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REVIEW

Current status and challenges of cytokine pharmacology

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The major concern of pharmacology about cytokines has originated from plentiful data showing association between gross changes in their production and pathophysiological processes. Despite the enigmatic role of cytokines in diseases, a number of them have become a subject of cytokine and anti-cytokine immunotherapies. Production of cytokines can be influenced by many endogenous and exogenous stimuli including drugs. Cells of the immune system, such as macrophages and lymphocytes, are richly endowed with receptors for the mediators of physiological functions, such as biogenic amines, adenosine, prostanoids, steroids, etc. Drugs, agonists or antagonists of these receptors can directly or indirectly up- and down-regulate secretion of cytokines and expression of cytokine receptors. Vice versa, cytokines interfere with drug pharmacokinetics and pharmacodynamics through the interactions with cytochrome P450 and multiple drug resistance proteins. The aim of the review is to encourage more intensive studies in these fields of cytokine pharmacology. It also outlines major areas of searching promising candidates for immunotherapeutic interventions.
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Abbreviations: Ab, antibody; BCA-1/CXCL13, B cell attracting chemokine-1; ENA-78/CXCL5, Epithelial-cell derived neutrophil activating factor-78; GCP-2/CXCL6, Granulocyte chemoattractant protein-2; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; Gro-α, -β, -γ/CXCL1, 2, 3, Growth-regulated oncogene-; IFN, interferon; IL, interleukin; IP-10/CXCL10, interferon-inducible protein-10; I-TAC/CXCL11, interferon-inducible T cell α-chemoattractant; LT-α, Lymphotoxin-α; MCP-1/CCL2, monocyte chemoattractant protein-1; MCP-3/CCL7, Monocyte chemoattractant protein-3; M-CSF, Macrophage colony stimulating factor; MIG/CXCL9, Monokine induced by γ-interferon; MIP-1α/CCL3, Macrophage inflammatory protein-1 alpha; MIP-1β/CCL4, Macrophage inflammatory protein-1 beta; NAP-2/CXCL7, Neutrophil-activating protein-2; PF-4/CXCL4, Platelet factor-4; RANTES/CCL5, Regulated upon activation, normal T cell expressed and secreted; SDF-1/CXCL12, Stromal cell-derived factor-1; SLC/CCL21, Secondary lymphoid-tissue chemokine; TGF-β, transforming growth factor-β; TNF-α, tumour necrosis factor-α

Cytokines and cytokine network

The story of cytokines may be dated back to the mid of the last century, to the discovery of interferon (IFN) (Isaacs and Lindenmann, 1957). The superfamily of cytokines, mostly small- to medium-sized polypeptides or glycoproteins (6–30 kDa) with multiple regulatory homeostatic functions, has expanded dramatically during the last few years. Presently, about 200 cytokines are recognized. In contrast to hormones, cytokines are usually produced by many cell types, and act in autocrine and paracrine modes of fashion. The typical feature of most cytokines is a low or no constitutive production and transient expression following inducing stimuli. A number of feedback mechanisms influence synergistically or antagonistically production and activity of individual members of the cytokine network. The biological effects of several cytokines are often overlapping (redundancy), and individual cytokines possess multiple regulatory functions (pleiotropy).

Widely accepted criterium of cytokine categorization is the production of cytokines in dependence on distinct lineages of T helper (Th) cells (Table 1). The Th1 cells produce IFN-γ, interleukin (IL)-2, IL-15 and lymphotoxin [tumour necrosis factor (TNF)-β]. The Th2 cells produce IL-4, IL-5, IL-6, IL-9 and IL-13 (Mosmann and Coffman, 1989; Romagnani, 1994). Both Th1 and Th2 cells produce IL-10 (O'Garra and Vieira, 2007). Conventional definition of Th1 and Th2 cells depends

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Table 1 Representative cytokines produced by different subsets of T cells, their receptors and signalling

Cytokine	*Major cell producers*		*Receptors**	*Signalling**
	T cells	*Other cell types*		
IFN-γ	Th1	$CD8^+$ T cells (Su *et al.*, 1998), natural killer cells (Perussia, 1991), B cells (Pang *et al.*, 1992), macrophages (Markus *et al.*, 1998), keratinocytes (Gröne, 2002), astrocytoma cells (Nitta *et al.*, 1994)	IFN-γRI; IFN-γRII	Jak1, Jak2/STAT1
IL-2	Th1	Thymocytes (Kroemer and Wick, 1989)	IL-2Rα; IL-2Rβ; γc	Jak1, Jak3/STAT3, STAT5
IL-15	Th1	Macrophages, monocytes, bone marrow stromal cells (Gosselin *et al.*, 1999), epithelial cells, fibroblasts, muscle cells (Yanagita *et al.*, 2002), keratinocytes (Gröne, 2002)	IL-15Rα; IL-2Rβ; γc	Jak1, Jak3/STAT3, STAT5
TNF-β (LT-α)	Th1	B cells, natural killer cells (Gray *et al.*, 1984), keratinocytes, mast cells (Middel *et al.*, 2000)	TNFR1, TNFR2	NF-κB
IL-4	Th2	Basophils (Brunner *et al.*, 1993), eosinophils (Moqbel *et al.*, 1995), mast cells (Petray *et al.*, 1993), natural killer cells (Hameg *et al.*, 1999)	IL-4Rα; IL-13Rα; γc	Jak1, Jak3/STAT6
IL-5	Th2	Natural killer cells (Warren *et al.*, 1995), eosinophils, mast cells (Cousins *et al.*, 1994); Lorentz *et al.*, 1999), basophils (Ying *et al.*, 1995), endothelial cells (Möhle *et al.*, 1997), epithelial cells (Salvi *et al.*, 1999)	IL-5Rα; βc	Jak2/STAT1, STAT3, STAT5
IL-6	Th2	B cells (Yin, 1990), macrophages (Lee Kim Lee *et al.*, 2007), mast cells (Song *et al.*, 1999), fibroblasts (Defilippi *et al.*, 1987), keratinocytes (Gröne, 2002), endothelial cells (Shalaby *et al.*, 1989), osteoblasts (Miwa *et al.*, 1999)	IL-6R; gp130	Jak1, Jak2, Tyk2/STAT1, STAT3, STAT5
IL-9	Th2	Eosinophils, basophils (Shimbara *et al.*, 2000)	IL-9R, γc	Jak1, Jak3/STAT1, STAT3, STAT5
IL-13	Th2	Natural killer cells (McDermott *et al.*, 2005), basophils (Li *et al.*, 1996), mast cells (Kelly-Welch *et al.*, 2003)	IL-13Rα; IL-4Rα; γc	Jak1, Jak2, Tyk2/STAT6
IL-17	Th17	$CD8^+$ T cells (Shin *et al.*, 1998), eosinophils (Molet *et al.*, 2001), neutrophils (Ferretti *et al.*, 2003)	IL-17R	Jak1, Jak2, Jak3, Tyk2/ STAT1, STAT2, STAT3, STAT4
IL-22	Th17	Natural killer cells (Wolk and Sabat, 2006)	IL-22R1, IL-10Rβ	Jak1, Tyk2/STAT1, STAT3, STAT5
IL-10	Tr1	B cells (O'Garra *et al.*, 1992), macrophages and monocytes (de Waal Malefyt *et al.*, 1991), keratinocytes (Gröne, 2002), glial cells (Mizuno *et al.*, 1994; Williams *et al.*, 1996)	IL-10Rα; IL-10Rβ	Jak1, Tyk2/STAT1, STAT3
TGF-β	Tr3 (Th3)	Macrophages (Assoian *et al.*, 1987), neutrophils, platelets (Schindler *et al.*, 1998), microglial cells (Chao *et al.*, 1995)	TGF-βRI, TGF-βRII	Smad

*Major references for receptors and signalling: (Bach *et al.*, 1997; Silvennoinen *et al.*, 1997; Imada and Leonard, 2000; Seidel *et al.*, 2000; Lejeune *et al.*, 2002) and references in the text.

strictly on the ability to secrete IFN-γ and IL-4 respectively. Mature Th0 cells secrete the both cytokine types. The Th1 cytokines inhibit growth of intracellular pathogens (viruses, bacteria, fungi) and tumour cells. They enhance the delayed type hypersensitivity, phagocytosis, oxidative burst, inflammatory reactions and expression of class I and II MHC molecules. The Th2 cytokines inhibit growth of extracellular parasites (helminths) and suppress phagocytosis. They augment B cell proliferation, drive antibody production and switch IgG to IgE class of antibodies. They are associated with the development of allergic and related IgE-mediated diseases.

It should be emphasized that production of Th1 and Th2 cytokines is not restricted to the Th1 and Th2 lymphocytes respectively. They are produced by many cell types (Table 1). This fact is reflected in the frequently used terms 'Th1 immune response' and 'Th2 immune response' describing changes in expression of these cytokines irrespective of the cell source.

Currently, there is a growing interest in recently revealed T cell clones exhibiting different cytokine profile from that of Th1 and Th2 cells. They include a third subset of Th cells (Th17) and T regulatory cells (Treg).

Th17 cells secrete IL-17, IL-17F, IL-22 and IL-25 as signature cytokines. They also produce IL-6 and TNF-α, and some of them IFN-γ. The Th17 immunity is an attractive therapeutic target because it is protective against extracellular bacteria and fungi. On the other hand, it may contribute to the development of allergic responses (IL-25), inflammation and autoimmune disorders (e.g. arthritis) (Annunziato *et al.*, 2007; Kaiko *et al.*, 2008).

There are several subsets of Treg cells. Their major function is maintaining self-tolerance via inhibition of effector T cells. The regulatory T cells type 1 (Tr1) are producers of large amounts of IL-10. They also secrete IFN-γ, IL-5 and low to moderate levels of transforming growth factor-β (TGF-β) and IL-2. The regulatory cells of the Tr3 subset (also called Th3 cells) produce preferentially high amounts of TGF-β and low amounts of IL-10. The regulatory cytokines IL-10 and TGF-β suppress pathological immune responses occurring in autoimmune diseases and transplantation. Both TGF-β and IL-10 negatively regulate production of Th1 and Th2 cytokines. Their overexpression may impair the immune mechanisms directed against pathogens and tumour antigens (Levings *et al.*, 2001; Liu and Leung, 2006; Roncarolo *et al.*,

Table 2 Target cells for biological effects of chemokines

Chemokine		*Target cells*												
		B	*T*	*NK*	*Dc*	*Mo*	*Ba*	*Eo*	*Ne*	*Fi*	*En*	*Ke*	*Mc*	*Sc*
CCL2	MCP-1: monocyte chemotactic protein-1		+			+	+						+	+
CCL3	MIP-1α: macrophage inflammatory protein-1α	+	+	+	+	+	+	+					+	+
CCL4	MIP-1β: macrophage inflammatory protein-1β		+			+								+
CCL5	RANTES: regulated upon activation, normal T cell expressed and secreted		+	+	+	+	+	+						
CCL7	MCP-3: monocyte chemotactic protein-3		+			+		+						
CCL8	MCP-2: monocyte chemotactic protein-2		+			+		+					+	
CCL11	Eotaxin							+						
CCL13	MCP-4: monocyte chemotactic protein-4		+			+		+						
CXCL1	Gro-α: growth-related oncogen-α								+		+			
CXCL4	PF-4: platelet factor-4					+			+		+			
CXCL5	ENA-78: epithelial derived neutrophil attractant								+					
CXCL6	GCP-2: granulocyte chemotactic protein-2								+					
CXCL7	NAP-2: platelet basic protein								+	+				
CXCL8	IL-8: interleukin-8		+	+			+		+		+	+		
CXCL9	MIG: monokine induced by γ-interferon		+	+		+								
CXCL10	IP-10: interferon-inducible protein-10		+	+							+			
CXCL12	SDF-1α/β: stromal cell-derived factor-1		+			+								

References supporting the Table: (Howard *et al*., 1996; Adams and Lloyd, 1997; Saunders and Tarby, 1999).
B, B cells; Ba, basophiles; Dc, dendritic cells; Eo, eosinophils; En, endothelial cells; Fi, fibroblsts; Ke, keratinocytes; Mc, mast cells; Mo, monocytes; Ne, neutrophils; NK, natural killer cells; Sc, stem cells; T, T cells.

2006). IL-10 possesses antifibrotic activities and may be valuable as a therapeutic cytokine for patients with liver cirrhosis (Rachmawati *et al*., 2007). The anti-inflammatory effects of IL-10 have led to its use in hyper-inflammatory states such as psoriasis, organ transplantation and Crohn's disease (Spellberg and Edwards, 2001). TGF-β is a multifunctional polypeptide that stimulates synthesis of many components of extracellular matrix, such as collagens, fibronectin and proteoglycans. Increased production of TGF-β1 is associated with normal reparative as well as pathological fibrotic processes in many organs (Gharaee-Kermani and Phan, 2001).

Immune functions of cytokines result from coordinated action of T cells, macrophages and dendritic cells and depend largely on their recruitment to the sites of infection, inflammation and other pathological lesions. The trafficking of immune cells to the sites of infection and inflammation is under tight control of a special class of cytokines with chemoattractant properties (chemokines). They target many cell types (Table 2). Chemokines are classified into four groups, depending on the relative position of the first N-terminal cystein residues. In the CC family (β-chemokines), the first two cysteins are adjacent; in the CXC family (α-chemokines), they are intervened by one amino acid (Table 2). In the CX3C family (δ-chemokines), the first two cysteins are separated by three amino acids. The C family (γ-chemokines) contains only two of the four conserved cysteins. Chemokines are produced by almost all cells. Their typical feature is binding to multiple chemokine receptors that are expressed on many cell types (Table 3). The inducible chemokines are stimulated by Th1 cytokines (IFN-γ, IL-2) and by pro-inflammatory cytokines (IL-1, TNF-α). The Th2 cytokines (IL-4) and Treg cytokines (IL-10, TGF-β) down-regulate secretion of chemokines (Adams and Lloyd, 1997).

Many of the chemokine–chemokine receptor interactions have been identified to be associated with disease conditions, including allergic diseases, asthma, atherosclerosis, multiple sclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel diseases, cancer and HIV infection. Both chemokines and chemokine receptors have become most attractive targets for drug development (Onuffer and Horuk, 2002).

Cytokines act within the cytokine network in all agonistic, antagonistic and synergistic manners. It is not surprising therefore that their biological effects of potential pharmacological interest are not necessarily bound to the typical T cell cytokine phenotypes (Table 4).

Cytokine receptors and signalling

Cytokines act through the binding with cytokine receptors that can be grouped in several distinct families on basis of the structural features (Pugh-Humphreys and Thomson, 1998; Vilček, 2003). The cytokine receptors are usually composed of several subunits. For example, the low-affinity receptor for IL-2 (IL-2R) contains only the α subunit (IL-2Rα), while the intermediate affinity IL-2R is composed of the βc and γc subunits (IL-2Rβ, γc/IL-2Rγ respectively). The high-affinity IL-2R contains all three subunits. The receptor subunits are shared by many cytokine receptors. The γc subunit ('common cytokine receptor γ chain', initially known as IL-2Rγ) is a component of the receptors for cytokines IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. These T-cell growth factors thus exhibit overlapping activities. The 'common cytokine receptor β chain' (the βc subunit) is shared by receptors for cytokines IL-3, IL-5 and granulocyte-macrophage colony stimulating factor (GM-CSF). The gp130 subunit is shared by IL-6 and IL-11 cytokine receptors.

Ligation of cytokines to the extracellular domains of the membrane-bound cytokine receptor subunits results in homo- or hetero-dimerization of individual subunits. The

Table 3 Ubiquitous cell expression of chemokine receptors and multiple binding of ligands

Receptor	*Cells expressing chemokine receptors*														*Chemokine ligands of receptors**													
															CCL subfamily								*CXCL subfamily*								
	a	*b*	*C*	*d*	*e*	*f*	*g*	*h*	*i*	*j*	*k*	*n*	*o*	*p*	*2*	*3*	*4*	*5*	*7*	*8*	*11*	*13*	*1*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*12*
CCR1	+	+	+	+	+	+	+	+	+	+				+		+	+	+	+	+		+									
CCR2	+	+	+	+	+		+	+		+		+	+		+				+	+		+									
CCR3	+						+	+	+		+			+		+	+	+	+	+		+									
CCR4	+	+			+		+	+						+	+			+													
CCR5			+	+	+	+	+						+			+	+	+	+	+											
CCR6	+	+		+			+																								
CCR7	+	+					+																								
CCR8	+	+			+												+														
CCR9	+				+		+								+	+	+	+	+	+		+									
CCR10												+	+																		
CXCR1	+	+	+	+	+	+	+			+			+										+		+	+	+	+			
CXCR2	+			+	+	+	+		+	+	+	+	+										+		+	+	+	+			
CXCR3		+	+		+		+		+				+	+										+					+	+	
CXCR4	+	+		+	+	+	+			+			+	+																	+
CXCR5	+	+		+	+	+																									
CXCR6	+						+																								

*The acronyms and names of chemokines are shown in Table 2.
The CCR6 receptor binds with chemokine CCL20/MIP-3α. The CCR7 receptor binds with chemokines CCL19/MIP-3β and CCL21/SLC. The CCR10 receptor binds with CCL27/CTACK and CCL28/MEC chemokines. The CXRC5 receptor binds with CXCL13/BCA-1. The CXCR6 receptor binds with CXCL16/small inducible cytokine B6 chemokine. Major references to support the table: (Devalaraja and Richmond, 1999; Ebnet and Vestweber, 1999; Mantovani, 1999; Schwarz and Wells, 1999; Rossi and Zlotnik, 2000; Owen, 2001; Onuffer and Horuk, 2002).
a, T cells; b, B cells; c, natural killer cells; d, macrophages; e, monocytes; f, astrocytes; g, dendritic cells; h, basophils; i, eosinophils; j, neutrophils; k, mast cells; n, fibroblast; o, endothelial cells; p, platelets.

Table 4 Pharmacologically important activities of cytokines

Activity	*Cytokines*
Anti-infectious	Th1: IFN-γ, IL-2, IL-15; Th2: IL-4, -13; others: IFN-α/β/λ, TNF-α, IL-1, -12, -18, GM-, M-, G-CSF; chemokines: MCP-1/CCL2, MIP-1α/CCL3, RANTES/CCL5, MCP-3/CCL7
Anti-tumour	Th1: IFN-γ, IL-2, -15; Th2: IL-4, -6, -13; Tr1: IL-10; others: IFN-α/β, TNF-α, IL-12, -18, -23, -24, GM-CSF
Inflammatory	Th1: IFN-γ; Th2: IL-6; others: TNF-α, IL-1, -12, -18, -19, -22; chemokines: MCP-1/CCL2, MIP-1α/CCL3, RANTES/CCL5, eotaxin/CCL11, MIG/CXCL9, IP-10/CXCL10, I-TAC/CXCL11, Fractalkine/CX3L21
Anti-inflammatory	Th2: IL-4, -6, -13; Tr1: IL-10; Th3: TGF-β; others: IL-11, -25, -32
Anti-allergic	Th1: IFN-γ; Tr1: IL-10
Anti-fibrotic	Th1: IFN-γ; Tr1: IL-10; others: IFN-α/β
Angiostatic	Th1: IFN-γ, Th2: IL-4, -13; others: IFN-α/β, IL-11, -12; chemokines: PF-4/CXCL4, MIG/CXCL9, IP-10/CXCL10, I-TAC/CXCL11, BCA-1/CXCL13, SLC/CCL21
Angiogenic	Th2: IL-6; Th17: IL-17; Th3: TGF-β; others: TNF-α, IL-1, G-CSF, GM-CSF; chemokines: Gro-α, -β, -γ/ CXCL1, 2, 3, ENA-78/CXCL5, GCP-2/CXCL6, NAP-2/CXCL7, IL-8/CXCL8, SDF-1/CXCL12, I-309/CCL1, MCP-1/CCL2, Fractalkine/CX3CL1
Hepatoprotective	Th1: IL-15; others: IFN-λ, IL-22
Wound healing	Th3: TGF-β; others: TNF-α, IL-1, GM-CSF, FGF, KGFS, ECGF; chemokines: Gro-α/CXCL-1, ENA-78/CXCL5, IL-8/CXCL-8, MCP-1/CCL2, MIP-1α/ CCL3

Major references: (Rossi and Zlotnik, 2000; Xing and Wang, 2000), and references in the text.

intracellular domains of the receptor then mediate the signal transduction cascades downstream of cytokine receptors. The signalling pathways depend largely on discrete families of tyrosine kinases.

One of the most important mechanisms of cytokine signalling is the Jak (Janus kinase)-STAT (signal transducer and activator of transcription) pathway (Fujii, 2007). It is used mainly by cytokines that bind with cytokine receptors lacking the intrinsic kinase activity [IFNα/β, IFN-γ, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-17, IL-20, IL-21, IL-22, granulocyte colony stimulating factor (G-CSF), GM-CSF]. The members of the Jak family of cytoplasmic tyrosine kinases (Jak1, Jak2, Jak3, Tyk2) activate the transcription factors of the STAT family (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6) through phosphorylation on a single tyrosine. The STATs form dimers that bind with the promoter sites of target genes. There is an overlapping linkage of different cytokine receptors to a specific array of Jaks and STATs (Liu *et al.*, 1998; Heim, 1999). It is presumed that cytokine specificity is achieved through the integration of the Jak-STAT transactivating pathway with other mechanisms of cytokine signal transduction and transcription (Silvennoinen *et al.*, 1997; Imada and Leonard, 2000).

Only several cytokine receptors contain the kinase activity motifs in their own cytoplasmic domains. The ligand-receptor complexes can thus directly bind and phosphorylate the

downstream intracellular signalling substrates. This is an intrinsic property of the receptors for the TGF superfamily of polypeptide growth factors including TGF-β. They signal through the hetero-tetrameric complexes of the type I and type II receptors exhibiting the serine-threonine kinase activity in their intracellular domains. Efficient signalling by certain members of the TGF superfamily further depends on participation of additional co-receptors such as betaglycan (TGF-β type III receptor). The type II receptors phosphorylate the type I receptors; the latter activate the Smad signal transduction pathway. The heteromeric Smad complexes translocate into the nucleus. They bind to DNA directly or indirectly and regulate gene expression (Wrana *et al*., 1994; Zhu and Burgess, 2001; Miyazawa *et al*., 2002).

Chemokines are ligands of the rhodopsin family of G protein-coupled seven-helix transmembrane receptors (Devalaraja and Richmond, 1999; Schwarz and Wells, 1999; Onuffer and Horuk, 2002). There are at least 10 distinct β-chemokine (CCR) and seven α-chemokine (CXCR) receptors, which bind β-chemokines (CCL) and α-chemokines CXCL) respectively. Each chemokine has affinity to various chemokine receptors. These receptors often show overlapping ligand specificities (Table 3). The receptor downstream signalling involves multiple pathways including mitogen-activated protein kinases and tyrosine and serine-threonine kinases. Important role is played by mobilization of intracellular Ca^{2+} following activation of phospholipase C.

In addition to the membrane-bound cytokine receptors, a number of them exist in a soluble form (Pugh-Humphreys and Thomson, 1998; Levine, 2004). Soluble cytokine receptors usually function as natural antagonists for the biological actions of the respective cytokines.

Cytokines in diseases

Gross alterations in cytokine production have been observed in human diseases of different etiological background. They include acute inflammation: wound healing (Gharaee-Kermani and Phan, 2001), chronic inflammation: rheumatoid arthritis (McInnes and Schett, 2007), atherosclerosis (Kleemann *et al*., 2008), asthma and allergy (Pease, 2006; Holgate and Polosa, 2008), chronic obstructive pulmonary disease (de Boer, 2005), autoimmunity: multiple slerosis (Szczuciński and Losy, 2007), lupus erythematosus (Lit *et al*., 2007), neurodegeneration: Alzheimer's disease (Tarkowski, 2002), Parkinson's disease (Sawada *et al*., 2006) and neoplasia (Oppenheim *et al*., 1997).

Many diseases have been suggested to be associated with a shift in levels of Th1/Th2 cytokines. A typical disease with the shift towards the Th2 immune response is tuberculosis caused by *Mycobacterium tuberculosis*. Accordingly, the Th1 cytokine IFN-γ has proved useful in the treatment of drug-resistant pulmonary disease (Suárez-Méndez *et al*., 2004). Insufficient production of Th1 cytokines is associated with increased susceptibility to infections and tumours (Xing and Wang, 2000). The Th1 cytokines IFN-γ, IL-2, TNF-α and TNF-β are effective to eliminate cancer cells whereas the Th2 cytokines are inhibitory on Th1-mediated anti-cancer effects (Gorelik *et al*., 1994; Takeuchi *et al*., 1997).

It is believed that restoration of the balance of the Th1/Th2 immune response may be a key to successful immunotherapeutic interventions (Murreille and Leo, 1998). However, a number of findings suggest that this concept requires a thorough re-evaluation as its general implication for human diseases suffers from considerable simplification (Kidd, 2003). The polarized production of Th1 and Th2 cytokines represents extremes in a cytokine spectrum. Intermediate patterns are frequently observed (Openshaw *et al*., 1995). Inconsistent findings may result at least partially from methodological problems. One of them is the timing of cytokine assays. The Th1 and Th2 cytokines have been observed to be sequentially up-regulated in the atopic asthmatic sensitized state. The airway smooth muscle cells exhibit an early increased mRNA expression of the Th2 cytokines (IL-5), later followed by enhanced mRNA expression of the Th1 cytokines (IFN-γ, IL-2, IL-12) and their receptors (Hakonarson *et al*., 1999). Similarly, while enhanced levels of Th2 cytokine IL-4 are observed in patients at early stage of rheumatoid arthritis, the Th1 cell clones producing IFN-γ and IL-2 dominate the advanced stages of the disease (Gerli *et al*., 2002). Conflicting data have been reported for the Th1/Th2 immune response in AIDS. Some data demonstrate a massive switch from Th1 to Th2 cytokines in HIV-infected patients (Clerici and Shearer, 1992). However, this has not been confirmed by other findings (Graziosi *et al*., 1994).

There are other sound reasons requiring revision of the Th1/Th2 cytokine dichotomy as a disease biomarker. It has been obsrved that diseases consensually considered as Th1 or Th2 diseases may coexist in the same patient. Asthma, a 'Th1-disease', has been found to occur more frequently in patients who suffer concomitantly from the 'Th2-diseases', such as celiac disease, insulin-dependent diabetes mellitus or rheumatoid arthritis, than in patients without these diseases (Kero *et al*., 2001). The evaluation of the role of Th1 and Th2 cytokines in lupus erythematosus and other autoimmune diseases has revealed that both classes of cytokines can modify the disease (Theofilopoulos *et al*., 2001). Although the pathogenesis of atopic disorders, such as allergen-induced asthma, anaphylaxis and rhinoconjunctivities, is associated with Th2 cytokines (IL-4, IL-5, IL-13), the conventional immunotherapy down-regulating these factors has shown only partial therapeutic effectiveness (Lewis, 2002).

Altogether, it seems unlikely that the dichotomous Th1 versus Th2 disease patterns can sufficiently characterize the disease complexity. The investigations on the role of cytokines in diseases remain still incomplete and much effort is needed to achieve more reliable views in this field. Undoubtedly, the models need substantial accomplishments, adding to the existing knowledge novel data on the biological functions of other cytokines including chemokines.

Cytokine and anti-cytokine therapies

It is often unclear whether the disease-associated changes in cytokine production are just an epiphenomenon or an etiological principle of the disease. Should it be a causal factor, it remains to be elucidated which of the cytokines or a group of cytokines can be regarded as disease-relevant targets. Despite

Table 5 Cytokines as targets for immunotherapeutic treatment of diseases

Cyokines	*Pharmaceutical products*	*Disease targets*
IFN-α	• Recombinant IFN-α2a: roferon; peginterferon α2a • Recombinant IFN-α2b: IntronA; peginterferon α2b; albinterferon • Others: wellferon (IFN-αn1); alferon (IFN-αn3)	Hepatitis B (+lamivudin), hepatitis C (+ribavirine) (Cooksley *et al.*, 2003; Clark, 2007)
IFN-β	• Recombinant IFN-β1a: avonex; rebif • Recombinant IFN-β1b: betaseron; berlex • Chemically modified IFN-β: soluferon	Multiple sclerosis (Bermel and Rudick, 2007)
IFN-γ	• Recombinant IFN-γ1b: actimmune • Humanized anti-IFN-γ Ab: fontolizumab	Chronic granulomatous disease (actimmune) (Marciano *et al.*, 2004); Crohn's disease (fontolizumab) (Hommes *et al.*, 2006)
TNF-α	• Fully human anti-TNF-α mAb: adalimumab; golimumab • Mouse/human chimeric IgG1anti-TNF-α mAb: infliximab • Mouse F(ab')2 anti-TNF-α fragment: afelimomab • Humanized mouse anti-TNF-α Ab: CDP-571 • Analogue of TNF-αR: etanercept • Recombinant human sTNFR p55: onercept	Rheumatoid arthritis, psoriasis, Crohn's disease, ankylosing spondylitis, chronic obstructive pulmonary disease, sepsis (afelimomab), juvenile idiopathic arthritis, asthma (etanercept) (Vincent, 2000; Danese *et al.*, 2006; Fan and Leong, 2007; Zhou *et al.*, 2007)
G-CSF	• Recombinant G-CSF: filgrastim; lenograstim; pegfilgrastim	Febrile neutropenia, bone-marrow transplantation (Cheng *et al.*, 2007)
GM-CSF	• Recombinant human GM-CSF: sargramostim; molgramostim	Neutropenia after chemotherapy (Waller, 2007)
TGF-β1	• Human anti-TGF mAbs: CAT-192 (metelimumab); CAT-152	Scleroderma, prevention of scarring induced by glaucoma surgery (Pinkas and Teicher, 2006)
IL-1	• Recombinant IL-1ra (an IL-1RI-binding molekule): anakirna Human IL-1R1-Fc IgG1 fusion protein: IL-1 Trap	Rheumatoid arthritis, juvenile idiopathic arthritis, Still's disease, Crohn's disease (Dinarello, 2005; Fan and Leong, 2007)
IL-2	• Recombinant IL-2: aldesleukin; telecleukin; proleukin • Human/mouse chimeric anti-IL-2Rα mAb: basiliximab • Humanized anti-IL-2Rα mAb: daclizumab	Metastatic renal cell carcinoma (aldesleukin, telecleukin) (Schmidinger *et al.*, 2004; Akaza *et al.*, 2006); renal transplantation (basiliximab, daclizumab) (Swiatecka-Urban, 2003)
IL-4	• Soluble recombinant human IL-4R: altrakincept	Asthma (Hendeles *et al.*, 2004)
IL-5	• Humanized anti IL-5 mAb: mepolizumab	Asthma (Leckie *et al.*, 2000)
IL-6	• Humanized anti-IL6R mAb: atlizumab; tocilizumab	Rheumatoid arthritis (Genovese, 2005; Lipsky, 2006)
IL-8	• Fully human anti-IL-8 Ab: ABX-IL8	Melanoma (Huang *et al.*, 2002)
IL-10	• Recombinant human IL-10: ilodecakin	Crohn's disease, rheumatoid arthritis, psoriasis, ulcerative colitis, multiple sclerosis (Marshall, 1999)
IL-11	• Recombinant human IL-11: oprelvekin	Thrombocytopenia, ulcerative colitis, psoriasis, rheumatoid arthritis, Crohn's disease (Sitaraman and Gewirtz, 2001)
IL-12	• Humanized anti-IL-12 Ab: ABT-874	Crohn's disease (suggested) (Sandborn, 2004)
IL-12 + IL-23	• mAb against p40 subunit of IL-12 and IL-23: ustekinumab	Psoriasis, psoriatic arthritis, multiple sclerosis, Crohn's disease (Wittig, 2007)
IL-13	• Humanized anti-IL-13 IgG1 mAb: Ab-01; Ab-02	Asthma (preclinical studies) (Vugmeyster *et al.*, 2008)
EPO	• Recombinant erythropoietin: epoetin alfa	Anaemia (Voravud and Sriuranpong, 2005)

the enigmatic role of cytokines in disease etiology, both cytokine and anti-cytokine therapies have been adopted in clinical practice (Table 5). The immunotherapeutic strategies have proved to be useful in various diseases, including hepatitis B and hepatitis C (IFN-α), chronic granulomatous disease (IFN-γ), chronic obstructive pulmonary disease (anti-TNF-α), multiple sclerosis (IFN-β, IL-10, anti-IL-12), rheumatoid arthritis (IL-10, IL-11, anti-TNF-α, anti-IL-1, anti-IL-6), asthma (anti-IL-4, anti-IL-5, anti-IL-13), psoriasis (IL-10, IL-11, anti-IL-12, anti-TNF-α), Crohn's disease (IL-10, IL-11, anti-IFN-γ, anti-TNF-α, anti-IL-1), ulcerative colitis (IL-10, IL-11), cancer (IL-2) and melanoma (anti-IL-8), scleroderma (anti-TGF-β) and others.

The effectiveness of the immunotherapies may vary, however. No evidence of efficacy has been found in some cases. For example, the human anti-TGF-β Ab (CAT-192) has remained ineffective to treat the cutaneous systemic sclerosis (Denton *et al.*, 2007). The therapeutic effectiveness of IL-2, widely used in oncology, is generally considered significant but rather low (Bambust *et al.*, 2007). IL-2 therapy produces overall response rates of 15–20% in patients with metastatic renal cell carcinoma, but it is associated with serious toxicities affecting all vital organ systems (Dutcher, 2002). It is uncertain whether the dose and combination of IL-2 (aldesleukin) with other agents substantially influence the treatment of renal cell carcinoma (Schmidinger *et al.*, 2004). Recombinant IFN-α2 has beneficial effects in about 30% of patients with well-compensated chronic hepatitis C (Perry and Wilde, 1998). A mainstay in multiple sclerosis treatment is IFN-β. It decreases the progression of disability in multiple sclerosis patients by 30% and reduces relapse rate by 30–50% (Clerico *et al.*, 2007). Highly appreciated is the prophylactic, long-lasting effectiveness of IFN-γ to reduce infections in patients with chronic granulomatous disease (Marciano *et al.*, 2004).

It is supposed that poor efficacy of cytokine and anti-cytokine therapies may be in part due to unfavourable bioavailability and pharmacokinetic profile of the agents. In order to improve these parameters, great attention is paid to pharmaceutical modifications of drugs. One of the most frequently applied approaches is the pegylation of cytokines and anti-cytokine monoclonal antibodies (mAb). It has been successfully applied to IFN-α (peginterferon α2a, peginterferon α2b), G-CSF (pegfilgrastim), mAbs against TNF-α (certolizumab pegol) (Blick and Curran, 2007). Pegylated human IL-1 receptor antagonist (IL-1ra) is under development (Yu *et al.*, 2007). Solubility and bioavailability of IFN-β has increased up

to sixfold after replacement of hydrophobic amino acids and cystein by hydrophilic serine in the protein structure (soluferon) (Eisle and von Henneicke, 2007). Another possible variant of pharmaceutical form of cytokine drugs is a binding of cytokines to high-molecular-weight proteins. Fusion of IFNα-2b to human albumin (albinterferon) improves the anti-HCV activity of IFN and extends its elimination half-time as compared with pegylated IFN. Reduced dosing frequency and improved tolerability and compliance have thus been achieved (Subramanian *et al.*, 2007). The cytokine-fusion platform can facilitate a specific tissue targeting of cytokines. For example, the therapeutic potential of IL-10 to treat liver cirrhosis may be enhanced through its fusion with manose-6-phosphate that binds to specific receptors on activated hepatic stellate cells (Rachmawati *et al.*, 2007).

However, it remains unlikely that the therapeutic usage of any individual cytokine can provide complete resolution of the disease. The major limitation is the pleiotropic nature of cytokines and integrated alterations within the cytokine network in diseased organism. The enhancement of efficacy of immunotherapeutic treatments may therefore lead only through more complex and novel strategies.

A promising approach how to overcome the drawbacks of systemic administration of cytokines, that is, to enhance therapeutic effectiveness of cytokines and decrease their toxicity, might be a cytokine gene therapy. In principle, cytokine genes in viral vectors are transduced into cells (e.g. tumour cells, fibroblasts, macrophages) or tissues. Cytokines are then produced locally, at the sites of injury. Preclinical studies have confirmed a proof-of-principle in animal models of disease, using various cytokines (Hao and Shan, 2006). The IFN-α gene therapy has proved effective in a mouse model of human superficial bladder cancer (Adam *et al.*, 2007). Administration of adenoviruses genetically manipulated to express IL-4 or IL-13 cytokine genes results in antiangiogenic effects in adjuvant-induced arthritis in rats (Haas *et al.*, 2006; Haas *et al.*, 2007). The field is now at the early stage of moving towards human trials (Loisel-Meyer *et al.*, 2008).

It should be recognized that any cytokine is probably a double-edge sword meaning both beneficial and detrimental effects to human health.

For example, enhanced levels of pro-inflammatory cytokines, such as IFN-γ, TNF-α, TNF-β, IL-1, IL-6 and IL-12, have been suggested to play a major role in the development of tissue damage in autoimmune diseases (La Cava and Sarvetnick, 1999). The IFN-γ treatment of patients with multiple sclerosis may induce exacerbations of the disease (Panitch *et al.*, 1987). Increased production of IFN-γ has been found to precede clinical attack of multiple sclerosis (Beck *et al.*, 1988). Also IFN-α is an important inducer of autoimmunity. Nearly 20% of patients with malignant tumours and receiving long-term treatment with IFN-α eventually manifest an autoimmune disease, including systemic lupus erythematosus (Rönnblom *et al.*, 2006). A frequent problem seen with IFN-α (not IFN-γ) therapy is induction of thyroid autoantibodies (Ioannou and Isenberg, 2000).

Enhanced levels of IFNs, IL-1, IL-6 and TNF-α are associated with the development of serious episodes of depression (Corcos *et al.*, 2002). IL-2 is a major producer of vascular leak syndrome (Gallagher *et al.*, 2007). Although IL-1 does not produce vascular leak syndrome, vasodilation and hypotension are the dose-limiting toxicities of IL-1 (Oppenheim *et al.*, 1997). Systemic IL-1 markedly enhances ischaemic brain injury via release of neutrophils into circulation, neutrophil adhesion to injured cerebrovasculature and central nervous system invasion, and cell death via activation of matrix metalloproteinase-9. IL-1 can promote metastatic spread as observed in tumour-bearing mice (Bani *et al.*, 1991). Tumour progression is also associated with chemokine monocyte chemoattractant protein (MCP)-1/CCL2, a key factor attracting macrophages to tumours. It has been shown that low to intermediate levels of the chemokine contribute to melanoma development (Gazzaniga *et al.*, 2007). IL-6 is known to have protective effects on survival of neurons. On the other hand, it may be associated with degeneration and cell death in neurological disorders such as Alzheimer's disease (Gadient and Otten, 1997). One of the many biological activities of IL-6 is up-regulation of the hepcidin. This peptide hormone in turn inhibits the supply of iron into plasma. The cumulative deficit of iron is then manifested as anaemia of inflammation, known as anaemia of chronic disease (Ganz and Nemeth, 2006). The immunosuppressive effects of IL-10, promising in the treatment of autoimmunity, are supposed to be one of the mechanisms that contribute to the escape of tumour cells from the local immunosurveilance (Kim *et al.*, 1995). IL-17 is essential in anti-microbial defence of the host, but it promotes bone destruction in arthritis, and augments the activity of osteoclastogenic cytokines TNF-α and IL-1β (Yu and Gaffen, 2008). It enhances angiogenesis and increases *in vivo* growth of human non-small cell lung cancer (Numasaki *et al.*, 2005).

Prospective candidates for drug development

Chemokines and chemokine receptors

A number of compounds, which are able to antagonize the chemokine receptors, have been suggested as promising drug candidates (Onuffer and Horuk, 2002; Houshmand and Zlotnik, 2003).

The important targets for drug development are chemokine receptors CXCR1 and CXCR2, which bind many CXCL chemokines including IL-8/CXCL8. They are involved in etiopathogenesis of diseases, such as sepsis, atherosclerosis, rheumatoid arthritis, psoriasis and chronic obstructive pulmomary disease. A non-competitive allosteric blocker of these receptor is benzeneacetamide reparixin (syn. repertaxin), which reduces the IL-8/CXCL8-mediated adhesion of polymorphonuclear cells. It is currently clinically investigated for the use in the prevention of ischaemia/reperfusion injury in organ transplantation (Casilli *et al.*, 2005). The function of CXCR1 and CXCR2 receptors is also efficiently antagonized by 3,4-diamino-2,5-thiadiazole-1-oxides (Biju *et al.*, 2008).

The chemokine receptor CXCR3 is involved in rheumatoid arthritis, multiple sclerosis, psoriasis and allograft rejection. The CXCR3 ligands are chemokines MIG/CXCL9, IP-10/CXCL10 and I-TAC/CXCL11. Several compounds of different chemical classes that potently antagonize the action of IP-10/CXCL10 and I-TAC/CXCL11 at the human CXCR3 receptor have recently been discovered (VUF10472, VUF10085/,

VUF5834, VUF10132, TAK-779) (Verzijl *et al.*, 2008). Novel di-substituted cyclohexanes, effective in nanomolar concentration, are antagonists of CCR2 receptor (Cherney *et al.*, 2008). A series of bipiperidinyl carboxylic acid amides have proved to be potent and selective antagonists of the chemokine receptor CCR4. They might be useful in asthma, allergy, diabetes and cancer (Kuhn *et al.*, 2007). A promising candidate for treatment of HIV-1 infection is the CCR5 receptor antagonist vicroviroc, an analogue of pyrimidine, 5-({4-[(3S)-4-{2-methoxy-1-[4-(trifluoromethyl)phenyl]ethyl}-3-methylpiperazin-1-yl]-4-methylpiperidin-1-yl}carbonyl)-4,6-dimethylpyrimidine (Strizki *et al.*, 2005). Another co-receptor of HIV entry in cells is the chemokine receptor CXRC4. A number of new antagonists of CXCR4 have been identified. The most attractive of them are bicyclam derivatives (Grande *et al.*, 2008).

There are only a few compounds known to directly inhibit synthesis of chemokines. One of them is bindarit, 2-methyl-2-[[1-(phenylmethyl)-1H-indazol-3yl]methoxy]propanoic acid. It selectively inhibits production of the monocyte chemotactic proteins MCP-1/CCL2, MCP-2/CCL8 and MCP-3/CCL7. This effect along with inhibition of TNF-α is a plausible explanation for therapeutically promising anti-inflammatory effects of bindarit in experimental models of pancreatitis, arthritis, lupus nephritis and colitis (Bhatia *et al.*, 2008; Mirolo *et al.*, 2008). The sub-antimicrobial doses of macrolide antibiotics (clarithromycin, roxithromycin, azithromycin, erythromycin) have been found effective in treatment of asthma, diffuse panbronchiolitis, inflammatory bowel disease and arthritis. It has been suggested that beneficial effects may be due to the suppression of cytokines, including chemokines IL-8/CXCL8 and MIP-1α/CCL3 (Shinkai *et al.*, 2008).

Agonists of toll-like receptors

A special class of agents with prevailing stimulatory effects on production of IFNs are ligands of toll-like receptors (TLRs). The TLRs belong to a superfamily of pattern-recognition receptors playing a crucial role in the detection of molecular patterns of extracellular and intracellular pathogens. So far, 10 members of TLR family have been revealed in humans. The endosomally localized TLR9 recognizes unmethylated CpG (cytosine-phosphate-guanine dinucleotide) motifs of bacterial and viral DNA. This leads ultimately to rapid activation of innate immune responses. A number of phosphorothioate-modified oligodeoxynucleotides with immunostimulatory sequences (CpG ODNs) have been synthesized and used in clinical trials I–III. They target diseases such as hepatitis B, hepatitis C, influenza, anthrax, asthma, allergy, non-Hodgkins lymphoma, melanoma and refractory solid tumours. The agonists of the TLR9 are major activators of type 1 IFNs (IFNα/β). They can produce other cytokines, for example, IFN-γ, IL-6, IL-10 and IL-1ra, as well (Verthelyi *et al.*, 2001; Dalpke *et al.*, 2002; Kandimalla *et al.*, 2005; Krieg, 2006). Therapeutic potential is also possessed by agonists of other TLRs, such as imidazoquinoline derivatives imiquimod and resiquimod. These agents act through the TLR7 and TLR8. Imiquimod was initially developed as an antiviral agent, and has been approved as a widely used immune response modifier for topical treatment of external genital warts, actinic keratoses and superficial basal cell carcinomas (Gaspari, 2007). Imidazoquinoline derivatives are inducers of IFNs IFN-α and IFN-γ. They also activate secretion of other cytokines (IL-1β, IL-6, TNF-α, IL-12p40) and chemokines (IL-8/CXCL8, MIP-1α/CCL3 and MCP-1/CCL2) (Gupta *et al.*, 2004; Thomsen *et al.*, 2004). On the other hand, imiquimod inhibits its production of Th2 cytokines IL-4 and IL-5 (Wagner *et al.*, 1999). TLR7 can be activated by certain guanosine analogues, such as 7-thia-8-oxoguanosine and 7-deazaguanosine. They stimulate secretion of IFN-α/β, IFN-γ, IL-6, IL-12 and TNF-α (Lee *et al.*, 2003).

Suppressors of cytokine signalling

Except of having physiological roles in developing organism (Kile and Alexander, 2001), members of the cytokine signalling (SOCS) family of intracellular proteins (SOCS1–7 and CIS) possess crucial roles in the negative regulation of activity of many cytokines. They act through association with Jak-STAT signalling pathways (Yasukawa *et al.*, 2000; Krebs and Hilton, 2001). SOCSs are rapidly induced by various cytokines, for example, IL-1β, IL-6, IFN-γ (Dogusan *et al.*, 2000), IFN-α (Wang *et al.*, 2000) and IL-10 (Cassatella *et al.*, 1999).

The expression of SOCSs can be modulated by various physiological mediators. SOCS-1 is up-regulated by thrombopoietin (Wang *et al.*, 2000). Phosphorylation of SOCS-3 is induced by insulin (Peraldi *et al.*, 2001), up-regulated by growth hormone while it is down-regulated by glucocorticoids (Paul *et al.*, 2000). SOCS proteins play an important role in differentiation of Th1, Th2, Th17 and Treg cells. They are thus involved in diseases of immune etiopathogenesis (Yoshimura *et al.*, 2007). SOCS3 expression is tightly correlated with pathology of asthma and atopic dermatitis. It has been suggested as a new therapeutic target for the development of antiallergic drugs (Seki *et al.*, 2003). The SOCS3 therapy may be useful in the treatment of cancer (He *et al.*, 2003), the SOCS1 therapy in type 1 diabetes (Flodström-Tullberg *et al.*, 2003). Both SOCS1 and SOCS3 have been suggested as factors involved in the resistance to IFN therapy of hepatitis C infection (Vlotides *et al.*, 2004; Imanaka *et al.*, 2005).

Both positive and negative pharmacological manipulation of SOCS proteins would be desirable, although there are no special drugs available in this field. A promising approach is the development of SH_2 domain inhibitors targeting protein tyrosine kinase signalling pathways involved in mechanism of SOCS action (Machida and Mayer, 2005). Interestingly, acetylsalicylic acid inhibits the STAT6 signalling pathways mediated by IL-4 and IL-13. This may be a mechanism of beneficial effects of aspirin and salicylate treatment of allergic diseases, including asthma (Perez *et al.*, 2002). The synthetic cannabinoid derivative PRS-211,092 devoid of psychotropic activity stimulates expression of SOCS1 and SOCS3, cytokines IL-6 and IL-10, and inhibits production of IFN-γ, TNF-α, IL-1β, IL-2 and MCP-1/CCL2 (Lavon *et al.*, 2003).

Inhibitors of cytokine maturation

Certain cytokines are produced in a form of precursors that must be further processed to become mature cytokines. The

process of maturation is mediated by various endogenous factors. For example, the caspase-1 is important in a chain of proteolytic transformations of IL-1β precursor (pro-IL-1β) to mature IL-1β (Beuscher *et al*., 1990). It also participates in the processing of the IL-18 precursor (pro-IL-18) to fully active IL-18 (Shtrichman and Samuel, 2001). Caspase 3 is involved in the final synthesis of immunomodulatory IL-16 protein from the 80 kD precursor, pro-IL-16 (Zhang *et al*., 1998). The regulatory cytokine TGF-β is formed as prepro- and pro-TGF-β precursors, requiring activation via a cascade of processes including proteolytic activation (Li *et al*., 2006). TNF-α is cleaved from the 26 kDa membrane-bound molecule to the active 17 kDa form. This is done by the TNF-α-converting enzyme (TACE; also referred to as a disintegrin and metalloproteinase 17, ADAM17) (Tsuji *et al*., 2002). The development of specific agents that would target these processes could be of interest.

So far several inhibitors of TACE were revealed. Marimastat, *N*-[2,2-dimethyl-1-(methylcarbamoyl) propyl]-2-[hydroxy-(hydroxycarbamoyl)methyl]-4-methyl-pentanamide, almost completely inhibits the lipopolysaccharide-induced soluble TNF-α production (Tsuji *et al*., 2002). TACE has become a validated therapeutic target for the development of oral TNF-α inhibitors. Very potent is a novel agent TMI-1, (2R, 3S)-2-([[4-(2-butynyloxy)phenyl]sulfonyl]amino)-N,3-dihydroxybutanamide. It inhibits the spontaneous release of TNF-α in human synovium tissue explants from patients with rheumatoid arthritis. TMI-1 effectively reduces adjuvant-induced arthritis in rats (Zhang *et al*., 2004).

Natural compounds – botanicals

Natural products, notably composite plant products (botanicals) have long been recognized as anti-cancer supportive remedies (Diwanay *et al*., 2004), and anti-infectious agents (Cowan, 1999) including HIV (Asres *et al*., 2005). Their beneficial effects may be at least partially mediated by multiple interventions with cytokine expression (Spelman *et al*., 2006). Herbal and other natural products thus represent a rich source of potential drugs including immunomodulatory agents. A huge effort is presently being done to reconcile the healing experience of traditional medicines with Western medical practice and research (Patwardhan and Gautam, 2005). The search for new therapeutic means is greatly facilitated by recent extensive progress in phytochemistry, analytical biochemistry, biochemistry and bio-analytical methods allowing isolation and identification of the bioactive principles in botanicals (Gullo *et al*., 2006). These approaches should hopefully overcome the problems inherent to herbal medicines, that is, standardization of the chemical content, their possible contamination with heavy metals, quality of the raw material, etc. (Khan, 2006). The following few examples should be taken as an un-exhaustive demonstration of the vast range of immune activities that many chemically identified compounds, isolated from the original herbal remedies, may provide.

Many flavonol compounds, such as kaempferol, quercetin and, more potently, fisetin, luteolin and apigenin, have been revealed to substantially inhibit production of Th2 cytokines IL-4, IL-5 and IL-13 (not IL-6 and IL-8/CXCL8) by human basophils (Higa *et al*., 2003; Hirano *et al*., 2004).

Steroidal lactones isolated from *Withania somnifera* (withanolides) have been reported to induce the Th1 (IFN-γ, IL-2), but not Th2 (IL-4) cytokines (Bani *et al*., 2006). Sesquiterpene lactone of guianolide-type thapsigargin from *Thapsia garganica* is a potent inducer of IFN-γ by human peripheral blood mononuclear cells (Kmoníčková *et al*., 2008). Selective affinity to the Th1 immune response is characteristic for naphthopyran derivatives isolated from *Eleuthrine americana*. While isoleutherin activates production of IFN-γ and IL-2 in $CD4^+$ Th mouse cells, eleutherinol inhibits the both (Hong *et al*., 2008).

Another inducer of IFN-γ is melanin that is present in many botanicals (e.g. *Nigella sativa*) traditionally used as immune enhancers. It also stimulates production of IL-6, and TNF-α by human peripheral blood mononuclear cells (El-Obeid *et al*., 2006). However, opposite effects, that is, inhibition of TNF-α, IL-1β, IL-6 and IL-10 (but not GM-CSF), have been observed with synthetic melanin in lipopolysaccharide-stimulated human peripheral blood mononuclear cells (Mohagheghpour *et al*., 2000).

Botanical agents, such as proanthocyanidins from *Vitis vinifera*, silymarin from *Silybum marianum* and polyphenols from *Camelia sinensis*, are inducers of IL-12 and suppressors of IL-10. These effects have been suggested as a plausible mechanism of chemoprotection against UV-induced immune suppression and photocarcinogenesis (Katiyar, 2007).

A number of natural compounds, including polyphenols (e.g. resveratrol, quercetin, luteolin, hesperetin, kaempferol, scopoletin, aucubin, nardostachin, honokiol), alkaloids (lycorine), terpenes (acanthoic acid, tanshinone), sterols (guggulsterol) and other chemical classes, have been revealed as inhibitors of production of TNF-α, IL-1β and IL-6 (Paul *et al*., 2006). These pro-inflammatory cytokines also are down-regulated by a polyphenol curcumin from *Curcuma longa* (Gonzales and Orlando, 2008). The mechanism of action is obviously inhibition of the TLR4 signalling induced by lipopolysaccharide (Youn *et al*., 2006).

Potent inhibitors of TGF-β production are emodin6-methyl-1,3,8-trihydroxyanthraquinone from *Rheum emodi* (Wang *et al*., 2007) and magnolol, 4-allyl-2-(5-allyl-2-hydroxyphenyl)phenol from *Magnolia officinalis* (Kim *et al*., 2007).

Fungal metabolites isolated from mycelia of *Verticimonosporium ellipticus*, *bis*-thiodiketopiperazines (emestrins) and cytochalasins are potent antagonists of chemokine receptor CCR2, a receptor for MCP-1/CCL2. The compounds are thus interesting agents for treatment of inflammatory processes associated with rheumatoid arthritis, multiple sclerosis and atherosclerosis (Herath *et al*., 2005).

A special position among natural products is possessed by a widely used coffee (caffeine) and relatively widely abused cannabis (cannabinoids). Tetrahydrocanabinol (THC), the major active constituent of marijuana, is recognized for its general immune suppressive activity. THC inhibits production of TGF-β (Gardner *et al*., 2002), TNF-α, GM-CSF, chemokines IL-8/CXCL8, MIP-1α/CCL3, MIP-1β/CCL4 and RANTES/CCL5 (Srivastava SrivastavaB *et al*., 1998), and Th1 cytokines IFN-γ, IL-12 (Newton *et al*., 2004) and IL-2 (Condie *et al*., 1996). However, cannabinoids inhibit the Th2 immune response as well. *In vivo* administration of cannabinol or THC attenuates the elevation of IL-4, IL-5 and IL-13 steady-state

mRNA expression elicited by ovalbumin challenge in the mouse lungs. These data suggest that cannabinoids might be beneficial in the treatment of allergic airway disease (Jan *et al.*, 2003). The THC-induced inhibition of cytokines probably does not depend on CB_1 or CB_2 cannabinoid receptors (Puffenbarger *et al.*, 2000). The major non-psychoactive cannabinoid in marijuana, cannabidiol suppresses secretion of all IFN-γ, IL-2 and IL-4 (Jan *et al.*, 2007).

The plant cannabinoids cannabidiol, cannabigerol, cannabichromene, cannabidiol acid and THC have been reported to supress tumour growth, the most effective being cannabidiol (Ligresti *et al.*, 2006). However, there also are opposite findings. The immune inhibitory cytokines IL-10 and TGF-β have been found up-regulated at both the tumour site and in the spleens of THC-treated mice. It has been suggested that the THC may promote the tumour growth by inhibiting antitumour immunity through the CB_2 receptor-mediated cytokine-dependent pathway (Zhu *et al.*, 2000).

The alkylamides (alkamides) from *Echinacea,* dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide and dodeca-2E,4E-dienoic acid isobutylamide, bind to the CB_2 receptor more strongly than the endogenous cannabinoids. Similar to the endogenous cannabinoid anandamide, they up-regulate constitutive IL-6 expression in human whole blood and inhibit TNF-α, IL-1β and IL-12p70 expression (Raduner *et al.*, 2006).

Caffeine possesses prominent cytokine-inhibitory effects. It suppresses production of all Th1 (IL-2, IFN-γ), Th2 (IL-4, IL-5) and T-regulatory (IL-10) cytokines (Horrigan *et al.*, 2006).

Probiotics

Probiotics are defined as 'live organisms which when consumed in adequate numbers confer a health benefit on the host' (Guarner and Schaafsma, 1998). Probiotics are typically lactic acid bacteria selected from the gut flora that are resistant to stomach acid and bile. They are mainly used for prevention and therapy of various gastrointestinal diseases (Damaskos and Kolios, 2008). The example of an effective probiotic therapy is the treatment of diarrhea caused by rotavirus infection in children (Saavedra, 2000). Lactobacilli have been demonstrated beneficial in reducing the urinary tract infections and bacterial vaginosis (Hoesl and Altwein, 2005), atopic dermatitis in children (Kalliomäki *et al.*, 2003), and pouchitis associated with colon surgery in ulcerative colitis (Cottone *et al.*, 2006).

Bacterial probiotic strains enhance the Th1 immune response in inducing secretion of IFN-γ both *in vitro* (Shida *et al.*, 2006) and *in vivo* in humans (Meyer *et al.*, 2007). Probiotics substantially elevate cytokines supporting the Th1 immune response, such as IL-12, IL-18 and pro-inflammatory cytokines TNF-α and IL-1 (Miettinen *et al.*, 1998; Cross *et al.*, 2004). The type I IFNs (IFN-α/β) have remained uninfluenced after *Lactobacillus casei* strain Shirota, or *Escherichia coli* Nissle and *E. coli* 2282 (Cross *et al.*, 2004). The Th2 cytokine IL-4 was either uninfluenced in humans *in vivo* (Meyer *et al.*, 2007) or, together with IL-5, down-regulated by oligodeoxynucleotide BL07S from a probiotic strain of *Bifidobacterium longum* in a murine model (Takahashi *et al.*, 2006). Production of another Th2 cytokine IL-6 by small intestinal epithelial cells was enhanced by a milk fermented with *Lactobacillus helveticus* R389 (Vinderola *et al.*, 2007), and by other types of lactobacilli, *Lactobacillus rhamnosus* E509, E522 and *Lactobacillus bulgaricus* E585 in human peripheral blood mononuclear cells (Miettinen *et al.*, 1998). The secretion of the regulatory and immunosuppressive cytokine IL-10 was activated by many types of probiotic bacteria (Shida *et al.*, 2006; Meyer *et al.*, 2007). On the other hand, no changes in production of the regulatory cytokine TGF-β were observed (Cross *et al.*, 2004). Comensal bacteria with probiotic properties, *Bifidobacterium infantis* and *Lactobacillus salivarius*, stimulated secretion of IL-10 and TNF-α, and decreased secretion of IL-8/CXCL8 in human intestinal epithelial cells (O'Hara *et al.*, 2006).

Active principles of probiotics are poorly understood. Unfortunately, the controlled clinical studies in this area are still sparse, and newly performed ones are urgently needed.

Modulation of cytokine secretion by physiological mediators

Endogenous neurotransmitters, second messengers and other mediators of physiological functions are important regulators of cytokine production. Special reviews have been devoted to the effects of adenosine (Abbracchio and Ceruti, 2007; Haskó *et al.*, 2007), α- and β-adrenergics (Haskó and Szabó, 1998), histamine (Packard and Khan, 2003), serotonin and nicotine (Cloëz-Tayarani and Changeux, 2007), cannabinoids (Klein *et al.*, 2003; Massi *et al.*, 2006), melatonin (Carrillo-Vico *et al.*, 2005) and glucocorticoids (Elenkov, 2004).

The effects may be due to the widespread expression of the respective receptors on the cells of immune system. The dopamine D2 and D3 receptor subtypes have been detected in lymphocytes (Ghosh *et al.*, 2003). Macrophages contain both α- and β-adrenoceptors (Miles *et al.*, 1996). Human peripheral blood mononuclear cells express mRNAs for serotonin receptor types/subtypes $5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, $5\text{-}HT_{1E}$, $5\text{-}HT_{2A}$, $5\text{-}HT_3$, $5\text{-}HT_4$, $5\text{-}HT_6$ (Yang *et al.*, 2006). Dendritic cells express the mRNA for all H_1, H_2 and H_3 histamine receptors (Idzko *et al.*, 2002). Cholinergic muscarinic receptor subtypes M_2, M_3, M_4 and M_5 have been identified in human peripheral blood lymphocytes (Tayebati *et al.*, 2001; Ricci *et al.*, 2008). Immune cells also express the cannabinoid CB_2 receptor (Galiegue *et al.*, 1995), and opioid μ3, κ and δ receptors (Wybran *et al.*, 1979; Wick *et al.*, 1996; Welters *et al.*, 2000). All A_1, A_{2A}, A_{2B} and A_3 adenosine receptors are present on monocytes and macrophages (Haskó *et al.*, 2007). Prostanoid receptors EP_1, EP_2, EP_3 and EP_4 are expressed on human macrophages (Ying *et al.*, 2004; Ratcliffe *et al.*, 2007). Intracellular receptors binding glucocorticoids are present in macrophages and monocytes (Werb *et al.*, 1978). Direct modulation of immune cells by oestrogen is facilitated by the presence of oestrogen receptors in all dendritic cells, macrophages and B lymphocytes (Nalbandian and Kovats, 2005).

Both stimulatory and inhibitory effects of distinct endogenous receptor ligands on cytokine production have been observed. The characteristic feature of activation of adenosine receptors is the inhibition of production of Th1 cytokines (IFN-γ, IL-2) and TNF-α, and stimulation of IL-10. Similar

effects are produced by prostaglandins and β_2-adrenoceptor agonists (Zídek, 1999). Data on regulation of cytokine secretion by other physiological mediators are largely conflicting. Activation of melatonin receptors may be ineffective (Di Stefano and Paulesu, 1994), stimulatory (Liu *et al.*, 2001) or inhibitory (Raghavendra *et al.*, 2001) with respect to the TNF-α secretion. Production of IL-10 has been reported both stimulated (Raghavendra *et al.*, 2001) and inhibited (Kühlwein and Irwin, 2001) by melatonin. Whereas suppression of TNF-α and up-regulation of IL-10 is usually produced by glucocorticoids, no effects on production of these cytokines have also been observed (Miyazaki *et al.*, 2000; Richards *et al.*, 2000).

The inconsistencies may arise from a variety of reasons. Obviously, the origin and type of cells are of a paramount importance. In dependence on the clone of human T cells, histamine does not influence, inhibit or enhance production of IFN-γ (Krouwels *et al.*, 1998). The strongly inhibited expression of IFN-γ and IL-2 genes by histamine has been found preceded by their activation early during immune stimulation (Arad *et al.*, 1996). Isoproterenol, the agonist of β-adrenergic receptors, inhibits the lipopolysaccharide-induced production of IL-6 by rat renal macrophages (Nakamura *et al.*, 1999). In contrast, it up-regulates the IL-6 production by rat thymic epithelial cells (von Patay *et al.*, 1998). Cannabinoids have been found unable to change serum levels of IL-10 in multiple sclerosis patients (Katona *et al.*, 2005), while cannabidiol inhibits IL-10 in mouse peritoneal macrophages (Sacerdote *et al.*, 2005). It should also be distinguished whether the results have been obtained from experiments *in vitro*, *ex vivo* or *in vitro*. Despite of many experimental findings, clear-cut conclusions cannot be drawn in many cases, and mechanisms of the action remain to be elucidated.

Interaction of cytokines with drug pharmacodynamics and pharmacokinetics

Interference of cytokines with cytochrome P450

The mixed-function oxidase system of cytochromes P450 (CYP) is responsible for the metabolism of a wide variety of drugs and their metabolites as well as for biosynthesis of endogenous compounds such as steroid hormones. The study of interactions between cytokines and drug metabolism was initiated by findings showing that many bacteria and their immune-active products can influence drug metabolism. Depression was observed after the treatment of animals with Freund's complete adjuvant (Whitehouse and Beck, 1973), Bacillus Calmette-Guérin (Farquhar *et al.*, 1976), and *Corynebacterium parvum* (Giampietri *et al.*, 1981). It was soon found that the effect resulted from enhanced production of cytokines (Descotes, 1985).

Effects of Th1 cytokines. It has been suggested that depression of CYP activities may be a common property of all IFN inducers. Changes in production of IFN-γ and/or other cytokines are tightly associated with down-regulation of CYPs and other enzymes resulting in altered bioactivation and detoxication of drugs (Prandota, 2005). The IFN-γ alone (Singh *et al.*, 1982) and IFN-γ-inducing agents, such as tilorone (Leeson *et al.*, 1976) and polyriboinosinic acid : polyribocytidylic acid (polyI : C) (Robbins and Mannering, 1984), depress the *in vivo* activity of the CYP system. The CYP3A1 and CYP3A2 mRNA, and CYP2C11 proteins have been found reduced by recombinant IFN-γ in cultured rat hepatocytes (Tapner *et al.*, 1996). The type I IFN (IFN-α; peginterferon alfa-2a) decreases the clearance of theophylline. The inhibition of the *de novo* synthesis of human CYP1A2 has been suggested as a plausible explanation of this effect (Perry and Jarvis, 2001). IFN-α/β produced by polyI : C augment the rate of loss of CYP1A1 and CYP1A2 in rat liver (Delaporte and Renton, 1997). The decrease in activity of CYP1A2 is associated with occurrence of side effects in patients treated with IFN-α2b (Islam *et al.*, 2002). In variance with these data, chronic administration of IFN-α in patients with hepatitis C has not been found to change the *in vivo* activities of CYP1A2 and CYP3A (Pageaux *et al.*, 1998). IL-2 decreases the total CYP content and the mRNAs and proteins of CYP2C11 and CYP3A in cultured rat hepatocytes (Tinel *et al.*, 1999). IL-2 monotherapy may be associated with decreased total CYP and monooxygenase activities in patients with hepatic metastases (Elkahwaji *et al.*, 1999).

Effects of Th2 cytokines. IL-4 has been found to increase fivefold the expression of CYP2E1 mRNA in primary human hepatocyte cultures (Abdel-Razzak *et al.*, 1993). IL-6 can down-regulate rat (Muntané-Relat *et al.*, 1995) and human (Jover *et al.*, 2002) CYP3A4 activity, and protein content of CYP1A2, CYP2C11, CYP2B1/2 and CYP3A2 in cultured rat hepatocytes (Carlson and Billings, 1996).

Effects of Treg cytokines. TGF-β1 seems to specifically down-regulate the CYP1 enzymes (CYP1A1, CYP1A2). Constitutive expression of other CYP forms (CYP3A1, CYP2B1/2, CYP2E1) remains unaffected by TGF-β in both humans and rats (Abdel-Razzak *et al.*, 1994; Müller *et al.*, 2000). IL-10 has been found to inhibit CYP4F expression, while IL-1β, IL-6 and TNF-α produce a general inductive response of this enzyme in cultured rat hepatocytes (Kalsotra *et al.*, 2007). IL-10 given to human volunteers significantly decreases CYP3A while no significant changes in CYP1A2 and CYP2D6 activities have been observed (Gorski *et al.*, 2000).

Effects of other cytokines. TNF-α can enhance induction of CYP1B1. On the other hand, it simultaneously suppresses the CYP1A1 expression in rat liver epithelial cells. The CYP1B1 induction has been suggested to be associated with enhanced genotoxic effects of carcinogenic polycyclic aromatic hydrocarbons (Umannová *et al.*, 2008). The pro-inflammatory cytokines TNF-α and IL-1 down-regulate the hepatocyte CYP1A2 in sepsis (Crawford *et al.*, 2004; Wu *et al.*, 2006). TNF-α also decreases protein levels of CYP2B1/2 and CYP3A2 in rat hepatocytes (Carlson and Billings, 1996). It decreases protein levels of CYP2C11 and CYP3A2 in rat liver. The expression of CYP2A1 and CYP2C6 remains unchanged (Nadin *et al.*, 1995). IL-1β has been found to antagonize polycyclic aromatic hydrocarbon-induced CYP1A gene expression (Abdel-Razzak *et al.*, 1994), and to depress expression of CYP2B6, CYP2C9 and CYP3A4 in human hepatocytes

Table 6 Effects of cytokines on expression and activity of distinct forms of cytochrome P450

CYP isoform	*Cytokines*								
	IFN-γ	*IFN-α*	*TNF-α*	*TGF-β1*	*IL-1β*	*IL-2*	*IL-4*	*IL-6*	*IL-10*
1A1		↓	↓	↓	↓				
1A2		↓	↓	↓	↓			↓	
1B1			↑						
2A1			⇔						
2B1/2			↓	⇔	↓			↓	
2B6					↓				
2C11	↓		↓		↓	↓		↓	
2C6			⇔						
2C9					↓				
2D6									⇔
2E1		⇔		⇔			↑		
3A						↓			↓
3A1	↓								
3A2	↓		↓		↓			↓	
3A4					↓			↓	
4F			↑		↑			↑	↓
CYP total	↓					↓			

CYP isoform is: ↓ decraesed, ↑ increased, ⇔ not changed.
References to support the table are cited in section 'Interference of cytokines with cytochrome P450'.

(Assenat *et al.*, 2004). IL-1β treatment of rat hepatocytes decreases levels of protein content of CYP1A2, CYP2C11, CYP2B1/2 and CYP3A2 (Carlson and Billings, 1996). The impairment of CYP synthesis after IL-1 has been suggested to be due to the suppression of hepatic haeme pool (Kihara *et al.*, 1999).

Mixtures of cytokines are usually more effective than single cytokines to alter expression of CYPs and their activities. The down-regulatory effect on human hepatocyte CYP2B6 is produced by a cocktail of IL-1/TNF-α/IFN-γ (Aitken *et al.*, 2008). Mixture of TNF-α and IL-6 decreases the total CYP, CYP2E1, CYP3A2 and CYP2C11 protein contents, and inhibits activities of CYP2E1, CYP3A2 and CYP2G11 in rat liver microsomes (Vuppugalla *et al.*, 2003).

The mechanisms of the interaction of cytokines with CYP protein and activity are not well understood. The prevailing suppressive effects of cytokines on cytochrome P450 metabolizing system can be mediated by cytokine-induced NO, although not necessarily so (Carlson and Billings, 1996; Aitken *et al.*, 2008).

The effects of cytokines on CYP protein content and/or CYP activities are summarized in Table 6. It can be concluded that cytokine-mediated alterations in total CYP content and activities of individual CYP enzymes may be reflected in changes in drug metabolism. These changes can contribute to frequently encountered variability in drug response and augment the risk of adverse drug effects in patients.

Interference of cytokines with P-glycoprotein

Cytokines have been shown to interfere with the intestinal efflux system. One of the important factors of this system is the multidrug resistance (MDR)-associated P-glycoprotein (known as P-gp, MDR1 or ABCB1). IFN-γ dose- and time-dependently reduces cellular uptake of cyclosporine A (but not methotrexate) in human intestinal cells. The effect is associated with activation of P-gp. The activation of efflux system is probably due to IFN-γ-activated nitric oxide production (Dixit *et al.*, 2005). The *ABCB1* gene encoding for P-gp has been found stimulated by IFN-γ also in human macrophages (Puddu *et al.*, 1999). In contrast, cytokines TNF-α (Belliard *et al.*, 2004), IL-1 (Sukhai *et al.*, 2001), IL-2 (Belliard *et al.*, 2002), IL-4 (Tambur *et al.*, 1998) and IL-6 (Hartmann *et al.*, 2001) reduce activity of P-gp. TNF-α plays a pivotal role in the down-regulation of P-gp by endotoxin (Miyoshi *et al.*, 2005). Cytokines may also influence the cerebral and hepatic expression of P-gp (Fernandez *et al.*, 2004).

Interestingly, P-gp is involved in the transmembrane transport of cytokines (e.g. IL-1β, IL-2, IL-4 and IFN-γ) out of the cells (Mizutani *et al.*, 2008).

Conclusions

The cytokine compartment of the immune system has evolved phylogenetically to ensure homeostasis of organisms. Dysbalance in cytokine production is associated with numerous diseases. Both cytokine and anti-cytokine immunotherapies have proved to provide beneficial therapeutic effects. Novel therapeutic strategies targeting the cytokine network are needed to enhance the effectiveness of present immunotherapeutic regimens. Drugs with more specific effects on secretion of cytokines are needed. Studies of prospective drug candidates of both natural and synthetic origin require more complex analysis of the effects within the cytokine network. Possible impact of manipulation of cytokine secretion on pharmacokinetic and pharmacodynamic behaviour of drugs should be more systematically evaluated.

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Conflict of interest

The authors state no conflict of interest.

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