Toll-Like Receptors, Endocrine Stress Response, and Arteriosclerosis

To the Editor:

There is increasing evidence that Toll-like receptor (TLR)-dependent signaling and cell activation is critically involved in the pathogenesis of arteriosclerosis.

The article by M. Kazemi et al impressively demonstrates that Toll-like receptor agonists induce lipid accumulation and proteins involved in atherosclerotic plaque development such as adipocyte fatty acid-binding protein (aP2) in macrophages.1 Therefore there is a molecular link between TLR and foam cell formation.

While bacterial toxins activate macrophages through Toll-like receptor -2 and -4, noninfectious stimuli such as minimally oxidized LDL also use the same signaling pathways and will trigger a TLR-4-dependent proinflammatory response in macrophages.2 TLR may, however, not only be a “central gateway to the vessel wall”3 and mediate the local process of atherosclerotic plaque formation but may also relate to systemic pathomechanism of arterial disease. The endocrine stress response, including the release of glucocorticoids and the activation of the renin–angiotensin aldosterone system, is clearly implicated in the process of endothelial dysfunction and arteriosclerosis both through the increase in blood pressure and direct effects on the endothelial cell wall.

We have recently demonstrated an important role for TLR-2 and TLR-4 in the adrenal stress response.4,5 TLRs are expressed in adrenal cells, and TLR agonists stimulate the release of steroids from human adrenal cells.6 TLR-2–deficient mice have an impaired steroid release during endotoxemia.7 Consistent with the increased lipid accumulation and adipocyte fatty acid binding protein (aP2) expression induced by Toll-like receptor agonists described by M. Kazemi et al,1 similarly mineralocorticoids and glucocorticoids are known to enhance cholesteryl ester formation and aP2 expression.8 Therefore, the activation of Toll-like receptors in the pathogenesis of atherosclerosis might include an endocrine stress response as well.

Thus TLR activation through both bacterial endo- or exotoxins and other noninfectious ligands will modulate atherosclerotic plaque development not only through local immune/inflammatory actions but also through a humoral-endocrine and systemic response.

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References


Response

Drs Bornstein and Morawietz report an interesting extension of our findings regarding TLR activation and expression of lipid metabolism genes in macrophages in which they describe a systemic response that promotes atherosclerosis.1 Direct activation of TLRs in the adrenal glands mediate induction of adrenocortical hormone release, which in turn may modulate foam cell formation in a manner similar to TLR ligands of microbial origin. Other systemic changes that occur during the acute phase response to infection or illness that would also promote atherosclerosis include alterations in the circulating level and composition of lipoproteins that enhance the uptake of these particles by macrophages and accelerate foam cell formation. These alterations include an increase in serum triglyceride and small dense LDL, a decrease in HDL cholesterol, and an increase in lipoprotein oxidation as well as ceramide and sphingomyelin enrichment of LDL.2 The work of Bornstein and Morawietz and others demonstrate that multiple changes in the acute phase response could contribute to the pathogenesis of atherosclerosis.

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References


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