Biochemical Pharmacology 78 (2009) 539–552

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Inflammatory cytokines in vascular dysfunction and vascular disease

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ARTICLE INFO

Article history:
Received 1 February 2009
Accepted 27 April 2009

Keywords:
Interleukins
Oxidative stress
Endothelium
Vascular smooth muscle
Matrix metalloproteinases
Aneurysm
Varicose veins
Hypertension

ABSTRACT

The vascular inflammatory response involves complex interaction between inflammatory cells (neutrophils, lymphocytes, monocytes, macrophages), endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and extracellular matrix (ECM). Vascular injury is associated with increased expression of adhesion molecules by ECs and recruitment of inflammatory cells, growth factors, and cytokines, with consequent effects on ECs, VSMCs and ECM. Cytokines include tumor necrosis factors, interleukins, lymphokines, monokines, interferons, colony stimulating factors, and transforming growth factors. Cytokines are produced by macrophages, T-cells and monocytes, as well as platelets, ECs and VSMCs. Circulating cytokines interact with specific receptors on various cell types and activate JAK-STAT, NF-κB, and Smad signaling pathways leading to an inflammatory response involving cell adhesion, permeability and apoptosis. Cytokines also interact with mitochondria to increase the production of reactive oxygen species. Cytokine-induced activation of these pathways in ECs modifies the production/activity of vasodilatory mediators such as nitric oxide, prostacyclin, endothelium-derived hyperpolarizing factor, and bradykinin, as well as vasoconstrictive mediators such as endothelin and angiotensin II. Cytokines interact with VSMCs to activate Ca^{2+}, protein kinase C, Rho-kinase, and MAPK pathways, which promote cell growth and migration, and VSM reactivity. Cytokines also interact with integrins and matrix metalloproteinases (MMPs) and modify ECM composition. Persistent increases in cytokines are associated with vascular dysfunction and vascular disease such as atherosclerosis, abdominal aortic aneurysm, varicose veins and hypertension. Genetic and pharmacological tools to decrease the production of cytokines or to diminish their effects using cytokine antagonists could provide new approaches in the management of inflammatory vascular disease.

1. Introduction

Inflammation is an essential component of the immune response to pathogens and damaged cells. Potent inflammatory stimuli include infectious agents, mechanical factors, oxygen radicals, immune complexes, angiotensin II (AngII), inflammasomes, heat shock proteins (HSP), cellular microparticles, adipokines, platelet products and coagulation factors. While the inflammatory response provides an important defense mechanism to injurious agent, injury to healthy bystander cells at the inflammatory site could also occur. Constituents of inflammation include circulating immune cells, vascular cells, connective tissue cells, and extracellular matrix (ECM). Acute inflammation is generally detected within minutes or days by the presence of neutrophils and fluid protein exudates. In blood vessels, acute inflammation involves vasodilation, increased vascular permeability, and blood stasis. Cytoskeletal changes in endothelial cells (ECs) lead to disruption of EC junctions and increased vascular permeability. A delayed sustained response involves inflammatory factors such as C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), protease-activated receptor (PAR) signaling, CD40/CD40 ligand interactions and cytokines such as interleukins, tumor necrosis factor-α (TNF-α), and interferon-γ (INF-γ). When ECs undergo inflammatory activation, an increase in the expression of adhesion molecules such as selectins, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) promotes the adherence of the inflammatory cells monocytes, neutrophils, lymphocytes, and macrophages and recruitment of additional cytokines, growth factors and matrix metalloproteinases (MMPs). The delayed inflammatory response

Abbreviations: AAA, abdominal aortic aneurysm; AngII, angiotensin II; BP, blood pressure; CSF, colony stimulating factors; CRP, C-reactive protein (CRP); ECM, extracellular matrix; EC, endothelial cell; EDHF, endothelium-derived hyperpolarizing factor; ET-1, endothelin; HTN, hypertension; IFN, inetrferon; IL, interleukin; MAPK, mitogen-activated protein kinase; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; NO, nitric oxide; NOS, NO synthase; $O_2^{-\bullet}$, superoxide anion; PAI-1, plasminogen activator inhibitor-1; PGI_2, prostacyclin; PKC, protein kinase C; RANTES, regulated on activation, normal T-expressed and secreted; ROS, reactive oxygen species; TGF, transforming growth factor; TNF, tumor necrosis factor; VSMC, vascular smooth muscle cell.

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doi:10.1016/j.bcp.2009.04.029

Table 1
Sources, receptors, cell targets and functions of representative cytokines.

Cytokine	Producing cell/serum level	Receptor	Target	Function
GM-CSF	Th cells, macrophages, ECs, lymphocytes <8 pg/mL	GM-CSFRα, GM-CSFRβ	Progenitor cells, hematopoietic stem cells, neutrophils, macrophages	Growth and differentiation of monocytes, dendritic cells, granulocytes, macrophages, pro-atherogenic
IFN-α	Leukocytes	IFNαR1, IFNαR2	Various	Viral replication, major histocompatibility complex (MHC I) expression
IFN-β	Fibroblasts	IFNβR	Various	Viral replication MHC I expression
IFN-γ	Macrophages, Th1 cells, Tc cells, B-cells, Natural killer (NK) cells, VSMCs	IFNγR1, IFNγR2	Various	Viral replication
			Macrophages, lymphocytes, NK cells, EC, SMC	Pro-inflammatory, promotes Th1 immune responses/secretion of Th1-associated cytokines, inhibits ECM synthesis by SMC
			Macrophages	MHC I expression Pathogen elimination
			Activated B-cells	Ig class switch to IgG_{2a}
			Th2 cells	Proliferation
			VSMCs	Migration, proliferation
			ECM	Remodeling, pro-atherogenic
MIP-1α, MIP-1β	Macrophages	IL-10R2	Monocytes, T-cells	Chemotaxis
TGF-β1, TGF-β2, TGF-β3	T-cells, monocytes	TGF-βR1, TGF-βR2	Monocytes, macrophages	Chemotaxis, IL-1 synthesis
			Activated B-cells	IgA synthesis
			Various	Proliferation, anti-atherogenic
TNF-α	Macrophages, mast cells, NK cells, VSMCs, T- and B-cells <6 pg/mL	TNFR1 (p55), TNFR2 (p75)	Macrophages, Various	Cytokine expression, pro-inflammatory, fever, neutrophil activation, bone resorption, anticoagulant
			Tumor cells	Cell death, tumor necrosis
			ECs	Activate, increase permeability, stimulate adhesion molecules, pro-atherogenic
TNF-β	Th1 cells, Tc cells, platelets, macrophages, Th3, Treg and B-cells, SMC	Type I and type II Ser/Thr kinase receptors	Phagocytes	Phagocytosis, NO production, pro-atherogenic
			ECs, VSMCs, various	Angigenesis, anti-inflammatory; profibrotic; promotes wound healing, suppresses Th1 and Th2 immune responses

leads to ECM deposition, granular tissue formation and connective tissue growth [1,2]. Inflammation is usually terminated when the injurious stimulus is removed and all the mediators are dissipated or inhibited. If vascular inflammation progresses unresolved, it can lead vascular disease. This review will focus on the role of inflammatory cytokines in vascular dysfunction and vascular disease. The review will briefly discuss the various cytokines, their sources, receptors and signaling mechanisms. The effects of cytokines on ECs, VSMCs and ECM will be described. The potential role of cytokines in specific vascular disease such as atherosclerosis, abdominal aortic aneurysm (AAA), varicose veins, hypertension (HTN) and preeclampsia will be discussed. The potential benefits of cytokine antagonists in the management of vascular disease will also be discussed.

2. Classification of cytokines

Cytokines are a diverse group of soluble short acting proteins, glycoproteins and peptides produced by various immune cells and vascular cells, and act in picomolar to nanomolar concentrations to activate specific receptors and modulate the functions of many cells and tissues. Some cytokines may be membrane-bound or associated with ECM, and switching between soluble and membrane forms may be an important regulatory event. Different cell types may secrete the same cytokine, and a single cytokine may act on several cell types (pleiotropy) and produce multiple biological activities depending on the cell type, timing, and context [3]. Cytokines are also redundant in their activity, meaning similar functions can be stimulated by different cytokines (cross-talk) [4]. Because of the cytokines' functional overlap, their pathophysiological role may be difficult to assess. Also, cytokines are often produced in a cascade, as one cytokine stimulates its target cells to make additional cytokines. Cytokines can also act synergistically (two or more cytokines acting together) or antagonistically (cytokines causing opposing activities).

Generally, cytokines can be classified into the following categories (Tables 1 and 2):

- Tumor necrosis factors (TNFs).
- Interleukins (ILs), cytokines made by one leukocyte and acting on other leukocytes.
- Lymphokines, initially thought to be produced exclusively by lymphocytes.
- Monokines, initially thought to be produced exclusively by monocytes.
- Interferons (IFNs), thought to be involved in antiviral responses, and include IFN-α, -β, -γ.
- Colony stimulating factors (CSFs), initially thought to support cell growth in semi-solid media, and include granulocyte G-CSF, monocyte M-CSF, and granulocyte–monocyte GM-CSF.
- Transforming growth factors (TGFs) include TGF-β1, 2, and 3, bone morphogenetic proteins (BMPs), activins and inhibins.
- Chemokines, thought to be involved in chemotaxis. The chemokine superfamily is divided into four subfamilies (XC, CC, CXC, and CX_3C) based on the presence of a conserved cysteine residue at the NH_2 terminus, and variable region "X". The XC