The heat shock protein (HSP) family consists of HSP90, HSP70, chaperon-containing TCP1, small HSP (sHSP) and mitochondrial HSP60. Some of these are reported to be increased during heart failure, hypertrophy and ischemia. It is clear that HSPs function as chaperones in response to stress in cardiomyocytes. In addition, extracellular HSPs and those on the plasma membrane act as cytokines instead of chaperones: therefore, HSPs have been called “chaperokines”. Extracellular HSPs exert pro-inflammatory effects as cytokines, whereas intracellular HSPs exert anti-inflammatory effect as chaperones. HSPs act on Toll-like receptors (TLRs) as cytokines, thereby activating the innate immune system in immune cells.

It is still controversial whether HSPs function as cytokines, because the effects of cytokines are thought to be exerted by the contaminants, lipopolysaccharide and Flagellin, that are co-purified with HSPs. Although cytokine functions have been extensively investigated in the immune system, highly purified HSPs are incapable of inducing cytokine effects on immune cells. In the cardiovascular system, HSP70 is systemically released from cardiomyocytes during open heart surgery. HSP60 is also secreted via the exosomal pathway, suggesting the possibility of HSPs as inflammatory cytokines binding to the TLR on either immune cells or cardiovascular cells. Indeed, TLRs are expressed on cardiac muscle and blood.

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Among the TLRs expressed on cardiomyocytes, upon binding to ligands, TLR2 and TLR4 initiate the recruitment of TIR domain-containing adaptor molecules, including TIRAP and myeloid differentiation primary-response gene 88 (MyD88), and consequently promote nuclear factor-κB-dependent and AP1-dependent transcription of the genes involved in inflammation, such as tumor necrosis factor-α and interleukins 1, 3, and 4.

In this issue of the Journal, Marthur et al show the HSP70 induces an inflammatory signal dependently upon TLR2 and MyD88 but not TLR2. In their study, the primary cardiomyocytes isolated from TLR2 knockout (KO) mice, TLR4 KO mice, and MyD88 KO mice were used to examine inflammation markers after treatment with HSP70. Another group has demonstrated that HSP60 induces apoptosis in cardiac myocytes dependently upon TLR4. Both groups used highly purified recombinant HSPs to test their effect on cardiomyocytes to avoid the effect of contaminated molecules on cardiomyocytes. These 2 reports clearly reveal that HSPs activate distinct TLRs expressed on cardiomyocytes.

The essential roles of TLR2 and TLR4 expressed on cardiomyocytes in ischemia–reperfusion or myocardial infarction have been studied using their KO mice. Even in these KO mice, the cells responsible for the inflammation have been unclear. Marthur et al can suggest that at least cardiac myocytes are 1 type of cell involved in the remodeling of the heart after cardiac ischemia. What are the ligands for TLR2 or TLR4 to induce inflammation in cardiomyocytes during ischemic heart diseases? Cardiomyocytes dying by necrosis or apoptosis may produce HSPs as well as high mobility group box 1. To clarify the essential roles for TLR2 and TLR4, a study using mice lacking TLR2 and TLR4 specifically in the heart will be required. Cardiovascular research on innate immunity proceeds steadily.

**References**

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