Apart from traditional risk factors, chronic “low grade” inflammation has been implicated in the pathogenesis of atherosclerosis and 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 cardiovascular disease 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 and other markers of inflammation underlying atherosclerosis. 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 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...
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


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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.