Programmed cell death, or apoptosis, is a multifactorial event that can be triggered by an array of pathophysiological conditions. The cellular mechanisms by which myocardial apoptosis occurs in response to stress-induced and/or neurocrine-mediated signaling pathways are quite complex. These have been the focus of numerous investigations over the past decade (1). Important conditions associated with cardiac myocyte apoptosis include ischemia-reperfusion (2), heart failure (3), and sepsis (4).

Exposure of heart to lipopolysaccharide (LPS), as happens in patients with sepsis, activates a myriad of cellular events. The adverse effect of LPS on cardiac function has been known for many years. Yang et al. (5) reported that left ventricular function was reduced after administration of LPS, and postulated that the activation of nitric oxide synthase (iNOS) and release of large amounts of nitric oxide (NO) in response to LPS was responsible for diminished cardiac pump function. Along the same line of thought, Li et al. (4) showed that activation of iNOS and subsequent cyclic guanosine monophosphate (cGMP) accumulation, and activation of local renin-angiotensin system led to myocyte injury resulting in cardiac dysfunction. Yasuda and Lew (6) reported that exposure of cardiac myocytes to LPS decreased cell shortening with no change in calcium transients, indicating decreased myofilament responsiveness to calcium. They demonstrated that these effects were mediated in large part via NO-cGMP–mediated mechanisms.

In this issue of the Journal, Suzuki et al. (7) describe a novel cellular mechanism by which LPS induces apoptosis in rat cardiac myocytes. After exposure to LPS, these investigators

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direct action on calcineurin or if other factors also contribute to this inhibition.

While the authors’ work has some novelty, further work needs to be done before the paradigm of the effect of LPS on cardiac myocyte apoptosis being mediated by calcineurin activation can be fully accepted. As the authors point out, these findings do not prove that calcineurin activation is required for LPS-induced apoptosis. Moreover, studies are needed to elucidate the downstream signaling pathways that are triggered after LPS-induced calcineurin activation.

Calcineurin activation in response to LPS described in this issue of the Journal expands the paradigm of organ preservation during injury. It remains to be determined whether calcineurin temporally regulates only the pathological development of hypertrophy, or whether it is also involved in the cellular mechanisms leading to cell death.

Apoptosis is an important mechanism of cell survival, replication, and death. The mechanisms involved in its genesis are far from clear. While a number of investigators have shown that apoptosis can be prevented, to the best of our knowledge no one has shown that program of cell death while in motion can be undone.

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