Pro-inflammatory Cytokines in Atherosclerosis

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Apart from traditional risk factors, chronic "low grade" inflammation has been implicated in the pathogenesis of atherosclerosis and in cardiovascular disease. Inflammatory cells including mononuclear leukocytes appear, and several pro-inflammatory cytokines including tumor necrosis factor-alpha, interleukin-1, IL-6 and others are abundantly produced by these cells early in the arterial wall [1-4]. Accelerated atherosclerosis and increased incidence of CVD have been associated with chronic inflammatory diseases, such as rheumatoid arthritis. In addition, the pro-inflammatory cytokines described above exert increased production in these diseases [2,3,5,6].

TNFα and IL-6 seem to be key players in vascular inflammation underlying atherosclerosis [2,4,5,7-10]. Increased production of these cytokines has been associated with the incidence of heart failure, as well as with insulin resistance, dyslipidemia and obesity [7]. Both TNFα and IL-6 are predictive of current as well as future CVD and cardiovascular mortality [11-13]. TNFα has been associated with increased common carotid intima media thickness [14]. These cytokines have been implicated in the pathogenesis of RA-related accelerated atherosclerosis [2,3,5]. We also found increased production of these cytokines in atherosclerotic aortic aneurysms [15,16].

Regarding the cellular and molecular effects of TNFα and IL-6 underlying atherosclerosis, TNFα is released by inflammatory leukocytes as well as by vascular endothelial and smooth muscle cells [1,10]. TNFα promotes the endothelial expression of cellular adhesion molecules and, thus, the migration of leukocytes into and through the vessel wall [1,17,18]. IL-6 is also a key pro-inflammatory cytokine, which also increases the hepatic production of C-reactive protein, an independent risk factor for atherosclerosis [1-3,19-21]. IL-6 induces endothelial dysfunction [22] and has been implicated in CVD, as well as cerebrovascular events and peripheral atherosclerosis [21,23].

While studies describing the role of TNFα and IL-6 in the pathogenesis of atherosclerosis and vascular diseases have mostly been based on non-invasive, epidemiological studies, there have been very few reports in this context based on coronary angiographic studies. In this issue of IMAJ, Gotsman and co-authors [24] investigate the role of pro-inflammatory cytokines in CVD by assessing patients undergoing coronary angiography. The degree of coronary stenosis (> 50% or > 70%) as well as the Gensini Severity Score were correlated with serum levels of pro-inflammatory cytokines and other markers of inflammation. In their study, more overt coronary occlusion and higher Gensini scores correlated with increased production of TNFα and IL-6 in patients with stable coronary disease. The combination of serum TNFα and IL-6 concentrations yielded to even closer correlation. These results are in accordance with known data described above. Serum TNFα and IL-6 levels could not be associated with acute coronary syndrome, suggesting that these pro-inflammatory cytokines may indeed be implicated in chronic "low grade" inflammation underlying atherosclerosis rather than acute vascular events. This result has been confirmed by other investigators [25].

Gotsman et al. [24] also found a weak correlation between the production of IL-1 receptor antagonist and obstructive vessel disease. This result may be somewhat controversial, since in numerous studies IL-1 rather than IL-1Ra is associated with atherosclerosis and CVD. Furthermore, in animal models, IL-1 and IL-1Ra deficiency resulted in accelerated and diminished atherosclerosis, respectively [reviewed in 4]. Yet, we recently found a strong inverse correlation between carotid atherosclerosis and IL-1 levels [6]. Furthermore, Dessein and colleagues [26] reported a negative correlation between IL-1 production and the release of soluble endothelial adhesion molecules. Thus, the role of IL-1 and IL-1Ra in atherosclerosis is unclear and needs further clarification.

Another important aspect of the role of pro-inflammatory cytokines in atherosclerosis is the possible beneficial effects of anti-cytokine biologics used in inflammatory diseases on CVD. Numerous recent reports have suggested that anti-TNF biologicals may have beneficial effects on the vasculature and lipid profile in RA patients. For example, infliximab may improve endothelial

IL = interleukin
CVD = cardiovascular disease
TNFα = tumor necrosis factor-alpha
RA = rheumatoid arthritis
IL-1Ra = IL-1 receptor antagonist

function and suppress carotid atherosclerosis [17,27,28]. There have been no reports regarding the possible vascular effects of tocilizumab, an anti-IL-6 receptor monoclonal antibody under development for the treatment of RA. However, based on the significant role of these pro-inflammatory cytokines in both atherosclerosis and arthritis, medications may have a favorable outcome on CVD.

In conclusion, pro-inflammatory cytokines such as TNFα and IL-6 may play a key role in atherosclerosis and CVD. Apart from non-invasive descriptive studies, coronary angiographic assessment of coronary occlusion confirmed this role. As cytokine production may be therapeutically controlled by drugs, this strategy may open new options to treat inflammatory atherosclerosis and vascular disorders.

References

1. Ross R. Atherosclerosis – An inflammatory disease. N *Engl J Med* 1999;340:115–26.
2. Sherer Y, Shoenfeld Y. Mechanisms of disease: atherosclerosis in autoimmune diseases. N*ature Clin Pract Rheumatol* 2006;2:1–8.
3. Shoenfeld Y, Gerli R, Doria A, et al. Accelerated atherosclerosis in autoimmune rheumartic diseases. C*irculation* 2005;112:3337–47.
4. Ohsuzu F. The roles of cytokines, inflammation and immunity in vascular diseases. J A*theroscler Thromb* 2004;11:313–21.
5. Szekanecz Z, Kerekes G, Dér H, et al. Accelerated atherosclerosis in rheumatoid arthritis. A*nn NY Acad Sci* 2007;1108:349–58.
6. Kerekes G, Szekanecz Z, Dér H, et al. Endothelial dysfunction and atherosclerosis in rheumatoid arthritis: a multiparametric analysis using imaging techniques and laboratory markers of inflammation and autoimmunity. J R*heumatol* 2008;35:398–406.
7. Giles JT, Post W, Blumenthal RS, et al. Therapy insight: managing cardiovascular risk in patients with rheumatoid arthritis. N*ature Clin Pract Rheumatol* 2006;2:320–9.
8. Ohashi R, Mu H, Yao Q, et al. Atherosclerosis: immunopathogenesis and immunotherapy. M*ed Sci Monit* 2004;10:RA255–60.
9. Hansson GK. Immune mechanisms in atherosclerosis. A*rterioscler Thromb Vasc Biol* 2001;21:1876–90.
10. Szekanecz Z, Strieter RM, Koch AE. Cytokines in rheumatoid arthritis: potential targets for pharmacological intervention. D*rugs Aging* 1998;12:377–90.
11. Cesari M, Penninx BW, Newman AB, et al. Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition [Health ABC] Study). A*m J Cardiol* 2003;92:522–8.
12. Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. C*irculation* 2000;101:2149–53.
13. Volpato S, Guralnik JM, Ferrucci L, et al. Cardiovascular disease, interleukin-6, and risk of mortality in older women: the women's health and aging study. C*irculation* 2001;103:947–53.
14. Skoog T, Dichtl W, Boquist S, et al. Plasma tumor necrosis factor-alpha and early carotid atherosclerosis in healthy middle-aged men. E*ur Heart J* 2002;23:376–83.
15. Szekanecz Z, Shah MR, Harlow LA, et al. Interleukin-8 and tumor necrosis factor-alpha are involved in human aortic endothelial cell migration. P*athobiology* 1994;62:134–9.
16. Szekanecz Z, Shah MR, Pearce WH, et al. Human atherosclerotic abdominal aortic aneurysms produce interleukin (IL)-6 and interferon gamma but not IL-2 and IL-4. A*gents Actions* 1994;42:159–62.
17. Popa C, Netea MG, van Riel PLCM, et al. The role of TNF-α in chronic inflammatory conditions, intermediary metabolism and cardiovascular risk. J L*ipid Res* 2007;48:751–62.
18. Collins T, Read MA, Neish AS, et al. Transcriptional regulation of endothelial cell adhesion molecules: NF-κ B and cytokine-inducible enhancers. FASEB J 1995;9:899–909.
19. Huber SA, Sakkinen P, Conze D, et al. Interleukin-6 exacerbates early atherosclerosis in mice. A*rterioscler Thromb Vasc Biol* 1999;19:2364–7.
20. Erren M, Reinecke H, Junker R, et al. Systemic inflammatory parameters in patients with atherosclerosis of the coronary and peripheral arteries. A*rterioscler Thromb Vasc Biol* 1999;19:2355–63.
21. Tzoulaki I, Murray GD, Lee AJ, et al.C reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population: Edinburgh Artery Study. C*irculation* 2005;112:976–83.
22. Bhagat C, Vallance P. Inflammatory cytokines impair endothelium-dependent dilatation in human veins in vivo. C*irculation* 1997;96:3042–7.
23. Hoshi T, Kitagawa K, Yamagami H, et al. Relation between interleukin-6 level and subclinical intracranial large-artery atherosclerosis. A*therosclerosis* 2008;197(1):326–32.
24. Gotsman I, Stabholz A, Planer D et al. Serum cytokine tumor necrosis factor-alpha and interleukin-6 associated with the severity of coronary artery disease: indicators of an active inflammatory burden? *IMAJ* 2008;10:494–8.
25. Sukhija R, Fahdi I, Garza L, et al. Inflammatory markers, angiographic severity of coronary artery disease, and patient outcome. A*m J Cardiol* 2007;99:879–84.
26. Dessein PH, Joffe BI, Singh S. Biomarkers of endothelial dysfunction, cardiovascular risk factors and atherosclerosis in rheumatoid arthritis. A*rthritis Res Ther* 2005;7:R634–43.
27. Hürlimann D, Forster A, Noll G, et al. Anti-tumor necrosis factor-α treatment improves endothelial function in patients with rheumatoid arthritis. C*irculation* 2002;106:2184–7.
28. Del Porto F, Lagana B, Lai S, et al. Response to anti-tumour necrosis factor α blockade is associated with reduction of carotid intima-media thickness in patients with active rheumatoid arthritis. R*heumatology* 2007;46:1111–15.

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The one important thing I have learned over the years is the difference between taking one's work seriously and taking one's self seriously. The first is imperative and the second is disastrous

Margot Fonteyn (1919-1991), British prima ballerina *assoluta*, considered the greatest English ballerina of her time