Cytokine and atherogenesis

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Rezumat

Numarul mare de citokine care au fost identificate in procesul de ateroscleroza, impreuna cu numarul mare de receptori de la nivelul macrofagelor, constituie importanti participanti in modificarile lezionale din cadrul aterosclerozei. Combinatia citokinelor prezente in leziuniel aterosclerotice cu receptorii de la nivelul macrofagelor determina interactiunea citokine-macrofage care are rol important in dezvoltarea lezionala aterosclerotica.

Abstract

The numerous cytokines that have been detected in atherosclerosis, combined with the expression of large numbers of cytokine receptors on macrophages, are consistent with this axis being an important contributor to lesion development. The combination of the many cytokines present in atherosclerotic lesions and the abundant cytokine receptors on macrophages is consistent with an important role of cytokine-macrophage interactions in lesion development.

Atherosclerosis is a lifelong disease in which the process of development of an initial lesion to an advanced raised lesion can take decades. According to international statistics, heart disease is the primary cause of morbidity and mortality across all ethnicities and genders. Hypertension, hypercholesterolemia, and diabetes are increasing at alarming rates and many individuals remain undiagnosed and untreated.

Risk factors lead to an environment in which the three principal oxidative systems in the vascular wall are activated: xanthine oxidases, NADH/NAD(P)H, and uncoupled e-NOS.

Inflammatory response is generalized and can be triggered by microbial invaders, mechanical stress, chemical stress, oxidative stress, other.

Inflammatory response includes four basic phenomena: changes in vascular tone of blood vessels, increased oxygen utilization by cells facilitating the response, changes in blood vessel walls (short term: inc. capillary permeability; long term: smooth muscle proliferation), changes in coagulation.

Origination of free radicals/ ROS is absorption of extreme energy sources, ultraviolet light, x-rays, endogenous (oxidative) reactions, enzymatic metabolism of exogenous chemical or drugs.

Atherogenesis can be related to an inflammatory response to endothelial damage:

- Inflammatory/Immune response
- Endothelium
- Cytokines
- Functions of “Good” Cholesterol
- Renin Angiotensin Aldosterone System (RAAS)

An amount of 98% of the current text of the Article was identified to have been lifted from five source which were not referenced.

This table relates only to the type gamma of interferons

TABLE 1. Cytokine regulation of macrophage lipoprotein receptors

Receptor	Cytokine	Effect on Receptor Abundance
Receptors facilitating transport of native lipoproteins into macrophages		
LDL receptor	IFN-γ	↑
	TGF-β	↓
VLDL receptor	IFN-γ	↓
LRP	IFN-γ	↓
	TGF-β	↑
	M-CSF	↔
Receptors facilitating transport of modified lipoproteins into macrophages		
SR-A	IFN-γ	↑
		↓
		↔
	TNF-α	↓
	TGF-β	↓
	IL-4	↑
	IL-6	↓
	GM-CSF	↓
		↑
	M-CSF	↑
CD36	IFN-γ	↔
		↓
	TGF-β1	↓
	IL-4	↑
	M-CSF	↑
LOX-1	TGF-β	↑
		↓
	TNF-α	↑
	IL-4	↑
CXCL16/SR-PSOX	IFN-γ	↑, associated with increased oxidized LDL uptake by THP-1 cells
Receptors that facilitate both lipid entry and efflux in macrophages		
SR-BI	IFN-γ	↓
	TNF-α	↓
	TGF-β1	↓

GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LOX-1, lectin-like oxidized low density lipoprotein receptor-1; LRP low density lipoprotein receptor-related protein; M-CSF, monocyte colony-stimulating factor; SR-A, class A scavenger receptor; SR-BI, scavenger receptor class B type I; SR-PSOX, scavenger receptor that binds phosphatidylserine and oxidized lipoprotein; TGF, transforming growth factor; TNF, tumor necrosis factor.

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Formation of oxidized LDL (ox-LDL) is a key step in the pathogenesis of atherosclerosis. The ox-LDL receptor (LOX-1) is present mostly on the surface of endothelial cells, vascular smooth muscle cells, macrophages, and platelets. LOX-1–mediated ingestion of ox-LDL activates mitogen-activated protein kinases (MAPKs) in the cell, which in turn activate nuclear factor-kB (NF-kB), a transcriptional factor involved in expression of monocyte chemoattractant protein-1 (MCP-1). In turn, MCP-1 leads to adhesion molecule expression.

Ang II, via the AT1 receptor, increases LOX-1 expression. Conversely, ox-LDL, via LOX-1, upregulates the AT1 receptor.

Immune response is more specific than the inflammatory response, Involves memory and specificity, antigen/antibody response and can sustain inflammatory response.

Excessive production of reactive oxygen species overwhelms endogenous

Terminological mistake

antioxidant mechanisms, leading to oxidation of lipoproteins, nucleic acids, carbohydrates, and proteins. The principal target of this oxidative stress is the vascular endothelium, although there may be other targets. Among the functional alterations induced by reactive oxygen species are impairment of endothelium-dependent vessel relaxation (following a reduction in nitric oxide bioavailability), increase in inflammatory mediators, and development of a pro-coagulant vascular surface. Ultimately structural alterations occur, including plaque growth, vascular wall remodeling, decreased fibrinolysis, vascular smooth muscle cell proliferation and migration, and other structural alterations.

Endothelium is more than a plasma barrier. It produces vasoconstrictors (endothelin) and vasodilators (nitric oxide, prostacycline). Have pro-thrombotic, anti-thrombotic and fibrinolytic substances and has an important role in adhesion molecules (platelets, monocytes, lymphocytes).

This table relates only to the type gamma of interferons

TABLE 2. Cytokine regulation of intracellular lipid metabolism in macrophages

Effect	Cytokine	Effect
Cholesterol distribution	IFN-γ	↑ in cholesteryl esters
ACAT-1	IFN-γ	↑
	TGF-β1	↑
	M-CSF	↑
Cholesteryl ester hydrolases	M-CSF	↑
Cholesterol 27-hydroxylase	IFN-γ	↑
Apolipoprotein E secretion	IFN-γ	↓ secretion, due to posttranslational effect
	IL-1	↓ synthesis
	GM-CSF	↓ synthesis
	TNF-α	↑ (only in monocyte, not macrophages)
	TGF-β	↑ secretion
ABCA1	IFN-γ	↓ expression, with Ø in cholesterol efflux
	TGF-β	↑ expression, with ≠ cholesterol efflux
ABCG1	TGF-β	↑
HDL binding	IFN-γ	↓, but in absence of effects on SR-BI
	TGF-β	↓

Journal of Lipid Research Volume 46, 2005

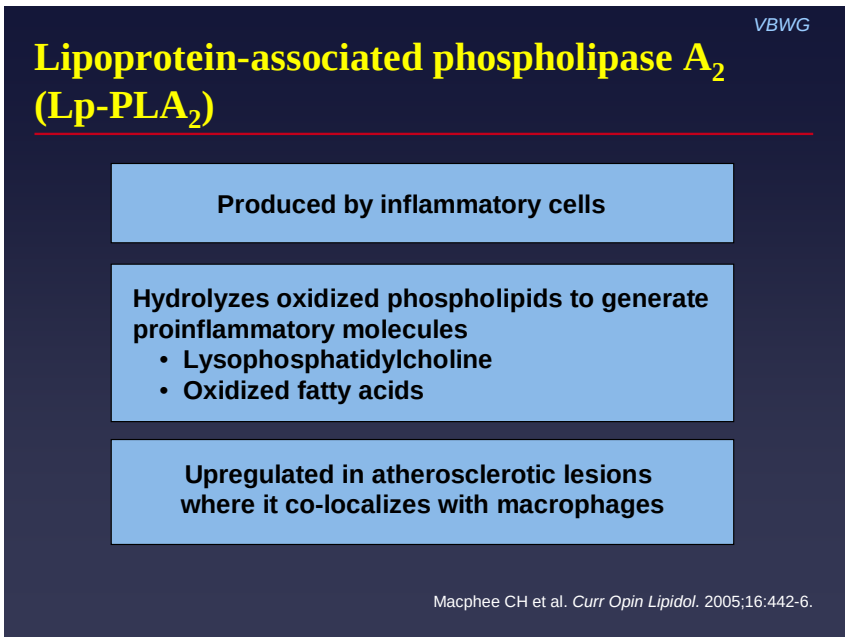
Any of several regulatory proteins, such as the interleukins and lymphokines, that are released by cells of the immune system and act as intercellular mediators in the generation of an immune response."

Bradykinin is a hypotensive tissue hormone which acts on smooth muscle, dilates peripheral vessels and increases capillary permeability. It is formed locally in injured tissue and is believed to play a role in the inflammatory process.

Tumor Necrosis Factor si one of a family of cytokines that has both anti-neoplastic and pro-inflammatory effects

Angiotensin II has pro inflammatory effects - production of ROS, Production of Cytokines and adhesion molecules. Up to 50% of all Angiotensin II is produced in the tissue, independent of the ACE pathway.

Tabel 3.



The above text does not describe IFN-alpha. Tables 1, 2 and 3 do not contain any information about IFN-alpha.

One of the most prominent changes in macrophages after entry into the sub endothelial space of developing atherosclerotic lesions is the engorgement of these cells with lipid. There have been numerous studies to determine the role of specific cytokines in the development of atherosclerosis.

As described above, one cytokine that has been studied extensively in cell culture studies is IFN-alfa, which is also one of the more extensively investigated cytokines in in vivo studies of atherogenesis.

Studies with cultured cells have demonstrated many effects of IFN-alfa on the intracellular accumulation of lipids in macrophages. These findings lead to the notion that IFN-alfa would retard atherosclerosis, especially by minimizing intracellular lipid accumulation in macrophages. In contrast, the effects of IFN- alfa on the development of atherosclerosis in mouse models of the disease have been quite consistent, but they have contradicted the original concept of IFN-alfa being anti-atherogenic.

HDL has anti-inflammatory, anti-oxidative, anti-aggregatory, anti-coagulant and pro-fibrinolytic role.

HDL Inhibits chemotaxis of monocytes, adhesion of leukocytes, endothelial dysfunction, apoptosis, LDL Oxidation, complement activation, platelet activation and Factor X activation.

HDL promotes endothelial cell repair/regeneration, smooth muscle proliferation, synthesis of prostacyclin, synthesis of naturietic peptide, activation of Protein C and Protein S.

Insults to endothelium increases production of AGEs - advanced glycosylation endproducts, reactive oxygen species, hyperinsulinemia, hypertension, activated the rtesp[onses of T-Cells/Lymphocytes, small dense LDL.

Smoking causes intimal injury, promotes oxidation, promotes inflammatory response in respiratory tract, enhances platelet aggregation, promotes vasoconstriction

The authors substituted IFN-gamma, mentioned in the original identified source, with IFN-alpha. This replacement is an error because IFN-alpha has not the same effects with IFN-gamma on lipid accumulation in macrophages.

Diabetes mellitus increases production of AGEs. hyperglycemia induces inflammatory response, frequently co-exists with small dense LDL. Insulin growth factor promotes smooth muscle proliferation

Chronic Infection, possible agents: peridontal disease, chlamydia pneumoniae, Helicobacter pylori, Herpes simplex virus, Cytomegalovirus.

The serum inflammatory markers are homocysteine levels, IL6, Chlamydia titers, Serum amyloids, CRP

Atherogenesis is the result of AND results in sustained chronic inflammation.

Atheroprotective immune innate mechanisms

Regulatory T cells

Produce antiinflammatory/immunosuppressive cytokines

TGF-b

IL-10

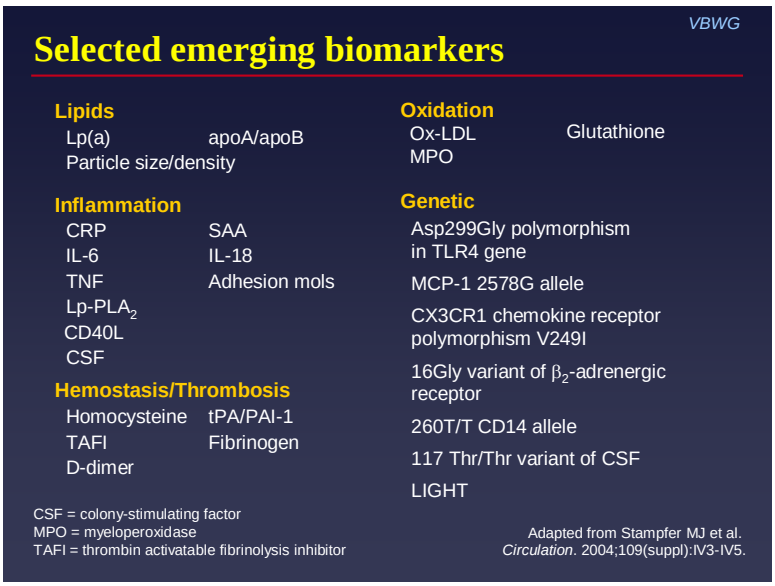
B cells

Spleen B cells; B1 cells

Stimulated by IL-5

Possibly due to production of ”natural” antibodies

Tabel 4.



Oxidative stress has been implicated in mechanisms leading to cell injury in various pathological states of aging process. The levels at which the HSPs are produced depend on age. They are known to help cells dismantle and dispose of damaged proteins. But what proteins are involved and how they relate to aging is still the subject of speculation and study.

Stimulation of various repair pathways by mild stress has significant effects on delaying the onset of various age-associated alterations in cells, tissues and organisms. What role HSPs play in the aging process is not yet clear. Given the broad cytoprotective properties of the heat shock response there is now strong interest in discovering and developing pharmacological agents capable of inducing the heat shock response.

Now there are new perspectives in medicine and pharmacology, and biomedicine and molecules inducing defense mechanism, possible candidates for novel cytoprotective strategies.

Manipulation of endogenous cellular defense represents an innovative approach to therapeutic intervention in preventing agging process.

REFERENCES

1. HEINECKE, J. W. 2003. *Oxidative stress: new approaches to diagnosis and prognosis in atherosclerosis*. Am. J. Cardiol. 91: 12A–16A.
2. VAN BERKEL. 2000. *Role of macrophage-derived lipoprotein lipase in lipoprotein metabolism and atherosclerosis.* Arterioscler. Thromb.Vasc. Biol. 20: E53–E62.
3. WILSON, K., G. L. FRY, D. A. CHAPPELL, C. D. SIGMUND, AND J. D. MEDH. 2001. *Macrophage-specific expression of human lipoprotein lipase accelerates atherosclerosis in transgenic apolipoprotein E knockout mice but not in C57BL/6 mice*. Arterioscler.Thromb. Vasc. Biol. 21: 1809–1815.
4. KOSAKA, S., S. TAKAHASHI, K. MASAMURA, H. KANEHARA, J. SAKAI, G. TOHDA, E. OKADA, K. OIDA, T. IWASAKI, H. HATTORI, ET AL. 2001. E*vidence of macrophage foam cell formation by very low-density lipoprotein receptor: interferon-gamma inhibition of very lowdensity lipoprotein receptor expression and foam cell formation in macrophages*. Circulation. 103: 1142–1147.
5. DAUGHERTY, A., AND D. L. RATERI. 2002. *T lymphocytes in atherosclerosis—the yin-yang of Th1 and Th2 influence on lesion formation*. Circ. Res. 90: 1039–1040.
6. CORTI, R., R. HUTTER, J. J. BADIMON, AND V. FUSTER. 2004. *Evolving concepts in the triad of atherosclerosis, inflammation and thrombosis.* J. Thromb. Thrombolysis. 17: 35–44.
7. B. W. AHN, AND Y. D. JUNG. 2002. *IL-1 beta induces MMP-9 via reactive oxygen species and NF-kappa B in murine macrophage* RAW 264.7 cells. Biochem. Biophys. Res. Commun. 298: 251–256.
8. BUONO, C., C. E. COME, G. STAVRAKIS, G. F. MAGUIRE, P. W. CONNELLY, AND A. H. LICHTMAN. 2003. I*nfluence of interferon-gamma on the extent and phenotype of diet-induced atherosclerosis in the LDLR-deficient mouse*. Arterioscler. Thromb. Vasc. Biol. 23: 454.
9. ISHIBASHI, M., K. EGASHIRA, Q. ZHAO, K. I. HIASA, K. OHTANI, Y. IHARA, I. F. CHARO, S. KURA, T. TSUZUKI, A. TAKESHITA, ET AL. 2004, *Bone marrow-derived monocyte chemoattractant protein-1 receptor CCR2 is critical in angiotensin II-induced acceleration of atherosclerosis and aneurysm formation in hypercholesterolemic mice.* Arterioscler. Thromb. Vasc. Biol. 24: e174–e178.
10. SATA, M., A. SAIURA, A. KUNISATO, A. TOJO, S. OKADA, T. TOKUHISA, H. HIRAI, M. MAKUUCHI, Y. HIRATA, AND R. NAGAI. 2002. H*ematopoietic stem cells differentiate into vascular cells that participate in the pathogenesis of atherosclerosis.* Nat. Med. 8: 403–409.
11. KANTERS, E., M. PASPARAKIS, M. J. J. GIJBELS, M. N. VERGOUWE, I. PARTOUNS, HENDRIKS, R. J. A. FIJNEMAN, B. E. CLAUSEN, I. FORSTER, M. M.KOCKX, K. RAJEWSKY, ET AL. 2003. I*nhibition of NF-kappa B activation in macrophages increases atherosclerosis in LDL receptordeficient mice.* J. Clin. Invest. 112: 1176–1185.

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The works mentioned in References section cannot be found in the current text. The original identified sources are not mentioned at this References section.