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Editorial

TOLL-erating cardiac hypertrophy following pressure overload

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See article by Ha et al. [4] (pages 224–234) in this issue.

Ah, broken is the golden bowl! the spirit flown forever! Let the bell toll!—a saintly soul floats on the Stygian river; . . .And I!—to-night my heart is light!—no dirge will I upraise, But waft the angel on her flight with a Paean of old days!"—Excerpted from "Lenore", by Edgar Allen Poe (1831)

Sensing and defeating microbial infections are essential to the survival of metazoan species and contingent upon the reliable detection of pathogens, which are characterized by rapid evolution and molecular heterogeneity. Multicellular species have developed two overall strategies to kill and remove parasites, to send them "*floating on the Stygian river*" (after the river *Styx* in *Hades*, the underworld, in Greek mythology), as alluded to in the poem "*Lenore*" from Edgar Allen Poe: an innate versus an adaptive immune recognition system. The first line of defense (the innate system) is limited to the recognition of evolutionarily conserved pathogen motifs, molecular patterns that are unique to the microbial world and invariable among classes of pathogens. In contrast, the adaptive system involves dynamic adaptation (e.g. antibody generation) to unique epitopes on pathogens in the environment. Induction of the innate immune system is fast (usual within hours) and depends upon targets of pattern recognition, *p*athogen-*a*ssociated *m*olecular *p*atterns or PAMPs that are recognized by *p*attern *r*ecognition *r*eceptors (PRRs) [1].

The Toll-like receptor (TLR) family is the best-characterized class of PRRs in mammalian species, and TLRs are ubiquitously expressed throughout species in plants, nematodes, flies, birds, and mammals. Most mammals have 10–15 TLRs that detect multiple PAMPs, including lipopolysaccharide or LPS (detected by TLR4), bacterial lipoproteins and lipoteichoic acids (TLR2), flagellin (TLR5), the unmethylated CpG DNA of bacteria and viruses (TLR3) and single-stranded viral RNA (TLR7). Unexpectedly, TLRs also seem to play a role in cardiovascular disease. The expression of TLR2 and TLR4 has been detected in atherosclerotic plaques, and TLR4 null mice are resistant to diet-induced atherosclerosis in an Apo−/− background. As atherosclerosis can develop without pathogens, endogenous ligands of TLR4 should exist and be able to activate this receptor in diseased vessels [2].

Several TLRs are expressed in cardiac muscle, and TLR4 expression increases after myocardial infarction in the mouse heart, in the myocardium of patients requiring left ventricular assist devices, and in the heart of patients with dilated cardiomyopathy secondary to enteroviral replication [2]. TLR2 knockout mice are resistant to myocardial infarction-induced cardiac dysfunction, but identification of the germane cell type involved in this effect is inherently complicated in this type of insult, with numerous cells from hematopoietic origin infiltrating the border zone of infarcts [3]. Combined, these studies suggest a strong correlation between TLR signaling and heart disease, although the spatial and temporal particulars of this pathological facet remain to be fully dissected.

In this issue of *Cardiovascular Research*, Ha et al. now present more definitive insight on the workings of TLR signaling in cardiac muscle [4]. By combining mouse genetics with microsurgical aortic banding techniques, they demonstrated that the absence of TLR4 abolished the increase in cardiac mass and myocyte size and reduced NFκB and PI3K/Akt/mTOR signaling following pressure overload. By studying a pressure overload model instead of myocardial infarction, it is much more likely that the TLR4

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effects occur on cardiac muscle itself, as opposed to infiltrating immune cells in an infarct model. Thus, TLR4 is a germane receptor on heart muscle that mediates cardiac hypertrophy in vivo and may be a logical target for drug development in heart disease. As cardiac muscle hypertrophy constitutes an independent clinical risk factor for heart failure development, elucidating the molecular circuitry controlling the initiation and maintenance of this phenomenon through integrative approaches as described in the study by Ha et al. adds significant information to the dozens of ligands, receptors, cytoplasmic signal amplifiers, and transcriptional effectors identified to mediate myocyte hypertrophy.

A particular strength of the study involves its meticulous analysis of the downstream effectors of TLR4 function in pressure overload hypertrophy, placing the NFκB and the PI3K/AKT/mTOR axis downstream of TLR4. Although not addressed in this study, transforming growth factor-β activated kinase-1 (TAK1) is a component of the TLR-NFκB B cascade in other cell types and may function as an intermediate from TLR to NFκB, even more so as TAK1 activation in transgenic mice results in severe hypertrophy and heart failure [5], while NFκB activity is a required transcription response for pressure overload hypertrophy [6]. As such, the authors place this receptor in the context of a large body of prior work that identified latter pathways to mediate the growth of cardiac muscle in response to excessive wall stress in the setting of hypertensive heart disease.

As with any good study, these new findings invoke many new questions. An obvious future experiment would be to verify whether hypertrophy signaling is a redundant feature among other cardiac TLR family members. Indeed, given the previous findings that TLR2 drives maladaptive remodeling following myocardial infarct, it would seem logical that other TLR family members, and TLR2 specifically, also signal cardiac hypertrophy, and, conversely, that TLR4 hypertrophy signaling is involved in post-infarction remodeling. Secondly, given that TLR4 can signal through the PI3K/Akt/mTOR axis, which promotes cardiac myocyte growth that is perhaps more physiological, as well as activate NFκB, which seems to incite more detrimental forms of cardiomyopathy, a vexing question remains whether long-term mechanical function is preserved in aortic-banded TLR4 (and TLR2) null mice. And perhaps most important, it remains to be identified which endogenous ligands signal upstream from TLRs and provoke hypertrophy, as–although it cannot formally be excluded beforehand–it is unlikely that in laboratory mice, extracellular, pathogen-derived LPS will act as the key natural ligand for TLR4 in mechanical load. Recent evidence suggests that heat shock proteins (HSPs) may act as endogenous ligands for TLRs. HSP60, HSP70, and HSP96 interact with TLR2 and TLR4 to activate NFκB in non-cardiac cells, cardiac overload transiently increases HSP70 and HSP72 expression in myocardium, and targeted overexpression of HSP56 promotes hypertrophy of cultured cardiac muscle cells [4]. Additionally, it has been hypothesized that oxidative stress signals to NFκB via TLR2. Increasing evidence implicates oxidative stress in the progression of heart failure [7]. In fact, intrinsic oxidative stress was demonstrated to increase with age and upon acute mechanical overload in the heart, due to impairment of transcriptional responses to oxidant stress, diminished expression of antioxidant defense enzymes, and as a result of (age-dependent) cardiac mitochondrial dysfunction [7].

Taken together, the study by Ha et al. [4] provides a platform for novel opportunities to define the precise involvement of TLRs in promoting heart failure and to investigate whether TLR antagonists could become useful therapeutic devices in our field. Reminiscent to the poem from Edgar Allen Poe, it would be indeed a strange twist of fate if a system as evolutionarily old as the innate immune system held the key to "*lighten the heart*" in response to biomechanical stress. If the ultimate beneficiaries are the victims of heart failure, the opportunity this ancient TOLL-like receptor offers will certainly sound like "*a Paean (triumphant song) of old days*".

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