Stirring the soup of innate immunity in the acute coronary syndromes

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This editorial refers to ‘Cellular actors, Toll-like receptors, and local cytokine profile in acute coronary syndromes†, by C.A. Wyss et al., on page 1457

Organisms have developed multiple host defence mechanisms through the millennia to deal with invading pathogens. The innate immune system constitutes one such protective pathway. Activation of innate immunity uses receptors on the surfaces of various cells that respond to a fairly restricted number of molecular patterns characteristic of pathogenic organisms. The engagement of these receptors rapidly triggers an intracellular signalling cascade that leads to the production of proinflammatory cytokines, lipids, and microbicidal substances, among other defensive mediators. Members of these families of ‘pattern recognition receptors’ include the Toll-like receptors (TLRs), scavenger receptors, and the receptors for advanced glycation end-products (RAGEs) (Figure 1). Ligands for these pattern recognition receptors include bacterial peptidoglycans, endotoxins, and other microbial cell wall constituents. The ancient, innate arm of host defences can thus mobilize very quickly in response to a limited repertoire of stimuli, and unleash a non-specific panel of proinflammatory substances. The adaptive arm of the immune response exhibits exquisite selectivity and great diversity, and arose much later in phylogeny. Each antibody, or antigen receptor on T lymphocytes, recognizes a very limited sphere of structures, in contrast to the promiscuity of the pattern recognition receptors that signal the afferent limb of innate immunity. The adaptive immune response mobilizes quite slowly to engender the generally more targeted and restricted inflammatory response than that generated by innate immunity. Together, these two complementary arms of host defences protect the species from microbial invaders, help heal wounds, and foster survival to reproductive age.

In the modern era, sanitation, vaccination, antibiotics, and other advances allow us to enjoy longer lives. We rely less on host defences for protection against pathogens, and indeed the very mechanisms that permitted the survival of our ancestors can now turn against us. Considerable evidence implicates both innate and adaptive immunity in the pathogenesis of chronic diseases, including atherosclerosis.1 While we understand well the range of exogenous ligands for pattern recognition receptors (e.g. from microbial pathogens), we have only just recently begun to unravel the identity of putative endogenous ligands that trigger their activation in the context of chronic diseases, in the absence of infectious agents. Certain heat shock proteins (hsp), secretory products of granulocytes and platelets, constituents of atherogenic lipoprotein, and advanced glycation end-products (AGEs) can bind pattern recognition receptors (Figure 1).

Cells subjected to various types of stress increase their production of hsp of several families. Hsp accumulate in human atherosclerotic plaques.2 By engaging TLR4, hsp represent one possible endogenous ligand for the innate immune response that operates during atherogenesis.3 Upon activation, granulocytes and platelets release a heterodimeric protein known as myeloid-related protein-8/14 (MRP-8/14). Emerging evidence suggests a pathogenic role for MRP-8/14 in myocardial infarction, vasculitis, and atherosclerosis.4 Circulating levels of MRP-8/14 rise following myocardial infarction and predict increased cardiovascular risk in apparently well individuals and in survivors of acute coronary syndromes.5–7 MRP-8 also binds to TLR4, providing another disease-related endogenous trigger for innate immunity.8 AGEs accumulate in the blood and in tissues of hyperglycaemic individuals; they also can bind TLRs.9 Much epidemiological evidence suggests that postprandial lipaemia promotes atherogenesis. Among the triglyceride-rich lipoproteins enriched after meals, very low-density lipoproteins (VLDLs)—particularly those bearing high levels of apolipoprotein CIII—are associated with elevated cardiovascular risk. Recent work has identified apolipoprotein CIII as an endogenous ligand for TLR2 that can instigate inflammatory activation of endothelial cells.10 These results take on particular pathophysiological significance, as mice lacking TLR2 on endothelial cells show attenuated atherogenesis.11 The examples illustrate how in the context of chronic diseases such as atherosclerosis, engagement by endogenous ligands of the TLRs, as model pattern recognition receptors, can contribute to pathogenesis.

Wyss et al. have reported overexpression of TLR4 on macrophages and of TLR2 on granulocytes in thrombi aspirated from...
patients with acute coronary syndromes. These results do not demonstrate causality, nor can we be sure that the overexpression of these pattern recognition receptors precedes rather than follows the acute insult. Yet, these observations stir the soup of innate immune signalling during acute coronary syndromes. More than half of the patients studied had dyslipidaemia. It would be interesting to know the concentration of apolipoprotein CIII in these individuals in relation to their leucocyte TLR2 expression. Considerable current interest concerns the special roles of proinflammatory subsets of mononuclear cells in atherosclerosis. It would also be of interest to know whether TLRs associate with monocytes bearing the markers of the proinflammatory subset—including high relative expression of CD14, a co-receptor for TLR4 signalling, or P-selectin glycoprotein ligand-1 (PSGL-1), a molecule which directs leucocyte adhesion to platelet-rich arterial thrombi through interaction with the platelet adhesion molecule P-selectin. Consistent with the findings of Wyss et al., leucocytes also increase expression of other inflammatory proteins, including Mac-1 and tumour necrosis factor-α (TNF-α), at sites of coronary artery injury and thrombosis.

Taken in context, increased expression of leucocyte TLRs at sites of coronary thrombosis provides a mechanism for amplification of proinflammatory signals (Figure 2). When thrombi complicate atheromatous plaques, platelets accumulate in the growing thrombus and platelet degranulation results in surface expression of P-selectin, CD40 ligand (CD40L) and myeloid-related protein-8/14 (MRP-8/14), resulting in paracrine and autocrine activation of innate immune pathways that can increase expression of inflammatory and thrombotic mediators, including tumour necrosis factor-α and tissue factor.
of P-selectin, which binds to leucocyte PSGL-1, thereby mediating monocyte and granulocyte activation and thrombus adhesion. Activated leucocytes and platelets within the thrombus will secrete the TLR4 ligand MRp-8/14 as well as RANTES (regulated upon activation, normal T-cell expressed, and secreted) and CD40 ligand, resulting in paracrine and autocrine activation of innate immune pathways that increase expression of inflammatory and thrombotic mediators. Through such mechanisms, innate immunity—so vital to the survival of our species in days of yore—can now turn against us in the modern age. As the challenge of microbial pathogens wanes, our toxic environment—favouring dyslipidaemia, dysglycaemia, and cellular stressors—can hijack our defence mechanisms to promote disease. As public health measures proved pivotal in overcoming microbes, we must strive to achieve a more salubrious lifestyle in contemporary society to restore innate immunity to its rightful place as a friend, rather than a foe, of human health.

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**References**