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Local inflammatory responses take their toll on the heart

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Toll like receptors (TLR) are a highly conserved group of innate immune receptors expressed by a variety of cell types and tissues, providing an important first line of defense. Besides recognizing exogenous pathogens, TLRs are in many diseases also activated by endogenous ligands from stressed or damaged tissue [1]. Among others, heat shock proteins and high-mobility group box-1 (HMGB1) have been suggested as important endogenous ligands for TLRs in cardiovascular disease and mostly target TLR2 and TLR4 [2,3]. However, most evidence on endogenous TLR ligands in cardiovascular disease comes from experimental animal models and hence more often than not does not directly translate to human disease.

In this issue of the *International Journal of Cardiology*, Rotter Sopasakis and colleagues describe their results from a unique cohort containing cardiac tissue of patients with and without cardiac disease in which they generated a profile of 84 genes involved in TLR signaling [4]. Among these genes, the TLRs 1, 3, 7, 8 and 10 were robustly upregulated in cardiac patients. One of the most striking observations is the apparent lack of regulation of TLR2 and 4; the 2 most extensively studied TLRs within the cardiovascular arena.

Several polymorphisms for TLRs have been described (e.g. Asp299Gly), but their association with cardiovascular disease risk is controversial. Clinical evidence from 2 large meta-analyses however neither supports a relevant role for the TLR4 Asp299Gly polymorphism in cardiovascular disease risk reduction [5] nor do TLR1, TLR2, TLR4, TLR7, TLR8 and TLR9 gene polymorphisms seem to be involved in the pathogenesis of atherosclerosis [6].

The observed upregulation of the TLRs 1, 3, 7, 8 and 10 in patients with cardiac disease renders them potential targets for therapeutic intervention. Unfortunately, as with every TLR, it yet remains elusive which endogenous targets actually bind to these TLRs. While TLR1 is expressed on the cell surface, TLRs 3, 7, 8 and 10 are intracellular receptors. So far, no ligand has been identified for TLR10, while all other TLRs described in this study specifically recognize RNA motifs, which is of particular interest in myocardial ischemia. Ischemia reperfusion injury results in RNA release of RNA from the infarcted heart that can bind to TLR3 [7]. The absence of TLR3 in a mouse myocardial infarction model resulted in decreased infarct size, without affecting cytokine release and neutrophil recruitment upon ischemia-reperfusion injury [8]. As TLR3, TLR7 and TLR8 bind to RNA, their expression is most likely upregulated in the ischemic myocardium where RNA release from necrotic cells is abundant. While the authors state that TLR signaling is enhanced in the ischemic compared to the non-ischemic group, the most markedly differentially expressed genes were not the TLRs themselves, but related to pro-inflammatory cytokines. Noteworthy, signaling of intracellular TLRs, such as TLR3, 7 and 8, is mostly associated with Interferon Regulatory Factors (IRFs) and type Interferon-α [9], which were not differentially regulated in the current study.

Nonetheless, the results presented by Rotter Sopasakis and colleagues in this issue of the *International Journal of Cardiology* [4] provide food for thought. The use of freshly isolated cardiac tissue is unique and provides insights on local rather than systemic responses. As such it is slightly disappointing but also interesting that the TLRs regulated in the heart appear to differ from the usual suspects in literature. Of course, these findings need to be validated in larger patient populations. Yet, they show the value of assessing local inflammatory responses and emphasize the need for robust human evidence to prevent getting lost in translation. Therefore, it would be especially interesting to test the performance of novel therapeutic agents developed for infectious disease treatment targeting intracellular TLRs, including small molecule inhibitors, and nano-inhibitors [10] in cardiovascular disease, both experimentally and clinically.

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