Interleukin-10 (IL-10): an update on its relevance for cardiovascular risk

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Inflammation plays a major role in the pathogenesis of atherosclerotic lesions of vascular walls. This concept, initially promoted by Ross [1], was confirmed by several lines of evidence in recent years. Components of the inflammatory system were found in the atheromatous plaque, a relation between lipid metabolism, endothelial damage and inflammation was pointed out, and progression or instability of cardiovascular disease is associated with a systemic inflammatory response. These findings directed attention towards interleukin (IL)-10 as one of the most important mediators that physiologically limits and down-regulates inflammation. Indeed, IL-10 proved to have several protective features acting against atherosclerotic disease. Interest in this cytokine was further strengthened by its role in patients with chronic renal failure, in whom a very high level of systemic inflammation is associated with an enormous burden of cardiovascular morbidity.

**Inflammation and atherosclerosis**

The Physicians Health Study introduced CRP as a parameter for systemic inflammation in asymptomatic men [2]. A highly sensitive assay was used, which could detect a significant variability among persons, in whom the standard assays would only have shown the absence of CRP elevation. Individuals in the highest quartile of CRP had three times the risk of myocardial infarction and twice the risk of stroke compared with those in the lowest quartile. Daily intake of acetylsalicylic acid was prophylactically effective in the upper CRP quartiles but not in the lowest. Similar results were also documented for women. A large population-based trial found a predictive value of CRP for cardiovascular events that was even stronger than that of LDL cholesterol [3].

Inflammatory and immune competent cells are regular constituents of the atheromatous plaque [1]. Lymphocytes and monocytes or macrophages are present at the site of vascular damage. The phagocytic cells take up lipids and may degenerate to foam cells. They produce their typical cytokines such as IL-6, which explains the presence of this pro-inflammatory factor within the plaque [4]. Cells of the monocytic lineage may also be very relevant for the destabilization of the atheromatous plaque. These cells are equipped with proteolytic enzymes such as matrix metalloproteinases (MMP), which are needed for their immune defence functions. They help the monocytes and macrophages circulating with the blood stream to access tissues invaded by pathogens. The macrophage located in the atherosclerotic plaque may also produce this enzyme, which has been documented in this position in animal models [5]. Expression of MMP within the plaque leads to digestion of the fibrous cap that separates the soft nucleus of the plaque from the blood stream. This process marks the development from stable atherosclerotic disease with a certain degree of vessel lumen obstruction to its unstable form, ending up with thrombocyte adhesion to subendothelial structures, thrombus formation and acute vascular occlusion. The role of inflammatory cells in the progression of vascular disease may thus be 2-fold: enhancement of slowly growing atherosclerotic plaques and destabilization of the lesion.

Two models have been discussed that try to explain a potential link between systemically detectable inflammation and the localized process within the vascular wall [6]. The first model suggests the presence of an intra-arterial inflammation, maintained by the stimulating effect of oxidized LDL on resident macrophages [7]. If this vessel wall inflammation is active in extended parts of the arterial system, some pro-inflammatory cytokines may spill over into the circulation and induce hepatic synthesis of CRP. The other model discusses an opposite causality. Extravascular activation of inflammation by chronic bronchitis, gastritis, periodontitis, smoking, obesity or other influences could lead to elevated circulating levels of acute phase proteins, among them CRP. These mediators might then enhance the process of vascular damage. CRP has indeed been found within the vascular plaque and experimental...
studies show that the protein can increase LDL cholesterol uptake by macrophages [8]. This point of view is supported by an epidemiological study, which showed that the presence of any kind of chronic bacterial respiratory, urinary, dental or other infection enhanced the risk to develop atherosclerotic alterations of the carotid arteries [9].

**IL-10 and cardiovascular disease**

IL-10 down-regulates inflammatory activation of monocytes and macrophages by transcriptional and post-transcriptional inhibition of the entire range of pro-inflammatory cytokines [10]. The protein is induced by the same stimuli in the same cell types that produce inflammatory factors. Its physiological function is the limitation and final shut-off of the inflammatory reaction in immune defence once the pathogen is eliminated. Its effects on macrophages are not limited to the down-regulation of cytokines but also include inhibition of the expression of adhesion molecules, HLA class II molecules, antigen presentation and lymphocyte activation. IL-10 is found within the atheromatous plaque, probably due to local production by the macrophages [11].

Since this single factor opposes a broad array of pro-inflammatory mediators, it attracted much attention in cardiovascular research. Animal experiments showed an astonishing anti-atherosclerotic effect of IL-10: the rapidly progressing atherosclerosis of LDL-receptor knockout mice could nearly completely be avoided by systemic or endothelial over-expression of human IL-10 [12]. Furthermore, IL-10 knockout mice, if grown under conditions that avoid the heavy inflammatory bowel disease that these animals typically develop, show enhanced formation of atherosclerotic vascular lesions [13]. This anti-atherogenic effect of IL-10 is supported by in vitro findings. IL-10 inhibits the adhesion of monocytes to endothelial cells by down-regulating the adhesion molecules CD18 and CD62-L on immune competent cells [14]. Monocyte adhesion to the endothelium is the first step of invasion into the vascular wall. IL-10 may also affect the enzymes associated with destabilization of the atherosclerotic plaque. The cytokine inhibits the synthesis of MMP-9 and induces the production of its physiologic inhibitor, tissue inhibitor of metalloproteinases-1 (TIMP-1) [15].

Clinical studies on plasma IL-10 during stable and unstable atherosclerotic disease are inconclusive. A Norwegian report on 44 patients with stable and 29 patients with unstable angina did not detect a difference between plasma IL-10 of the two groups [16]. These authors could document higher pro-inflammatory plasma TNF-α levels in the unstable patients. A slightly larger study from the UK measured clearly higher IL-10 plasma levels in 50 patients with stable than 45 patients with unstable coronary syndromes [17]. These studies may or may not confirm the clinical relevance of IL-10 as a plaque stabilizing cytokine. However, it is quite likely that production rates by monocytes and macrophages or even the number of IL-10 producing cells in circulation or within the plaque is more relevant than plasma levels. These types of data are still missing.

Recent studies focused on the fact that many, probably all cytokine genes have variations, which in
some cases influence the quantitative production of the protein. The IL-10 gene has at least two polymorphisms that are relevant for cytokine production. The G→A base exchange at position −1082 in the promoter of the gene leads to some 30% less IL-10 protein upon a definite stimulus [18]. This gave rise to the hypothesis that genetically determined IL-10 low-producer might have a poorer cardiovascular prognosis than those with high IL-10 production. However, two large studies investigating patients with angiographically proven coronary artery disease or myocardial infarction could not find a difference in the IL-10 genotype prevalence compared with healthy controls [19,20]. From these studies no firm conclusion can be drawn, but on the other hand this data does not disprove the concept that IL-10 is relevant to atherosclerotic disease. Until now it is not clear if the polymorphism-associated variability of IL-10 is strong enough to influence the grade of inflammation, which is present in the vascular patient. The discussion became more controversial by findings in patients with chronic renal failure.

**IL-10 in cardiovascular disease of end-stage renal disease**

Chronic renal failure is a situation of enhanced and chronic systemic inflammation. The reasons for this are quite well understood. Probably most important is the uraemic intoxication in that the kidney loses its clearance function for immunoactive proteins. This changes kinetics of most cytokines and enhances the area under the curve of systemically acting proteins such as IL-1 or IL-6. Many other proteins, e.g. soluble immune receptors (CD14, CD23, CD40) are retained. Chronic inflammation in end-stage renal disease is further increased by the influence of renal replacement therapy, which in the case of haemodialysis confronts the patient with the frequent unphysiologic contacts between the blood and artificial surfaces of the dialyser membrane.

Many studies documented elevated plasma levels of pro-inflammatory cytokines in dialysis patients [21,22]. Even more importantly, in these patients the circulating monocytes are much more prone for cytokine production than in the healthy [23]. It is conceivable that this pre-activation of monocytes due to uraemia and renal replacement therapy may lead to more active monocyte and macrophage infiltration in the atherosclerotic plaque and a tendency towards destabilization. Cardiovascular disease is very common in dialysis patients and mortality is high. Atherosclerotic sequelae occur much earlier in life and progression is enhanced [24]. Similar to the general population, there is a good relationship between markers of inflammation such as CRP [25] or IL-6 [22] and cardiovascular mortality; however, levels of inflammation are some 10-fold higher in dialysis patients and mortality is 14–20% annually in most series.

In view of the intensity of such chronic systemic inflammation, the importance of IL-10 is potentiated. Its potential effects on atherosclerosis are depicted in Figure 1. The cytokine can control over-production of pro-inflammatory factors in these patients if produced at high levels [26]. However, only a few patients are able to produce enough IL-10 to compensate for uraemic inflammation. Several studies confirmed elevated levels of IL-10 [27,28]; however, only the genotyping of dialysis patients for the IL-10 promoter polymorphisms could explain why less than one-third of them can compensate the inflammatory load [29]. In contrast to studies in patients with normal renal function, the IL-10–1082 G→A polymorphism turned out to be highly predictive for cardiovascular events in dialysis patients [30]. Taken together, chronic renal failure seems to be a situation in which the inflammatory component in the pathogenesis of atherosclerotic disease is strongly enhanced. Consequently, the relevance of IL-10 as an anti-inflammatory agent is strengthened as well. In this environment, the genetic variability of IL-10 levels becomes predictive for the extent of cardiovascular disease.

Conflict of interest statement. None declared.

**References**

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Transplantation tolerance: a journey from ignorance to memory

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Transplantation tolerance can be defined as long-term allograft survival in the absence of continuous immunosuppressive therapy. Implicit to this definition is that tolerant recipients of organ transplants are unresponsive to donor antigens but maintain reactivity to other (third-party) antigens. In other words, a tolerant patient is capable of mounting an effective immune response against microbial pathogens but is incapable of rejecting the transplanted organ.

Despite a wealth of information on how tolerance to self-antigens is maintained (Figure 1), the induction of tolerance to a transplanted organ remains elusive because of several biological barriers. These barriers include the relatively large magnitude of the alloimmune response, the limitations of peripheral tolerance mechanisms, and the unavoidable fact that immune responses to foreign antigens, by virtue of evolutionary design, are destined to generate immunologic memory [1]. Here, I would like to relay the trials and tribulations of my research group, as well as those of others, to understand how tolerance to a transplanted organ can be achieved.