A p53-Upregulated Modulator of Apoptosis (PUMA)
A Novel Proapoptotic Molecule in the Failing Heart

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As the leading cause of mortality in the United States, heart failure (HF) represents a disease state affected by a complex interplay between genetic, physiological, and environmental factors. Understanding the molecular mechanisms underlying the progression from normal cardiac function to ventricular dysfunction and overt HF will facilitate the identification of new therapeutic targets. Specifics of the underlying ultrastructural and molecular determinants of the progression to ventricular dysfunction and HF are still incompletely elucidated. The early adaptive response to increasing myocardial load and functional demand is characterized by cell hypertrophy and angiogenesis before pathological hypertrophy develops. A balance between compensatory hypertrophy and apoptotic pathways exists in the early stages of ventricular dysfunction, whereas upregulation of apoptotic pathways leading to myocyte damage and apoptosis as well as subsequent myocardial fibrosis is indicative of the progression to HF.1,2 There is evidence that apoptosis rates are increased in patients with HF,3 leading to the hypothesis that abrogation of apoptotic molecular pathways may be protective against the progression of disease.

In this issue of Circulation, Mandl et al4 present convincing evidence for a novel mechanism contributing to the progression of heart failure through a proapoptotic pathway mediated by p53-upregulated modulator of apoptosis (Puma), a BH3-only member of the Bcl-2 family, which induces apoptosis mediated partly via the tumor suppressor gene p53 pathway.5 This study demonstrates that Puma contributes to the apoptotic signaling pathway, which contributes to ventricular remodeling and HF. To model a pressure-overloaded state, Puma-deficient and wild-type mice were subjected to transverse aortic constriction. At 4 weeks after surgery, mice with gene deletion of Puma maintained normal fractional shortening, left ventricular end-diastolic diameter, and left ventricular end-systolic diameter compared with wild-type mice, which showed a decline in fractional shortening and increased left ventricular end-diastolic diameter and end-systolic diameter at 4 weeks. By 12 weeks after surgery, Puma−/− mice showed a decline in fractional shortening, suggesting that Puma knockdown delayed, but did not fully prevent, pressure-overload cardiac dysfunction. Of note, Puma−/− mice exposed to pressure overload had rates of hypertrophy similar to those of their wild-type counterparts, as measured by the ratio of heart weight to body weight, posterior wall thickness, and myocyte cross-sectional area. Additionally, there was no difference in the expression of angiogenic factors, such as vascular endothelial growth factor between the 2 groups, indicating that Puma does not induce pressure overload–induced angiogenesis. Because wild-type mice started showing nonadaptive hypertrophy with a decline in fractional shortening at 4 weeks but not 1 week after transverse aortic constriction surgery, the authors questioned whether this was mediated by Puma, showing that at 1 week after surgery the Puma levels in wild-type mice were similar to those at baseline, but that by 4 weeks there was a 2.75-fold increase, indicating that induction of a Puma is part of a molecular pathway leading to myocardial dysfunction and failure. To answer the question of whether Puma is in part regulated by p53 transcriptional activation, the authors analyzed Puma expression patterns in p53 knockout mice and found that transverse aortic constriction did not induce Puma at 4 weeks, suggesting that transcriptional activation is in part induced by p53. Next, the authors demonstrated that in Puma−/− mice the number of cells undergoing apoptosis by terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) and caspase-3 assays was significantly less than in wild-type mice, suggesting that Puma ablation suppresses apoptosis induced by pressure overload. The progression to fibrosis represents a critical step in ventricular remodeling; thus, the authors analyzed whether pressure overload–induced fibrosis was attenuated in Puma−/− mice, finding that in wild-type mice there was a 10-fold increase in fibrosis compared with Puma−/− mice, which showed only a 2- or 3-fold increase. The final question of this study was whether Puma ablation was protective against pressure overload–mediated myocardial dysfunction and failure in an unrelated genetic model of HF. The authors tested whether ablation of Puma could rescue the dilated cardiomyopathy phenotype in mdm4 knockout mice, and indeed were able to demonstrate that ablation of Puma in mdm4 gene deletion mice restores fractional shortening to nearly normal levels, decreases the rate of wall thinning associated with dilated cardiomyopathy, and decreases myocardial apoptosis as measured by TUNEL assays. Taken together, these data suggest a novel mechanism of progression from adaptive cardiac hypertrophy in the setting of pressure overload to pathological cardiac remodeling.
invoking a partially p53-dependent pathway though transcriptional activation of *Puma* that induces myocyte apoptosis and fibrosis. This elegant study shows that ablation of *Puma* reduces the progression to HF without affecting angiogenesis by decreasing stress-induced apoptosis and fibrosis and that it can rescue a genetically unrelated phenotype of dilated cardiomyopathy.

For the clinician, functional inhibition of *Puma* represents a new potential therapeutic target for inhibiting the progression to HF. *Puma* inhibitors are already being evaluated for their role in mitigating intestinal damage and apoptosis after abdominal radiation procedures for colon cancer,6 and deletion of *Puma* appears to protect hematopoietic stem cells during ionizing radiation for malignancy.7 Additionally, recent oncological studies have investigated whether *Puma* ablation can rescue nonmalignant cells from DNA damage caused by gamma radiation– and glucocorticoid-induced apoptosis in lymphoid cells.8 More specifically for the cardiologist, in a model of mouse myocardial infarction, *Puma* gene deletion mitigated the loss of cardiac function via cardiomyocyte death (both necrosis and apoptosis) on ischemia and reperfusion injury.9 Further studies can help to identify the mechanism through which *Puma* mediates apoptosis and to clarify the specific role of p53, especially in HF. For example, given that *Puma* mediates apoptosis is only partially dependent on p53-mediated transcription, it would be interesting to determine whether p53 mediates activation of *Puma* through cytoplasmic mechanisms as suggested by a recent study.10 Nevertheless, further studies are needed to investigate whether inhibition of *Puma*-mediated proapoptotic responses results in any potentially detrimental effects such as a neoplastic transformation of certain cell types.

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**Disclosures**

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**References**

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