Journal of Cellular Biochemistry 104:1150–1160 (2008)

Factors Influencing Collagen Biosynthesis

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Abstract The importance of collagen, the major structural protein of animal kingdom, in maintaining the normal structure and function of the skin is well known. The same property is exploited widely in medical and industrial fields in finding agents, which could influence the synthesis of this protein. In this context in vitro production of collagen is of high significance. A literature survey has been made to analyze the various factors that influence collagen biosynthesis. There are various physical and biological factors that can either induce or inhibit collagen biosynthesis at various levels of gene expression. However reports concentrating on the effects of plants-derived compounds in stimulating collagen synthesis are scanty. Since extracts of many plants are known to be beneficial in the wound healing process, plants-derived compounds will have a definite role in the regulation of collagen synthesis. The present study emphasizes the need for unearthing the role of these plant derived factors on collagen synthesis which will be of immense application in the medical field. J. Cell. Biochem. 104: 1150–1160, 2008.

Key words: collagen synthesis; collagen regulating factors

Collagen is the most abundant protein in the animal kingdom and constitutes 30% of human total proteins. It is the major component of the extra cellular matrix and provides strength, integrity and structure. Collagen has an important role in wound healing also.

There are nearly 27 different types of collagen, each encoded by a specific gene, listed in Table I [Canty and Kadler, 2005]. About 80–90% of the collagen in the body consists of types I, II, and III. These collagen molecules pack together to form long thin fibrils of similar structure. Each collagen molecule is composed of very long protein chains. These chains comprise a repeating Gly-X-Y triplet, in which X and Y can be any amino acid residue but are usually represented by proline and hydroxyproline respectively [van der Rest and Garrone, 1991]. This triplet motif results in a left handed helix that can intertwine with two other helices to form a right handed triple helical structure which can be homodimeric or heterodimeric based on the type of collagen. Different types of collagens have different amino acid compositions and are having specific functions in the body. Type IV collagen forms a two-dimensional reticulum; several other types associate with fibril-type collagens, linking them to each other or to other matrix components. The various collagens and the structures they form all serve the same purpose, to help tissues withstand stretching.

Properties of collagen could be effectively exploited. Collagen as such or collagen enhancers are invariable constitutes of commercial products such as lotions firming gels, wrinkle injections, eye pads etc. It is also used as wound dressing materials and as skin substitutes and even in anticancer treatment.

COLLAGEN PRECURSOR SYNTHESIS

Each collagen type is coded by a specific gene and collagen family of proteins were listed by Canty and Kadler [2005] (Table I). The mRNA formed from each gene undergoes processing and the processed mRNA then attaches to the site of actual protein synthesis on rough endoplasmic reticulam [Diegelmann, 2001].

Abbreviations used: CYR 61, cysteine rich 61; MMP, matrix metalloproteinase; TGF, transforming growth factor; CS, chondroitin sulfate; glcN, glucosamine; TNF, tumor necrosis factor; PDGF, platelet derived growth factor; HDAC, histone deacetylase; PTH, parathyroid hormone; IGF, insulin like growth factor.

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Received 12 January 2008; Accepted 18 January 2008
DOI 10.1002/jcb.21728

TABLE I. Collagen Types and Their Genes

Collagen type	Genes	Supramolecular organization in tissue	References
I	COLIAI	Fibrils, tendons, bone, skin, cornea and blood vessel walls	Chu et al. [1982]
	COL1A2		Myers et al. [1981]
II	COL2A1	Fibrils in cartridge	Miller and Matukas [1969]
III	COL3A1	Forms heterotypic fibrils with type 1 collagen	Cameron et al. [2002]
IV	COL4AI	Network in basement membrane	Timpl and Brown [1996] and Timpl et al. [1981]
	COL4A2		
	COL4A3		
	COL4A4		
	COL4A5		
	COL4A6		
V	COL5AI	Forms heterotypic fibrils with type 1	Birk [2001]
	COL5A2		
	COL5A3		
VI	COL6AI	Fine microfibrils with ubiquitous distribution (distinct from fibrillin-containing microfibrils)	Kielty et al. [1992]
	COL6A2		
	COL6A3		
VII	COL7AI	Forms anchoring fibrils in skin at the dermal/epidermal junction (basement membrane)	Keene et al. [1987]
VIII	COL8AI	3D hexagonal lattice in descemets membrane in the eye	Kapoor et al. [1986, 1988] and Stephan et al. [2004]
	COL8A2		
IX	COL9AI	Associated with type 2 collagen fibrils	Olsen [1997] and Shimokomaki et al. [1990]
	COL9A2		
X	COL10AI	Mat-like structure/hexagonal lattice in the hypertrophic zone of the growth plate	Kwan et al. [1991]
XI	COL11AI	Forms heterotypic fibrils with type II	Mendler et al. [1989]
	COL11A2		
	COL2AI		
XII	COLI2AI	Associated with type I fibrils	Keene et al. [1991], Nishiyama et al. [1994], and Zhanag et al. [2003]
XIII	COLI3AI	Transmembrane and possibly involved in cell adhesion	Latvanlehto et al. [2003]
XIV	COLI4AI	Associated with type I fibrils	Young et al. [2000, 2002]
XV	COLI5AI	Specialized basement membrane, cleaved to produce antiangiogenic fragment (restin)	Myers et al. [1996] and Ramachandran et al. [1999]
XVI	COLI6AI	Component of specialized fibrils in skin and type II collagen fibrils in cartilage	Kassner et al. [2003]
XVII	COL17AI	Transmembrane component of hemidesmosome, which attach epidermis to basement membrane in skin	Hopkinson et al. [1998]
XVIII	COL18AI	Cleaved to produce antiangiogenic fragment	Sasaki et al. [1998]
XIX	COL19AI	Radially distributed aggregates formed by association at one end in vitro	Myers et al. [2003]
XX	COL20AI	May be associated with type I collagen fibrils	Koch et al. [2001]
XXI	COL21AI	May be fibril associated, wide spread expression pattern	Fitzgerald and Bateman [2001]
XXII	COL22AI	Located in specific tissue junctions and may be associated with microfibrils	Koch et al. [2004]
XXIII	COL23AI	Transmembrane collagen identified in cell cultures	Banyard et al. [2003]
XXIV	COL24AI	Expressed in tissues containing type I collagen	Koch et al. [2003]
XXV	COL25AI	Transmembrane collagen, cleaved form present in Alzheimers amyloid plaques in neurons	Hashimoto et al. [2002]
XXVI	COL26AI	Expressed in testes and ovary of adult tissues	Sato et al. [2002]
XXVII	COL27AI	Widespread expression particularly in cartilage	Boot-Handford et al. [2003] and Pace et al. [2003]

Collagen is synthesized as its precursor, the pro-collagen [Church et al., 1971] which contains non-helical amino and carboxy procollagen extension propeptides which make the molecules very soluble and therefore easy to move within the cells as it undergoes further modifications. Proteolytic removal of the propeptides results in triple helical collagen molecules that have short telopeptides at either ends and can assemble into highly ordered string like aggregates called fibrils. Procollagen is post-translationally translocated in to the lumen of the endoplasmic reticulam in which the folding and further modifications take place [Canty and Kadler, 2005]. The procollagen is converted into collagen by the removal of C and N propeptides by procollagen N and C proteinases [Leung et al., 1979]. This triggers self assembly of collagen into fibrils [Kadler et al., 1987]. It is proposed that the processing of procollagen into collagen is not sufficient for the formation of collagen fibrils. Interaction of collagen with

fibronectin and specific integrins either at the cell surface or within post golgi carrier might also be required [Canty and Kadler, 2005].

Any factor or agent that affects any of these complex steps, during the transcription, translation and post-translational trafficking or modification can also affect the tissue level of the corresponding collagen type. The net effect can be either stimulatory or inhibitory. By this study an attempt has been made to understand the various factors that influence the synthesis of collagen.

COLLAGEN SYNTHESIS AS A FUNCTION OF AGE

During developmental growth, collagens are believed to be continuously deposited into the extracellular matrix, which is increasingly stabilized by the formation of covalent cross-links throughout life. However, several events such as alteration in the extracellular matrix, loss of cell proliferative capacity and decreased responsiveness to cellular growth factors etc are associated with cellular aging. There are marked age-related changes in rates of collagen metabolism. The rate of collagen synthesis decreases with age in rat tissues. Bulk of collagens produced is destined to be degraded also [Mays et al., 1991]. Relative levels of collagen synthesis in dermal fibroblasts from different aged donors appear inversely related to age in a study conducted by Phillips et al. [1994]. Similar result has been observed in the study conducted by Rodrigues et al. [1990] in cultured somatic testicular cells. These results indicate that the synthesis, distribution and molecular characteristics of interstitial collagens change with the age of the animal. There is a recent report by Quan et al. [2006] that CYR61 is significantly up regulated in dermal fibroblasts in chronologically aged and photo aged human skin. Cysteine rich 61 (CYR61) is a secreted extracellular matrix associated signaling molecule that belongs to CCN gene family [Lau and Lam, 1999]. CYR61 activates transcription factor AP-1, which is the major driving force of matrix metalloproteinase-1 (MMP-1). CYR61 also down regulates the TGFβ type II receptor (TβRII) and inhibits basal and TGFβ1 induced TGFβ reporter activity. This impairs the TGFβ pathway, which is involved in the stimulation of collagen synthesis and down regulation of collagen degrading MMPs.

COLLAGEN SYNTHESIS IN LIVER INJURY

The early stages of the hepatic injury associated with liver cirrhosis often show an increased collagen level. Macromolecular collagen components in normal liver and at the different stages of human liver cirrhosis were studied under various extraction conditions. The collagen content at the typical stage of liver cirrhosis was more than fivefold higher than that of the normal state. Both type I and type III collagens, especially the former, increased, reflecting enhanced levels of total collagen with the progression of liver cirrhosis. At the early stage, the remarkable increase in type V collagen started much earlier than at the typical stage when the ratio of type I to type III changed [Murata et al., 1984]. The increased collagen of both types was responsible in part for the observed distortion of the architecture of the cirrhotic livers associated with increased rigidity of the stroma [Rojkind and Martinez-Palomo, 1976]. Alcohol is one of the principle causes of liver cirrhosis. But it is not the alcohol, which is directly involved in the pathology, but the acetaldehyde. Acetaldehyde increases production of collagen and slightly inhibits procollagen secretion. The steady state levels of collagen α1(I) and collagen α2(I) mRNAs have been shown to be increased by acetaldehyde. Transcriptional activity of collagen α1(I) and collagen α1(III) have also been found to be increased by acetaldehyde [Brenner and Chojkier, 1987]. The process is mediated by a series of signal transducers and gene regulators. Acetaldehyde directly activates c-jun N-terminal kinase (JUK), an enzyme involved in the signal transduction pathway. JUK phosphorylates c-jun, which activates the trans activator protein 1, AP-1. AP-1 is composed of either jun–jun homodimers or fos-jun heterodimeric complex. Activated AP-1 binds to the promoter of BTEB gene whose product is an important protein involved in the collagen regulation. BTEB protein binds to the distal GC box in the upstream of α1(I) collagen gene and stimulates its expression [Chen and Davis, 2000].

COLLAGEN SYNTHESIS AFTER RADIATION EXPOSURE

Collagen synthesis also increases as a result of radiation therapy or accidental radiation. This results in a condition called fibrosis characterized by increased accumulation of

extra cellular matrix, especially collagen. The irradiation mediated collagen synthesis is mediated by a fibrogenic cytokine called transforming growth factor (TGFβ). Irradiation of Human intestinal smooth muscle cells specifically increased collagen type III biosynthesis during the first 48 h of exposure [Alexakis et al., 2001]. This increase was correlated with a significant increase in TGFβ in pericellular domain of irradiated cells. It was also observed that the effect could be reverted by a heparin mimetic RG 1503. This molecule is capable of competing with TGFβ for its receptor. Collagen I and III have a TGFβ binding site in their promoter. The expression of these two collagens is modulated by differential transcriptional mechanisms [DeCrombrugghe et al., 1990]. RG 1503 may exert control on collagen mRNA transcription via pathway involving cellular localization and distribution of TGFβ [Alexakis et al., 2001].

ASCORBIC ACID AS A REGULATOR OF COLLAGEN SYNTHESIS

Study conducted by Schwarz and Bissell [1977] reported the role of ascorbate in regulating collagen synthesis. Ascorbate is essential for the collagen molecule to maintain its triple helical structure. The collagen molecule, after formation undergoes post-translational modifications, which invariably includes the hydroxylation of proline and lysyl residues. Hydroxylation of proline residues is essential for the formation of intermolecular cross-links in collagen molecules [Ghosh, 2002]. These provide stability for collagen molecules and facilitate hydroxylation of lysyl residues, which is essential for the linkage of carbohydrate residues to collagen molecules [Murad et al., 1981]. This modification is carried out by prolyl hydroxylase and lysyl hydroxylase respectively. Ascorbate forms the co-factor for these enzymes [Peterofsky and Udenfried, 1965; Kivirikko and Myllyla, 1980]. Total collagen production can be increased by ascorbate supplementation [Murad et al., 1981; Chojkier et al., 1989]. The distribution of collagen also changes based on the presence or absence of ascorbic acid. In the absence of ascorbate, unhydroxylated collagen molecules will accumulate in the rough endoplasmic reticulum, which inhibits further synthesis of collagen [Pacifici and Iozzo, 1988]. This block can be relieved by ascorbic acid supplementation [Schwarz, 1985]. The increased collagen synthesis in the presence of ascorbate is unrelated to its role in hydroxylation of collagen. Moreover the two enzymes involved in the collagen hydroxylation are regulated independently by ascorbate [Murad et al., 1981]. The study conducted by Davidson et al. [1997] has confirmed ascorbate's role in stabilizing the collagen I mRNA. Ascorbate is also found to be able to generate lipoperoxide, which produces reactive aldehydes that could act upon the transcriptional machinery [Chojkier et al., 1989; Geesin et al., 1990, 1991]. Increased collagen level as a result of treatment with ascorbate was also reported by Kalcheim et al. [1982].

PROTEOGLYCANS AS REGULATORS OF COLLAGEN SYNTHESIS

A mixture of chondroitin sulfate and glucosamine has been extensively tested for the clinical efficacy of symptomatic relief in patients with osteoarthritis. This is because of the chondroprotective effect of this mixture. Since collagen is the major component of the connective tissues, the mixture may also have some collagen regenerative property. Very few publications have been devoted to the effect of glcN and CS on collagen synthesis and there are great disparities among the results reported by different groups. Bassleer et al. [1998] found that CS had no effect on the human cartilage collagen synthesis. However the data of Jimenez et al. [1996] and O'Grady et al. [2000] have indicated increased gene expression for collagen synthesis as influenced by both agents as well as with a combination of agents. This disparity in results may be a reflexion of the dose used, the culture system employed or may indicate that the increase in mRNA level is not reflected in the actual assayable product [Lippiello, 2006]. Lippiello [2006] observed that the combination of glcN and CS effectively stimulated neosynthesis of collagen in cell cultures of ligaments, tendons and cartilage tissues. However with an increase in dose a reciprocal result was observed. This effect is probably due to the presence of CS, as reports are available on the inhibitory effect of CS on collagen synthesis [Collier and Ghosh, 1989; Verbruggen et al., 1999].

GLUCOSE AS A REGULATOR OF COLLAGEN SYNTHESIS

Aging and age related diseases alter the extra cellular matrix components considerably. The

effect of high glucose concentration (characteristic of diabetes) on collagen synthesis was checked by Benazzoug et al. [1998]. They investigated the effect of high-glucose concentration (mimicking diabetic conditions) on in vitro cell aging [comparing 4th-passage fibroblasts (P4) to 15th-passage fibroblasts (P15)] and also on collagen and fibronectin synthesis. It was observed that in control conditions (5 mM glucose) collagen III production increased along with in vitro cell aging. High glucose concentrations (10 and 15 mM) increased specifically collagen III synthesis both at the mRNA and protein levels, without altering collagen I production. Fibronectin synthesis was also increased both during in vitro cell aging and in high glucose exposures of fibroblasts.

CELLULAR GROWTH FACTORS AND THEIR INFLUENCE ON COLLAGEN SYNTHESIS

There is a differential effect for human epidermal growth factor in the collagen synthesis and the synthesis of other extracellular proteins. Recombinant human epidermal growth factor specifically inhibited the production and accumulation of type I collagen in cultured human fibroblasts while it stimulated the production of non-collagenous proteins [Kurata and Hata, 1991]. In this experiment it is clear that human EGF reduced steady state levels of mRNAs for both proα1(I) and proα2(I) chains and also influenced the levels of transcription of these genes. However, the actual mechanism involved in the regulation mediated by human EGF is not clear.

TNFα is a cytokine released by activated macrophages that locally elicits a wide spectrum of metabolic responses and cellular activities. These pathways in part influence cellular gene expression by modulating the activity and synthesis of various transcription factors. TNFα reduces ECM deposition by inhibiting the synthesis of structural components. TNFα counteracts transforming growth factor β (TGFβ) mediated stimulation of collagen synthesis. TNFα and TGFβ have opposing effects on the regulation of collagen synthesis [Inaggaki et al., 1995]. Greenwel et al. [2000] showed that TNFα mediated the down regulation of genes coding for α1 chain of type I collagen. This was effected by stimulating the synthesis and binding of a repressive CCAAT/enhancer protein (C/EBPs) to TNFα responsive element. The mode of action of TGFβ varies with respect to the cell types and also depends on a number of factors. There are reports on the role of TGFβ on increased transcription of collagen genes and the differential effect of TGFβ on the stability of procollagen mRNAs [Ignotz and Massague, 1986; Penttinen et al., 1988]. Roberts et al. [1986] pointed out the role of TGFβ in the incorporation of proline to collagen chain. Over recent years the mode of action of TGFβ has been worked out. TGFβ activates TGFβ receptor which transphosphorylates the signal transducer smads and transcriptional co-activators p300/CBP to regulate TGFβ target gene transcription. Co-activator p300/CBP induces COLI A2 promoter and endogenous typeI collagen mRNA. The intrinsic histone acyl transferase activity of p300/CBP is required for the stimulation of COLI A2 gene transcription [Ghosh and Varga, 2003]. The p300/CBP also plays a significant role in the negative regulation of type I collagen by tumor suppressor protein p53 or IFNγ induced STAT1 α and CIITA [Ghosh and Varga, 2003].

The role of platelet derived growth factor (PDGF) in collagen synthesis is still not clear. There are contradictory reports in the literature. It increases the production of collagen type I and type III by venous smooth muscle cells [Amento et al., 1991] and in muraine mesangial cells [Lei et al., 1998]. Nevertheless there is a reported negative effect on human arterial smooth muscle cells [Okada et al., 1993]. The recent study by Absood et al. [2004] showed that PDGF caused increased collagen production by synthetic smooth muscle cells but not by contractile smooth muscle cells. The oxLDL induced increase in collagen production was blunted by the addition of anti-PDGF antibody, suggesting that PDGF mediated the stimulation of collagen synthesis.

THE MINERAL MICROENVIRONMENT THAT REGULATES COLLAGEN SYNTHESIS

The choice of cells to synthesize different types of collagen invariably depends on their microenvironment and the influence of the extracellular matrix. In the study carried out by Deshmukh and Kline [1976] it was observed that monolayer culture of chondrocytes produced type I collagen and in suspension cultures the choice depended on the presence or absence of calcium. In the absence of calcium, the cells produced their specific type II collagen and in

the presence of calcium type I collagen was synthesized. The increased influx of calcium (induced) in monolayer culture stimulated these cells to produce type I collagen in suspension culture even in the absence of calcium in the extracellular matrix [Deshmukh et al., 1976]. The extra cellular factors involved in this experiments were not restricted to calcium alone. There is an invariable relationship between calcium and cAMP in the stimulation of chondrocytes in suspension culture in the modulation of collagen types synthesized by these cells. cAMP is believed to be involved in the mobilization of intracellular calcium pool of chondrocytes and produce an effect similar to that of extracellular calcium [Deshmukh and Sawyer, 1977]. Swaney et al. [2005] reported that cAMP has the ability to blunt myofibroblast formation, thus inhibiting collagen synthesis.

ESTROGEN AS A REGULATOR OF COLLAGEN SYNTHESIS

Estrogen replacement is one of the most common and effective strategies used in preventing osteoporosis in postmenopausal women. Earlier it was thought that estrogen prevented osteoporosis exclusively by inhibiting bone resorption. Later studies revealed that estrogen stimulated cell proliferation in a dose dependent manner and increased the steady state levels of mRNA encoding $\alpha 1$ chain of type I collagen [Ernst et al., 1988; Nasu et al., 2000]. In vivo administration of estradiol to rats also could enhance the proαI collagen gene expression in the uterus [Komm et al., 1987]. Recently it has been observed that estrogenic compounds may enhance bone formation by increasing the transcription of bone morphogenetic protein (BMP) gene [Zhou et al., 2003]. Estrogen receptor has been shown to have a role in collagen gene expression. In mesangial cells, estrogen suppressed the collagen synthesis. This is mediated by increasing the activity of AP-1 via up regulation of MAP Kinase [Silbiger et al., 1998; Neugarten et al., 1999]. Selective estrogen receptor modulators LY-117018 and tamoxifen suppress COL4A1 gene transcription and type IV collagen protein synthesis in a dose dependent manner in mesangial cells [Neugarten et al., 2000]. Estrogen receptor β mediates this suppressive effect. Phytoestrogen genistein also shows the same effect on collagen synthesis in mesangial cells.

PHYTOESTROGENS THAT INFLUENCE COLLAGEN SYNTHESIS

A number of beneficial effects have been attributed to the consumption of soy. This is due to the presence of soybean isoflavins, genistein, daidzein, and glycitein. Genistein exhibits a biphasic effect on cultured cells, stimulating proliferation at low concentrations and inhibiting proliferation at higher concentrations [Messina and Loprinzi, 2001]. Studies at the cellular level have provided insight into the ability of soybeans to prevent osteoporosis [Akiyama et al., 1987; Bames, 1998]. Recent studies have reported the effect of genistein on the induction of increased collagen synthesis [Varani et al., 2004; Morris et al., 2006].

WOUND HEALING BY HERBS

Ocimum sanctum is a herb which is widely used in Ayurvedic medicines. Recently it was reported that the aqueous and alcoholic extracts of this plant displayed a stimulatory effect on wound healing [Shetty et al., 2007]. Wound healing is a complex process, which involves granulation, collagen maturation and scar formation. Aqueous extract of Ocimum stimulated the interleukin-8 production, which is involved in the recruitment of various inflammatory cells to the wound site. It also increases the gap junctional intracellular communication in cultured fibroblasts and induces a more rapid maturation of granulation tissue. Cell proliferation and collagen synthesis at the wound site is also promoted by the plant extract along with the increase in total protein content. Hexuronic acid and hexosamine, which are the components of glycosaminoglycans, are the other factors which are increased by Ocimum extract. These are known to stabilize the collagen fibers by enhancing ionic and electrostatic interactions with glycosaminoglycans. This is crucial for the proper deposition and alignment of collagen fibers. Ocimum contains many flavanoids which have been reported to have antioxidant property. This anioxidant activity of flavanoids is considered to be the factor responsible for the increase in collagen synthesis.

MISCELLANEOUS FACTORS THAT INFLUENCE COLLAGEN BIOSYNTHESIS

Histone deacetylase (HDAC) has the ability to modulate gene expressions. HDAC promotes

type II collagen expression. This is by inactivation of the factor Wnt-5, which inhibits type II collagen transcription. HDAC deacetylates the promoter of Wnt-5 thus blocking its transcription [Huh et al., 2007].

Vertebrate myotrophin upregulates protein synthesis in myocytes [Sen et al., 1990]. Sponges (Porifera) contain myotrophin related molecules which share high sequence similarity with vertebrate cardiac myotrophin. It is seen that these molecules causes a strong increase in the collagen gene expression in dissociated sponge cells [Schroder et al., 2000].

Lipids are supposed to play a role in enhanced collagen synthesis. In a study conducted by Absood et al. [2004], it is reported that oxidized LDL and superoxide generator LY-83583 induce higher level of collagen synthesis in graft and aortic smooth muscle cells. Superoxides are known to stimulate collagen synthesis by hepatocytes and fibroblast in vitro [Hussain et al., 1987; Chandrakasan and Bhatnagar, 1991]. But hydrogen peroxide does not have a role in collagen synthesis [Absood et al., 2004].

Certain factors present in the embryonic brain extract can stimulate the synthesis of collagen type I, III, and V in cultured muscle cells. The effect is restricted to collagen and other proteins are not affected by this factor. The possible reason for this phenomenon is explained as the increased prolyl hydroxylation [Kalcheim et al., 1982].

Retinoids play important role in maintaining the tissue collagen level. It is reported that the increased level of collagen in retinoic acid treated human skin is mainly due to the reduction of collagen degrading metalloproteases [Lateef et al., 2004]. However, previous studies have demonstrated that types I and III pro collagens are increased in aged skin following retinoid treatment and this can be seen as elevated mRNAs for both types I and III procollagens [Varani et al., 2000].

Tharaux et al. [1999] reports that endothelin-1 is a major activator of type I collagen in rats. Endothelin-1 has mitogenic activity and has the ability to activate extracellular component synthesis by vascular smooth muscle cells. NO pathway is associated with activation of endothelin. By this study it was revealed that inhibition of NO pathway resulted in an enhanced expression of collagen 1α1 mRNA and procollagen I.

Another factor, which affects collagen synthesis, is the parathyroid hormone (PTH). It was earlier reported that PTH reduced collagen synthesis by altering the levels of procollagen mRNAs [Kream et al., 1980]. Partridge et al. [1989] reported that the concentration of PTH that reduced collagen synthesis by 35–45% (10(−8) M), caused a net decrease of approximately 80–96% in the number of procollagen transcripts together with a small reduction in beta-actin mRNA levels. The antibiotic doxycyclin (DOX) has also been shown to have a suppressive effect on type II collagen synthesis in articular chondrocytes. The molecular mechanism by which DOX exerts its effect is yet to be understood [Tekoppele et al., 1998]. PTH stimulates osteoblast collagen synthesis in the presence of estrogen but not in its absence. PTH stimulates insulin like growth factor binding protein IGFBP-5mRNA expression by pre-treatment with estrogen, which increases type I procollagen mRNA expression [Nasu et al., 2000]. The breakdown of collagen in relation to estrogen action through the mediation of enhanced collagenase activity has been demonstrated earlier [Premkumar and Thampan, 1992; Anuradha and Thampan, 1993, 2003].

FOCUS ON PLANTS

Plants-derived factors that enhance the synthesis of collagen by animal cells in cultures are being identified. The beneficial effects of such factors are not difficult to be recognized. The emphasis, under these conditions will be on the wound healing process. These factors will be of immense use in post-operative care of wounds and also in the treatment of severe burn injuries. A systematic study on these plants-derived agents is highly recommended.

ACKNOWLEDGMENTS

The authors thank the SAFI trustees for the opportunity given to them to carryout the studies.

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