MUC5AC* but increased expression of *MUC2* was found in patients with cholecystitis [362].

Expression of *MUC3* and *MUC5B* was of the same degree in the superficial epithelium and deep folds. Whereas, expression of *MUC5AC* was significantly higher in the superficial epithelium and that of *MUC6* was significantly higher in the deep folds [363]. In gallbladder, bile demonstrates two secretory mucin proteins: *MUC5AC* and *MUC5B* with no expression of *MUC3* and *MUC6*. Vilkin *et al.* [364] reported increased secretion of mucin in the gallbladder may play an important role in stone formation, particularly in formation of pigmented brown stones.

Gallblader carcinoma: the precise molecular abnormality which causes neoplastic transformation in the gallbladder epithelium is still unclear [347]. Transformation to malignant state results in the alteration in genes. Rate and pattern of *MUC1* protein expression suggest that *MUC1* would be a marker of malignant

transformation of invasion of gallbladder cancer [365, 366]. Prognostic value of mucin (*MUC1* and *MUC2*) in gallbladder carcinoma along with other tumor growth factors (like p53 was carried out but Mucin expression was found to be independent of various tumor growth factors and clearly reflected the prognosis of gallbladder cancer [367].

Eye

Dry eye disease (DED)

Dry eye is a multifactorial disease of tears and the ocular surface due to tear deficiency or excessive tear evaporation, which may be due to disturbance in ocular surface mucin leading to a dysfunction of mucin, resulting in dry eye. Takeji *et al*. [368] investigated the effect of rebamipide, an anti-ulcer agent, on glycoconjugate production (as an indicator of mucin-like glycoprotein) in cultured corneal epithelial cells. They reported effect of rebamipide on the gene expression of membrane-associated mucins which is mediated by *MUC1* and *MUC4* regulation. They reported rebamipide increased the gene expression of *MUC1* and *MUC4*, but not *MUC16*.

Keratoconjunctivitis sicca (KCS), also called dry eye syndrome (DES) or keratitis sicca, is an eye disease caused by eye dryness, which in turn, is caused by either decreased tear production or increased tear film evaporation. KCS is the most common eye disease, affecting 5–6 % of the population. Several classes of medications (both prescription and OTC) have been hypothesized as a major cause of dry eye, especially in the elderly. Particularly, cholinergic medications that also cause dry mouth are believed to promote dry eye [369].

Mucins have been known to have a role in tear film formation and stability. Cooperation between the ocular surface, transmembrane mucin and secretory mucin is necessary for the stability of the tear film. The corneal and conjunctival epithelia produce transmembrane mucins such as *MUC1*, *MUC2*, *MUC4* and *MUC16* [370, 371], which form a glycocalyx at the epithelium-tear film interface. In contrast, goblet cells produce the gel-forming secretory mucin, *MUC5AC*. The lacrimal gland produces *MUC7* [370, 372]. Limited reports are available on the relationship between mucin and dry eye disease, however, it is hypothesized that secreted mucins form a hydrophilic blanket that moves over the glycocalyx of the ocular surface to clear debris and pathogens. Glycocalyx mucins prevent cell-pathogen adherence. Expression and glycosylation of mucins are altered in drying, leading to Keratoconjunctivitis sicca and other keratinizing ocular surface diseases. A relationship between mucin 5 AC (*MUC5AC*) concentrations in tears, working hours and the frequency of ocular symptoms in visual display terminal (VDT) users has been studied. The study suggests that office workers with prolonged VDT use, as well as those with an increased frequency of eye strain, have a low *MUC5AC* concentration in their tears. Furthermore, *MUC5AC* concentration in the tears of patients with Dry Eye Disease (DED) may be lower than that in individuals without DED [373]. It was also demonstrated that Neurturin (a neurotrophic factor for parasympathetic neurons)-deficient mice develop dry eye and keratoconjunctivitis sicca via reduction in *MUC4* and 5 AC mucin and goblet cell density [374]. Various therapies to treat DED have also been shown to work through differential regulation of mucins [375, 372].

Ethmoid bones

Ethmoid sinusitis

Ethmoid Sinusitis, is related to sinusitis and chronic inflammation of the ethmoid sinuses. An important gene associated with Ethmoid Sinusitis is *MUC7* associated to the tissues of eye, brain and prostate. Several studies have reported that the major mucins expressed in chronic sinusitis (CS) are *MUC2*, *MUC5AC* and *MUC5B* [376–380] and an inverse relationship was found between MUC2 and MUC5AC expression levels and this was strong in the presence of nasal polyps [377].

Jung *et al*. [381] have investigated the profiles of *MUC* genes expressed in chronic ethmoiditis mucosa and normal ethmoid mucosa using RT-PCR, and the morphology of chronic ethmoiditis by a combination of light and electron microscope was observed. Increase in number of goblet cells with higher production of mucus in comparison to normal ethmoid mucosa was reported. The results suggest that *MUC4*, *MUC5AC*, *MUC5B*, *MUC7* and *MUC8* are major mucins in the ethmoid mucosa and are up-regulated by chronic inflammation.

Ali and Pearson [382] have studied the sinus mucin fragmentation that helped in understanding of the physical and biological properties of sinus mucins in CS that could help to develop therapeutic modalities to alter these properties and facilitate mucus drainage and relieve relevant CS symptoms such as rhinorrhea, chronic cough and globus pharyngeus. The fragmentation of sinus mucin produced mucin subunits and glycopeptide units of smaller molecular sizes that are likely to have lower viscoelastic properties. This suggested that the physical and biological properties of the mucus could be altered by applying this *in vivo*. These data suggest that there may be different pathological processes occurring at the cellular level on chronic sinusitis.

Mouth

Chronic periodontitis

Chronic periodontitis is a common disease of the oral cavity consisting of chronic inflammation of the periodontal tissues that is caused by accumulation of profuse amounts of dental plaque. Periodontal disease is an inflammatory reaction of periodontal tissues in response to infection caused by a specific group of bacteria [383]. A positive correlation was observed between salivary mucin and preodontitis [384]. Periodontitis induces an increase in the output of proteins, including mucin and amylase, thereby enhancing the protective potential of saliva [385]. There was a significant decrease in the amounts of *MUC1* transcripts in elderly subjects, which is positively correlated with the level of periodontal inflammation [386]. The *MUC7* gene product, a soluble 180-kDa salivary mucin named MG2, is well recognized as a key component of the oral host defence system. *MUC7* is also known to display genetic polymorphism that generates a variable number of tandem repeat (VNTR) domains [387]. *MUC7* typically encodes 6 heavily glycosylated tandem repeats (TRs) [388], each with 23 amino acids.

It has been reported that *MUC7* is present in the pellicle formed on cementum surfaces [389], that it exhibits candidacidal activity [390], kills the periodontal pathogen *Aggregatibacter actinomycetemcomitans* [391] and forms heterotypic complexes with specific salivary proteins in the oral environment [392, 393]. Some polymorphisms (allele at IL-1A +4845 and IL-1B+3954) alter the expression and function of genes, affecting phenotypes and leading to disease susceptibility [394]. Specific forms of genes can produce variations in tissue structure, the adaptive immune response, and the expression of inflammatory mediators. Periodontitis is associated with the presence of certain Gram-negative bacteria in the oral cavity, such as *Actinobacillus actinomycetemcomitans*, which has been shown to adhere only to mucin-glycoprotein-2 (MG2) [395].

Sánchez *et al.* [396] have reported a positive correlation found between proteins and amylase or mucin concentrations among the different groups, indicating their change in concentrations, response of salivary glands to the disease and enhancement of the protective potential of saliva which lower concentration of mucin in mild periodontitis group. Mechanical stimulation induced an increase in flow rate and output of proteins, amylase and mucin.

Mucoepidermoid carcinomas of salivary glands

Mucoepidermoid carcinoma (MEC) is the most common type of malignant salivary gland tumor and the second most common tumor of bronchial gland origin [397, 398]. Mucoepidermoid carcinoma can also be found in other organs, as bronchi, lacrimal sac and thyroid that are thought to originate from precursor cells in excretory and intercalated ducts of the salivary gland [397].

MECs are characteristically composed of mucous-forming goblet cells, epidermoid cells and intermediate cells that might differ considerably in their proportions from one tumor to another. Generally, high-grade tumors contain a high proportion of epidermoid cells and a correspondingly lower proportion of mucous-forming cells (less than 10 % of the cells), whereas in low-grade tumors the mucous forming cells usually constitute more than half the tumor mass [399].

MUC1 and *MUC4* are frequently expressed in normal salivary glands, mainly in ductal cells, *MUC5B* and *MUC7* is present in mucous and serous acini, respectively, of submandibular and minor salivary glands, *MUC5AC* and *MUC2* were poorly detected in excretory ducts. Alos *et al.* [400] has reported the expression level of various membrane-bound mucins (*MUC1* and *MUC4*) and secreted mucins (*MUC2*, *MUC5AC*, *MUC5B*, *MUC6* and *MUC7*) in mucoepidermoid carcinomas of salivary glands. It was reported that *MUC1* expression is related to tumor progression and worse prognosis, whereas *MUC4* expression is related to a better prognosis. Based on these reports it was suggested that the expression pattern of mucin could be a useful diagnostic tool for MEC.

Shemirani *et al.* [401] have evaluated MEC for expression of a number of more recently identified mucin genes not previously examined in MEC including: *MUC12*, *MUC13*, *MUC17*, *MUC18* and *MUC 19* and investigated the correlation between mucin expression and tumor characteristics or clinical behaviour. Investigators reported that qPCR measurements of *MUC 4* expression can be utilized to predict favourable prognosis and *MUC 1* and *MUC 19* to predict less favourable prognosis.

Ear

Middle ear with chronic otitis media

Chronic otitis media (COM) is one of the most common otological diseases that endanger hearing in humans. It is the medical term for middle ear inflammation characterized by ear discharge rich in mucus. There are 2 major types of otitis media: acute otitis media and otitis media with effusion. The former is usually symptomatic, especially ear pain (otalgia), whereas the latter is most commonly without acute symptoms. Song *et al.* [228] have reported acrolein to be a hazardous air pollutant that decreased cell viability, induced an inflammatory response and increased mucin gene expression in human middle ear epithelial cell lines (HMEECs). These findings support the hypothesis that acrolein, a hazardous air pollutant in tobacco smoke and ambient air, is a risk factor for otitis media.

The common cause of all forms of otitis media is dysfunction of the Eustachian tube [402], which is usually due to inflammation of the mucous membranes in the nasopharynx, which in turn can be caused by a viral URI or possibly by allergies [403]. Lin *et al*. [404] have demonstrated the expression of *MUC5B*, *MUC5AC*, *MUC4*, and *MUC1* in the human Eustachian tube, whereas only *MUC5B* mucin expression was demonstrated in non-inflamed middle ears. *MUC5B* and *MUC4* mucin genes were upregulated 4.2- and 6-fold, respectively, in middle ears with chronic otitis media (COM) or mucoid otitis media (MOM). This upregulation of mucin genes was accompanied by an increase of *MUC5B* and *MUC4* producing cells in the middle ear mucosa.

Moon *et al*. [405] investigated the factors that regulate these secretory products and their morphological phenotype using cultured human middle ear epithelial cells. They reported that decrease in the secretion of mucin and lysozyme, and in the cellular expression of *MUC 2*, *MUC 5 AC* and *MUC 5B* mRNA as caused by omission of retinoic acid (RA) and removal of triiodothyronine (T3) caused an increase in the secretion of mucin and the level of *MUC5AC* mRNA therefore culture system can serve as an *in vitro* model for study of the regulation of various cellular secretions in human middle ear epithelium.

In the middle ear ciliated tract, mucins are transported toward the nasopharyngeal orifice by regular movements of the cilia. Since mucins are able to bind to proteins in the outer membrane of bacteria [406, 407] they play an essential role in the defense of the middle ear epithelium against invading pathogens under normal conditions.

Kawano *et al*. [408] have reported that normal human middle ear expresses *MUC5B* and eustachian tube expresses *MUC5B* and *MUC5AC* [409]. *MUC5B* has been shown to be a major mucin expressed in human airway submucosal glands [410], gallbladder epithelium [355], submaxillary glands [410] and Eustachian tube submucosal glands and epithelium [409].

In situ hybridization and immunohistochemistry demonstrated the expression of *MUC5B* mucin mRNA and its product, *MUC5B* mucin. Reports state that the expression of *MUC5B* mucin in middle ear epithelium was related to infiltration of inflammatory cells in the submucosa, suggesting that in COM, inflammatory cell products are involved in production of *MUC5B* mucin in the middle ear mucosa.

Kerschner *et al*. [411] have reported *MUC5AC* as fundamentally important in the development of ME mucoid effusions, hearing loss that also provides middle ear (ME) mucosal protection and bacterial clearance. This demonstrates *MUC5AC* gene changes in patients with otitis media (OM) and highlights the need for greater understanding of the molecular responses in OM; particularly that of mucin.

Uterus

Uterine cervix

A cervix uterus is the lower part of the uterus in the human female reproductive system. In a non-pregnant woman, the cervix is usually between 2 and 3 cm long and roughly cylindrical in shape. Cervical mucus is used in several methods of fertility awareness, such as the Creighton model and Billings method, due to its changes in consistency throughout the menstrual period. The two types of epithelia meet the squamocolumnar junction. Infection with the human papilloma virus (HPV) can cause changes in the epithelium, which can lead to cancer of the cervix.

The expression of human *MUC* genes (*MUC1*, *MUC2*, *MUC5B*, *MUC5AC* and *MUC8*) was investigated by Hebbar *et al*. [412] in human endometrium and cervix, which then compared, quantitated the expression of *MUC* genes in normal and cancerous tissues. They reported increased expression of *MUC1*, *MUC5B* and *MUC8* in Endometrial tumors compared to normal. *MUC1* appears to be increased, in cervical tumors where as low to neglible levels of *MUC2* and *MUC5AC* were observed in all studied endometrial and cervical tissues.

Mucin expression also shows some correlation with prognosis in patients with various cancers. However, few studies have been conducted on adenocarcinomas of the uterine cervix. Mitsuhashi *et al*. [413] have studied a significant reduction of *MUC5AC* expression that was evidenced in the adenocarcinomas of the cervix in comparison with that in the normal endocervical epithelium (53.2 % vs. 100 %; $P<.001$). *MUC5AC* expression was correlated with paracervical invasion and histological type. Patients with negative *MUC5AC* expression showed poorer survival than those with positive *MUC5AC* expression.

Thyroid

Graves' disease

Graves' disease (or Flajani-Basedow-Graves disease) is an autoimmune disease. It most commonly affects the thyroid, frequently causing it to enlarge to twice its size or more (goitre), become overactive with related hyperthyroid symptoms such as increased heartbeat, muscle weakness, disturbed sleep and irritability. It can also affect the eyes, causing bulging eyes (exophthalmos). It affects other systems of the body, including the skin, heart, circulation and nervous system.

It affects up to 2 % of the female population, sometimes appears after childbirth, and occurs seven to eight times more often in women than in men. Genetic factors are a major

influence accounting for possibly around 80 % of the risk [414].

The signs and symptoms of Graves' disease virtually all result from the direct and indirect effects of hyperthyroidism, with main exceptions being Graves' ophthalmopathy, goitre and pretibial myxedema (which are caused by the autoimmune processes of the disease). The Genome wide association study on Graves' disease on Chinese Han population samples has shown an association with a polymorphism rs4947296, which is lying between *MUC21* and *C6orf15* indicating a role of *MUC21*, but as this region is close to major histocompatibility complex (MHC) its independent association is yet to be analysed [415]. The association is also reported in Medscape [416].

Chelala *et al*. [417] studied the history of medically controlled Graves' disease in a woman seen with an extensive Superior limbic keratoconjunctivitis (SLK) involving 5 mm of the superior cornea. They reported tapering treatment as essential for long-term success of remission.

Bladder

Bladder cancer

Bladder cancer is the 9th leading cause of cancer that occurs in approximately 80–90 % of the patients with 430,000 new cases [418] and 165,000 deaths during 2012. Bladder cancer is any of several types of cancer arising from the epithelial lining (*i.e*., the urothelium) of the urinary bladder. Rarely the bladder is involved by non-epithelial cancers, such as lymphoma or sarcoma, but these are not ordinarily included in the colloquial term "bladder cancer." It was suggested that the mutations at HRAS, KRAS2, RB1, and FGFR3 may be associated in some cases (OMIM). Under normal conditions, mucin genes protect the epithelial surfaces; however, mucus hypersecretion leads to inflammatory diseases such as asthma, as well as carcinomas [3, 31].

MUC5B, which is expressed in many organs that secrete mucus, including the lungs [419], urogenital tract [420] and breasts [421] as well as in the gallbladder [422] was studied for its involvement in bladder cancer.

Most mucin genes contain a central region with a variable number of tandem repeats (VNTR) [190, 423]. Tandem repeats sequences have been classified into two groups, minisatellites and microsatellites. Ahn *et al*. [424] had analyzed three (*MUC5B-MS3*, *-MS6*, and *-MS7*) of seven minisatellites that were found to be polymorphic in *MUC5B* and evaluated the putative functional significance of allelic variation in these minisatellites with respect to the susceptibility for carcinomas. Based on their analysis the minisatellites have been characterized in detail for the complete *MUC5B* region and they have reported that the loci of *MUC5B* minisatellites may function as indicators of the risk of bladder cancer.

Bones (joints)

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, autoimmune systemic disorder of unclear etiology that results in symmetrical joint inflammation. It occurs more frequently in women than in men with a ratio of 3:1. The onset of RA may occur at any age, but most often affects individuals between the ages of 25–50 years.

The process involves an inflammatory response of the capsule around the joints (synovium) secondary to swelling (turgescence) of synovial cells, excess synovial fluid and the development of fibrous tissue (pannus) in the synovium. It also affects the underlying bone (focal erosions) and cartilage (thinning and destruction). The mucin proteins play a vital role in examining the expression of synovial tissues in RA. Neidhart *et al*. [425] measured the synovial fluid levels of soluble CD146 (*MUC18*) in various human joint diseases, including rheumatoid arthritis (RA) as *MUC18* is a marker of tumor progression and metastasis formation in human melanoma. In addition, they have studied the distribution of *MUC18* in normal and RA synovial tissues. Since *MUC18* is expressed almost exclusively by vascular endothelium, high levels of soluble *MUC18* in RA synovial fluid, particularly in patients with early disease, could reflect increased activity of endothelial cells and angiogenesis.

Intra-articular expression of proinflammatory cytokines such as interleukin (IL)-6, IL-1α, and tumor necrosis factor-α (TNF-α) plays a critical role in the pathogenesis of RA . High levels of IL-6 are produced in the joints of patients with RA and large quantities can be detected in their serum [426]. IL-6 plays a pivotal role in the inflammatory process, in osteoclast-mediated bone resorption and in pannus development through increased vascular endothelial growth factor expression. Hamaguchi *et al*. [427], has reported that mucins, including *MUC1* derived from RA synovial fluid, induce IL-6 production on peripheral blood mononuclear cells (PBMCs) and that *MUC1* was expressed on synovial cells and mononuclear cells in RA synovial tissues. They have stated that *MUC1* could be a new target specific for inflamed joints in the treatment of RA.

Volin *et al*. [428] has performed immunohistochemistry, Western blotting, and reverse transcriptase-polymerase chain reaction to determine expression patterns of *MUC1*, *MUC2*, *MUC3*, and *MUC5AC* in RA, osteoarthritic (OA), and normal human synovial tissue (ST). They demonstrated the up-regulated *MUC* expression by ST cells and suggest a novel role of *MUC3* and *MUC5AC* in the pathogenesis of arthritis.

Gland

Adenocarcinoma

The term adenocarcinoma is derived from adeno- meaning "pertaining to a gland" and carcinoma, which describes a cancer that has developed in the epithelial cells. Adenocarcinoma is a type of cancerous tumor that can occur in several parts of the body. It is defined as neoplasia of epithelial tissue that has glandular origin, glandular characteristics or both. Adenocarcinomas are part of the larger grouping of carcinomas. Cancers that are adenocarcinomas are often usually called by more precise terms omitting the word, where these exist. Mucins are large glycoproteins expressed by all mucosal epithelial tissues and commonly by adenocarcinomas arising from these tissues.

Packer *et al*. [107] compared the expression of *MUC1*, *MUC3*, *MUC4*, *MUC11*, *MUC12* and *MUC13* mRNA in epithelial cancers cell lines with non-malignant tissues and reported expression of *MUC3*, *4*, *11*, *12* and *13* at highest levels in gastrointestinal non-malignant tissues,, whereas *MUC1* was more widely distributed. In colonic cancers down-regulation of the *MUC4*, *MUC12* and *MUC13* genes was observed compared with normal tissue, whereas *MUC1* was upregulated. No significant difference was found in any of the six mucin genes in rectal cancers when compared to those in normal rectal tissues. Both *MUC1* and *MUC4* were down-regulated in gastric cancers, whereas cancer and normal tissue levels were similar for *MUC3*, *11*, *12* and *13*. The reported expression profiles of the cell surface mucin gene family will help direct biological and clinical studies of these molecules in mucosal biology and in malignant and inflammatory diseases of epithelial tissues.

Epithelial tissue can be derived embryologically from any of the germ layers (ectoderm, endoderm or mesoderm). To be classified as adenocarcinoma, the cells do not necessarily need to be part of a gland, as long as they have secretory properties. Adenocarcinoma is the malignant counterpart to adenoma, which is the benign form of such tumors. Sometimes adenomas transform into adenocarcinomas, but most do not.

Most breast cancers start in the ducts or lobules and are adenocarcinomas. The vast majority of colorectal cancers are adenocarcinomas. This is because the colon has numerous glands within the tissue. Normal colonic glands tend to be simple and tubular in appearance with a mixture of mucus secreting goblet cells and water absorbing cells. These glands are called glands because they secrete a substance into the lumen of the colon, this substance being mucus. The purpose of these glands is twofold. The first is to absorb water from the feces back into the blood. The second purpose is to secrete mucus into the colon lumen to lubricate the now dehydrated feces. This is crucial as a failure to lubricate the feces can result in colonic damage by the feces as it passes towards the rectum.

Clinical evidence has shown that patients with long lasting inflammatory bowel disease (IBD) are at an increased risk for developing colon cancer. Inflammation of the colon is hypothesised to predispose to abnormal cell growth, which over time can give rise to adenoma (dysplasia) and adenocarcinoma. However, colon cancer is a heterogeneous and multifactorial disease. Adenomatous polyps (tubular adenoma and tubulovillous adenoma) are recognised as precursor lesions to colon cancer. Altered mucin expression has long been associated with the pathology of epithelial diseases such as inflammatory bowel disease [429] and respiratory diseases, including cystic fibrosis [430].

Mizejewski [431] reviewed the literature of the multiple alpha-fetoprotein (AFP) receptors previously including their cellular uptake, transmembrane passage and partial biochemical characterization. They proposed that AFP may not be the receptor for tumor cells but rather widespread mucin protein that functions primarily in protecting and lubricating epithelial mucosal layers, and engaging in signal transduction works as tumor cell receptors, as evidenced from computer modeling, proteolytic/fragmentation cleavage patterns, domain structure analysis and protein binding software analysis.

Gut microbiota and type 2 diabetes

International Diabetes Federation has reported that 382 million people living with diabetes worldwide and the number are expected to rise to 592 million by 2035 [432]. Prevention of diabetes mellitus (1994) [433] has reported that nearly 85–95 % of people with diabetes have type 2 diabetes mellitus (T2DM). According to the World Health Organization [434], the global prevalence of diabetes is approximately 10 %, reaching up to 33 % of the population in some regions. Diabetes is a condition of multifactorial origin, including genetic and environmental factors, and accounts for 3.5 % of the mortality cases due to non-communicable chronic diseases. The adult human intestine is colonized by about 100 trillion bacteria, which is about 10 times the number of total cells in the human body [435]. Han and Lin [436] have reported and focused on the underlying role of intestinal microbiota in the pathogenesis of T2DM and the therapeutic potential of modulating gut microbiota in T2DM.

Gut microbiota plays an active role in intestinal physiology [437]. Approximately 160 species of different bacteria per person per fecal sample in the microbiota were reported by Rodriguez *et al*. [438] that play an important role in human health. The gut microbiota is said to affect numerous biological functions throughout the body and its characterisation has become a major research area in biomedicine. Tilg *et al*. [439] suggested that gut bacteria plays an active role in the diseases such as obesity, diabetes and cardiovascular disease. Obesity

and type 2 diabetes are characterized by altered gut microbiota [440], inflammation [441] and gut barrier disruption [442–444]. First human metagenome-wide association studies demonstrated highly significant correlations of specific intestinal bacteria, certain bacterial genes and respective metabolic pathways with T2D.

Backhed *et al*. [445] has reported the presence of *Bifidobacterium*, *Lactobacillus*, *Bacteroides*, *Clostridium*, *Escherichia*, *Streptococcus* and *Ruminococcus in a* healthy adult's gut, approximately 60 % of the bacteria belong to the *Bacteroidetes* or *Firmicutes* phyla. It was reported that altered intestinal microbiota leads to increased intestinal permeability and mucosal immune response, which leads to the development of type 2 diabetes.

The enteric tract contains a complex ecosystem that is composed of trillions of microbial cells that are associated with mucus that are secreted by specialized intestinal epithelial cells (IEC)-type, the goblet cell, [446]. Approximately 10 l of mucus is secreted per day in humans [447]. The small intestine is mainly covered by a loosely attached mucus layer (150–400 μm), which is thinnest in the jejunum, where the major nutrient uptake takes place [448]. Van Klinken *et al.* [422] reported the dual role of mucus in relation to microbiota; it protects the underlying mucosa from undesired interactions with microbes such as pathogens; besides it provides an initial adhesion site, nutrient source and matrix on (and/or in) which bacteria can proliferate and thrive.

Tilg *et al*. [439] reported presence of *Akkermansia muciniphila*, a mucin-degrading Gram-negative bacterium [449], that is highly prevalent and constitutes about 3–5 % of the gut's microbiota, to be inversely correlated with overweight and diabetes in murine and human studies. Another study by Everard *et al*. [450] reported *Akkermansia muciniphila* as a potential microbiota that reduces the inflammation and offers protection against the development of obesity and T2D. Therefore, this can be used as a 'gut signature' in T2D, for better understanding of the role of the mucin interacting microbiota in diabetes, which might provide new aspects regarding its pathophysiological relevance and paves the way for new therapeutic principles.

Summary and future prospects

The study of interactions between mucins, human diseases and its associated organs along with other components of mucus could unwind the mucin blackbox in medical science. Therefore, mucins can be explored for their potential use as diagnostic, prognostic markers and as therapeutic targets in various diseases. This in turn could be a breakthrough for novel drug design and discovery for various diseases that play an important role in human health and diseases especially obesity and diabetes (T2D) which is known as multifactorial origin, including genetic and environmental factors and accounts for 3.5 % of the mortality cases due to non-communicable chronic diseases.

Mucins are the glycoproteins, which can be considered as connective tissues similar to blood tissues that coats and protect the epithelial cells from various microbial pathogens. They play a central role in human health and disease, in spite of their key role there are many gaps in the knowledge of mucus and mucins with reference to its physiology in different organs and organ specific diseases. This review has collated and unzipped the pathophysiological role of secretory and membrane bound mucins in different non-communicable human diseases associated with various organs. The potential of mucins as diagnostic and prognostic markers and as therapeutic targets in various diseases have also been discussed. Mucins overexpression and aberrant glycosylation are mainly associated with cancer formation, prognosis and metastasis. Like *MUC1*, in various epithelial cancers other carcinomas as well. Therefore, it provides unique targets for imaging and therapy mainly for breast and pancreatic cancers. *MUC2* is an intestinal marker for the cell lineage of epithelial cells of gastric carcinoma. *MUC4* is a potential diagnostic and prognostic marker for ductal carcinoma *MUC13* is expressed in gastrointestinal carcinomas. *MUC14* is associated with Angiolipoma. *MUC15* may serve as a prognostic marker and potential novel therapeutic target in papillary thyroid carcinoma. *MUC18* is expressed at very high levels in premalignant and malignant prostatic epithelium, including metastasis and therefore, may lead to a new marker of human prostate cancer.

Some mucins have a role in diseases due to inflammatory conditions. Like, *MUC3*, *MUC9*, *MUC11* and *MUC12* play a key role in Ulcerative colitis and/or Crohn's disease and *MUC5* in Lung disease, Gallstone formation, Mucoepidermoid carcinomas of salivary glands and in Middle ear with chronic otitis media. *MUC7* has a role in the pathophysiology of asthma. *MUC8* expression is associated with chronic sinusitis and is known to be an important airway mucin.

A few *MUCs* are expressed in infectious conditions and are involved in transition of a viral infection to carcinomic progression like, aberrant *MUC6* expression was often seen in gastrointestinal diseases and in Epstein-Barr virus-associated gastric carcinoma.

There are some mucins which having a role in both carcinomas and inflammation not leading to carcinomas. One such is *MUC16* which is involved in megis syndrome, ovarian cancer as well as in kerato-conjunctivitis. Similarly, *MUC17* is expressed in biliary papillomatosis, adenocarcinoma as well as inflammatory and neoplastic diseases of the colon. *MUC18* is trophoblastic tumors, pulmonary metastasis and also in lung inflammation, rheumatoid arthritis, inflammatory skin disease. *MUC20* is expressed in injured kidney, colorectal cancer and also in immunoglobulin A (IgA) nephropathy. The factors

that regulate *MUC20* can be used as therapeutics for the development and progression of renal diseases.

MUC19 is involved in patients of chronic autoimmune disease known as Sjögren syndrome.

MUC21 and *MUC22* are involved in lung carcinomas as well as major autoimmune diseases, Graves' disease, and inflammatory disease like diffuse panbronchiolitis.

Although, no reports are available on mucins role in T2D, but human mucins are known to play dual role in relation to microbiota; it protects the underlying mucosa from undesired interactions with microbes such as pathogens; besides it provides an initial adhesion site, nutrient source and matrix on (and/or in) which bacteria can proliferate and thrive. This in turns helps in maintaining the gut microbiota /flora of human gastro-intestine which is known to be involved in T2D. This colonisation of microbiota helps in energy harvest from human diet which is a major component in T2D.

The above description represents the role that all the 22 mucins play in various organ specific diseases and human health. Most of the diseases are supposed to be originated from malfunction or hyper-secretion of the mucins. The polymorphisms represented at various mucins VNTR's domains tend to play a key role in different aspects of human health and diseases. These polymorphisms are also helpful in identification of various biomarkers that in turn could be a diagnostic and prognostic tool.

Acknowledgments The work was supported by the financial assistance from the extramural research grant of Indian Council of Medical Research (ICMR), Second Phase of Biomedical Informatics Centres of ICMR Grant Number: BIC/12(19)/2013. The Authors acknowledge Department of Science and Technology, Government of India, New Delhi, for granting inspire fellowship to Mr. Ardhendu Bhusan Praharaj. The authors also acknowledge Regional Medical Research Centre (ICMR), Bhubaneswar for providing infrastructure facilities to carry out this work.

Conflict of interest The authors declare that there is no conflict of interest.

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