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Commentary

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Nipping at cardiac remodeling

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Much of the mortality following myocardial infarction results from remodeling of the heart after the acute ischemic event. Cardiomyocyte apoptosis has been thought to play a key role in this remodeling process. In this issue of the *JCI*, Diwan and colleagues present evidence that Bnip3, a proapoptotic Bcl2 family protein, mediates cardiac enlargement, reshaping, and dysfunction in mice without influencing infarct size (see the related article beginning on page 2825).

Postinfarct remodeling: the road to heart failure

Thrombotic occlusion of an epicardial coronary artery triggers acute myocardial infarction. This cataclysmic event, which takes place approximately 1 million times per year in the US, sets into motion a spatially and temporally complex set of processes. In the region supplied by the occluded coronary artery (Figure 1), cardiomyocytes undergo massive cell death by apoptosis and necrosis (1). The sudden loss of a significant portion of myocardium leads to decreases in contractile function. These changes are compensated by increases in left-ventricular volume, which augment contractility in the noninfarcted myocardium via the Frank-Starling mechanism. A negative consequence of enhanced left-ventricular volume, however, is intensified wall stress. This is partially counteracted by scar formation in the infarct zone and cardiomyocyte hypertrophy in the noninfarcted myocardium. These mechanisms provide temporary compensation for the loss of myocardium. While most patients recover from acute myocardial infarction, those with larger infarcts often progress to chronic heart failure due to cardiac remodeling (2). This process involves both expansion of the infarct and changes in the geometry of the noninfarcted myocardium. The result is an enlarged, more spherical, and thin-walled left ventricle with poor contractile function. Drugs that attenuate postinfarct remodeling improve cardiac function and reduce mortality (2). The mechanisms underlying cardiac remodeling are incom-

pletely understood, but inflammation (3), extracellular matrix remodeling (3), and cardiomyocyte hypertrophy (4) and apoptosis (5) have been implicated.

Apoptosis: a mechanistic component of myocardial infarction

Apoptosis accounts for a significant portion of the large burst of cell death during acute myocardial infarction. Whole animal studies in which myocardial infarction was induced by ischemia/reperfusion (occlusion of a coronary artery followed by resumption of blood flow) have shown that genetic or pharmacologic inhibition of cardiomyocyte apoptosis decreases infarct size with concomitant preservation of cardiac function (6, 7). These studies indicate a causal role for cardiomyocyte apoptosis in the pathogenesis of infarction. In contrast to the infarct, lower levels of cardiomyocyte apoptosis are present in the noninfarcted myocardium in the weeks to months following infarction (5) and may play a role in remodeling and progression to heart failure (8).

Apoptosis is mediated by two pathways, one involving cell surface receptors and the other the mitochondria and endoplasmic reticulum (9). During apoptosis, the mitochondria are stimulated to release apoptogens, including cytochrome *c*, that activate downstream caspases and bring about the demise of the cell. The transmission of death signals to the mitochondria involves Bcl2 homology domain 3–only (BH3-only) proteins, a proapoptotic subclass of the Bcl2 family (10). BH3-only proteins are activated through transcriptional and posttranslational mechanisms and translocate to the outer mitochondrial membrane. Interactions between BH3-only proteins and multidomain Bcl2 proteins trigger the release of apoptogens, thereby causing apoptosis (11, 12).

Bcl2 and nineteen-kilodalton interacting protein–3 (Bnip3) is an atypical BH3-only

protein because its BH3 domain possesses limited homology and, in contrast to typical BH3-only proteins, this domain is not required for cell death (13, 14). Bnip3 is present at low levels in several tissues, but its expression is markedly induced by hypoxia in a hypoxia-inducible factor–1α–dependent manner (15). In healthy cells, Bnip3 is loosely associated with mitochondria (16). In response to certain apoptotic signals, however, it inserts via a transmembrane domain into the outer mitochondrial membrane and triggers cell death. Whether this cell death occurs through apoptotic or nonapoptotic means remains controversial (17–21).

Inactivation of Bnip3 decreases cardiac remodeling following infarction

In this issue of the *JCI*, Diwan et al. inactivated Bnip3 in the mouse and gained insights into the role of apoptosis in cardiac remodeling (22). Loss of other BH3-only proteins has been shown to limit infarct size (23). Surprisingly, Diwan et al. found no difference in infarct size in wild-type and *Bnip3*-null mice subjected to ischemia/reperfusion. In contrast, *Bnip3* ablation decreased apoptosis in the noninfarcted myocardium in the days following infarction. Moreover, the remodeling that takes place in the weeks following infarction was markedly attenuated in *Bnip3*-knockout mice as compared with wild-type mice. Increases in left-ventricular end-diastolic volume and sphericity were greater in wild-type mice than *Bnip3*-knockout mice. While systolic function decreased acutely in both groups following infarction, it continued to deteriorate in wild-type mice while stabilizing in *Bnip3*-knockout mice. These data indicate that Bnip3 mediates both cardiomyocyte death in the noninfarcted myocardium and cardiac remodeling.

Bnip3 in the infarct zone: too little, too late?

How is it that Bnip3 is involved in cell death in the noninfarcted myocardium but not in the infarct itself? The authors posit that this may be attributable to differences in Bnip3 levels in these two zones. *Bnip3* is expressed at low basal levels and induced by hypoxia in a variety of cell types, including cardio-
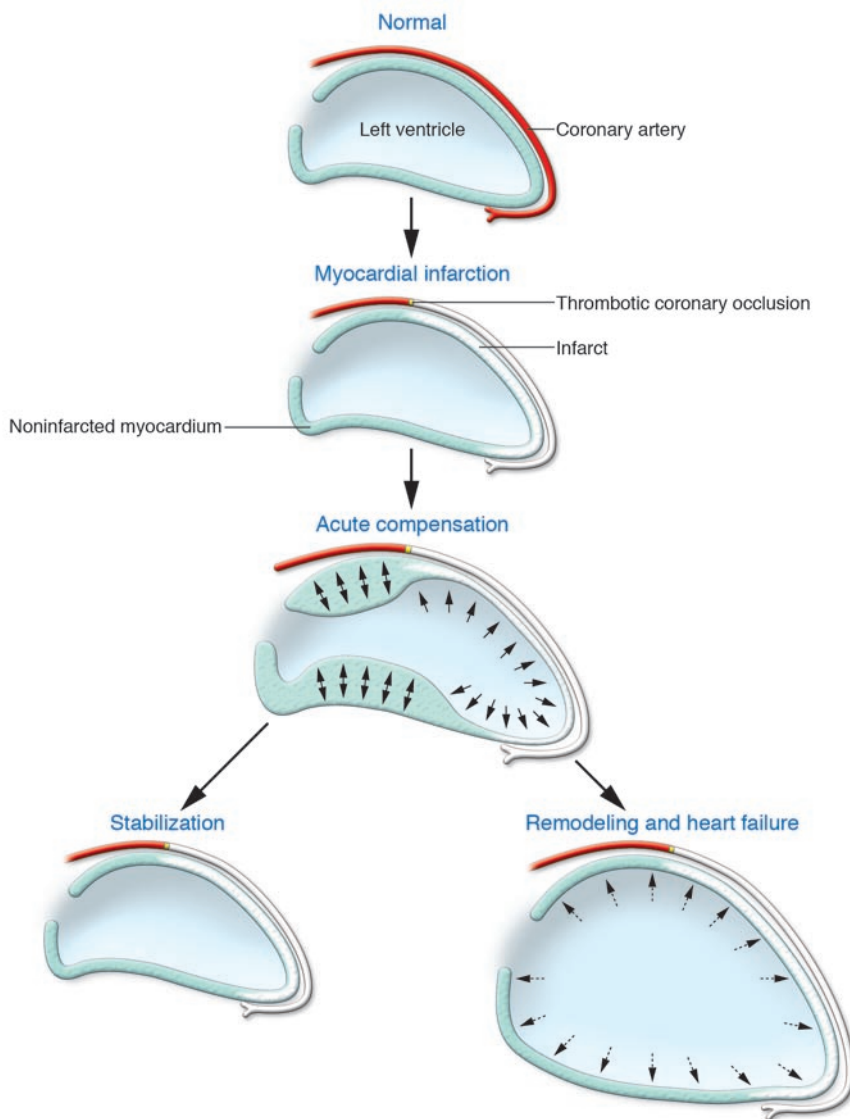
Figure 1
Postinfarct myocardial remodeling. Thrombotic occlusion of a coronary artery precipitates myocyte death in the ischemic zone creating a myocardial infarct (white area). The abrupt loss of functioning myocardium decreases contractile function. Acute compensation is provided by increases in left-ventricular volume (arrows) that augment function (the Frank-Starling mechanism) and neurohumoral factors that increase contractility in the noninfarcted myocardium. Augmented wall stress, a deleterious effect of increased left-ventricular volume, is reduced by myocyte hypertrophy in the noninfarcted myocardium (double-headed arrows). In addition, scar formation in the infarct limits expansion, preventing further increases in wall stress (not shown). In some patients, ventricular function is preserved. Other patients, especially those with larger infarcts, experience cardiac remodeling. In this process, the left ventricle undergoes dilation (dashed arrows), wall thinning, and a change in shape from ovoid to spherical, causing reduced contractile function and chronic heart failure. Strategies that inhibit postinfarct remodeling preserve left-ventricular geometry and function and prevent heart failure.

tant reductions in wall stress and ventricular dilation. If this hypothesis is correct, this sequence of events represents an additional mechanism — one that originates within the infarct zone rather than the noninfarcted myocardium — by which Bnip3 absence would ameliorate postinfarct remodeling. These effects of Bnip3 in the infarct zone may complement those described by Diwan et al. in the noninfarcted myocardium.

Putting the brakes on cardiac remodeling
Limitation of infarct size and inhibition of remodeling are currently the cornerstones of therapy for myocardial infarction (2). Coronary reperfusion reduces infarct size, resulting in preservation of functional myocardium and thereby limiting the primary stimulus for remodeling. Postinfarct remodeling is inhibited using pharmacological (e.g., angiotensin I–converting enzyme [ACE] inhibitors) or mechanical unloading therapies in patients with significant systolic dysfunction. Despite optimal therapy, however, substantial numbers of patients progress to chronic heart failure following myocardial infarction. For this reason, there is a need for additional pharmacological strategies directed specifically against critical mediators of remodeling.

Bnip3 appears to be one such critical mediator of remodeling and possesses

myocytes (15, 24). While Bnip3 is sufficient to kill cardiomyocytes (18), there appears to be inadequate time for *Bnip3* expression to increase in a developing infarction. On the other hand, one would predict robust induction of *Bnip3* expression in the noninfarcted and severely hypoxic myocardium. To address these issues, it will be necessary to assess the temporal and spatial localization of hypoxia, Bnip3, and cell death in the postinfarct heart.

Which cell types mediate cardiac remodeling?
Diwan et al. (22) attributed improvement in postinfarct remodeling to inhibition of cardiomyocyte apoptosis in the noninfarcted myocardium. Postinfarct remodeling involves a complex interplay among multiple hematopoietic and resident cardiac

cell types (3). The use of a generalized *Bnip3* knockout in this study raises the question as to which cell type(s) mediate remodeling. Although Diwan et al. showed that the number and distribution of hematopoietic cells under basal conditions were unaffected by *Bnip3* inactivation, these cells were not analyzed following recruitment into the milieu of the infarcting heart. As one example, macrophages in an infarct stimulate fibroblast proliferation and matrix remodeling and, after exerting their effects, undergo apoptosis (3). Since *Bnip3* expression is induced by hypoxia in macrophages (25), it is possible that apoptosis of these cells in the healing infarct zone is impaired in *Bnip3*-knockout mice. Abnormal macrophage persistence could account for a thicker scar in the infarcts of *Bnip3*-knockout mice, as observed by Diwan et al., and resul-

some attractive biological characteristics as a drug target. First, its site of action within the central death machinery may provide a target for specific inhibition of cell death. Second, its low basal levels in most tissues may minimize the possibility of untoward effects in nontarget organs. Third, the fact that Bnip3 is induced in response to hypoxia suggests that there is a temporal window, prior to significant Bnip3 accumulation and cell death, during which treatment could be beneficially instituted. Despite these characteristics, significant logistical hurdles exist in designing a practical pharmacological approach to inhibit this intracellular protein.

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1. Kajstura, J., et al. 1996. Apoptotic and necrotic myocyte cell deaths are independent contributing variables of infarct size in rats. *Lab. Invest.* **74**:86–107.
2. Sutton, M.G., and Sharpe, N. 2000. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation.* **101**:2981–2988.
3. Frangogiannis, N.G. 2006. The mechanistic basis of infarct healing. *Antioxid. Redox Signal.* **8**:1907–1939.
4. Anversa, P., Beghi, C., Kikkawa, Y., and Olivetti, G. 1985. Myocardial response to infarction in the rat. Morphometric measurement of infarct size and myocyte cellular hypertrophy. *Am. J. Pathol.* **118**:484–492.
5. Mani, K., and Kitsis, R.N. 2003. Myocyte apoptosis: programming ventricular remodeling. *J. Am. Coll. Cardiol.* **41**:761–764.
6. Yaoita, H., Ogawa, K., Maehara, K., and Maruyama, Y. 1998. Attenuation of ischemia/reperfusion injury in rats by a caspase inhibitor. *Circulation.* **97**:276–281.
7. Matsui, T., et al. 2001. Akt activation preserves cardiac function and prevents injury after transient cardiac ischemia in vivo. *Circulation.* **104**:330–335.
8. Odashima, M., et al. 2007. Inhibition of endogenous Mst1 prevents apoptosis and cardiac dysfunction without affecting cardiac hypertrophy after myocardial infarction. *Circ. Res.* **100**:1344–1352.
9. Danial, N.N., and Korsmeyer, S.J. 2004. Cell death: critical control points. *Cell.* **116**:205–219.
10. Adams, J.M., and Cory, S. 2007. Bcl-2-regulated apoptosis: mechanism and therapeutic potential. *Curr. Opin. Immunol.* In press.
11. Willis, S.N., et al. 2007. Apoptosis initiated when BH3 ligands engage multiple Bcl-2 homologs, not Bax or Bak. *Science.* **315**:856–859.
12. Kim, H., et al. 2006. Hierarchical regulation of mitochondrion-dependent apoptosis by BCL-2 subfamilies. *Nat. Cell Biol.* **8**:1348–1358.
13. Yasuda, M., Theodorakis, P., Subramanian, T., and Chinnadurai, G. 1998. Adenovirus E1B-19K/BCL-2 interacting protein BNIP3 contains a BH3 domain and a mitochondrial targeting sequence. *J. Biol. Chem.* **273**:12415–12421.
14. Ray, R., et al. 2000. BNIP3 heterodimerizes with Bcl-2/Bcl-X(L) and induces cell death independent of a Bcl-2 homology 3 (BH3) domain at both mitochondrial and nonmitochondrial sites. *J. Biol. Chem.* **275**:1439–1448.
15. Bruick, R.K. 2000. Expression of the gene encoding the proapoptotic Nip3 protein is induced by hypoxia. *Proc. Natl. Acad. Sci. U. S. A.* **97**:9082–9087.
16. Chen, G., et al. 1997. The E1B 19K/Bcl-2-binding protein Nip3 is a dimeric mitochondrial protein that activates apoptosis. *J. Exp. Med.* **186**:1975–1983.
17. Vande Velde, C., et al. 2000. BNIP3 and genetic control of necrosis-like cell death through the mitochondrial permeability transition pore. *Mol. Cell. Biol.* **20**:5454–5468.
18. Regula, K.M., Ens, K., and Kirshenbaum, L.A. 2002. Inducible expression of BNIP3 provokes mitochondrial defects and hypoxia-mediated cell death of ventricular myocytes. *Circ. Res.* **91**:226–231.
19. Kubasiak, L.A., Hernandez, O.M., Bishopric, N.H., and Webster, K.A. 2002. Hypoxia and acidosis activate cardiac myocyte death through the Bcl-2 family protein BNIP3. *Proc. Natl. Acad. Sci. U. S. A.* **99**:12825–12830.
20. Hamacher-Brady, A., Brady, N.R., Gottlieb, R.A., and Gustafsson, A.B. 2006. Autophagy as a protective response to Bnip3-mediated apoptotic signaling in the heart. *Autophagy.* **2**:307–309.
21. Kubli, D.A., Ycaza, J.E., and Gustafsson, A.B. 2007. Bnip3 mediates mitochondrial dysfunction and cell death through Bax and Bak. *Biochem. J.* **405**:407–415.
22. Diwan, A., et al. 2007. Inhibition of ischemic cardiomyocyte apoptosis through targeted ablation of Bnip3 restrains postinfarction remodeling in mice. *J. Clin. Invest.* **117**:2825–2833. doi:10.1172/JCI32490.
23. Toth, A., et al. 2006. Targeted deletion of Puma attenuates cardiomyocyte death and improves cardiac function during ischemia-reperfusion. *Am. J. Physiol. Heart Circ. Physiol.* **291**:H52–H60.
24. Guo, K., et al. 2001. Hypoxia induces the expression of the pro-apoptotic gene BNIP3. *Cell Death Differ.* **8**:367–376.
25. Sowter, H.M., Ratcliffe, P.J., Watson, P., Greenberg, A.H., and Harris, A.L. 2001. HIF-1-dependent regulation of hypoxic induction of the cell death factors BNIP3 and NIX in human tumors. *Cancer Res.* **61**:6669–6673.

Obesity and the β cell: lessons from leptin

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In this issue of the *JCI*, Morioka et al. report on mice with a whole-pancreas knockout of the leptin receptor that exhibit improved glucose tolerance due to enhanced insulin secretion (see the related article beginning on page 2860). At first glance, their findings are very different from those reported in another recent study in which β cell–specific and hypothalamic knockout of the same gene caused obesity and impaired β cell function. The differences, which are understandable when one considers the body weights of the animals studied, provide new insight into the links among insulin, leptin action, and β cell function.

The prevalence of both obesity and type 2 diabetes are increasing at an alarming rate. Clearly, an improved understanding of the mechanisms involved in energy homeostasis will be required to halt these epidemics. In 1994, the cloning of the peptide hormone leptin, an adipocyte-derived factor secreted in proportion to body fat, opened new doors for exploring the molecular mechanisms underpinning energy homeostasis (1). However, despite an avalanche of new knowledge gained since then, many fundamental questions remain unanswered, including how systems regulating energy homeostasis interface with those that regulate glucose homeostasis.

Leptin and glucose homeostasis

Mice and humans that are deficient in either leptin (in the case of *ob/ob* mice) or the leptin receptor (*db/db* mice) not only develop obesity, but become both insulin resistant and glucose intolerant and are at high risk to develop diabetes (1–3). The pro-