Mechanism of Angiogenesis in the Damaged Heart

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Prolonged cardiac hypertrophy causes heart failure, but its mechanisms are largely unknown. Pressure overload, which is produced by constricting transverse aorta of mice, induced cardiac hypertrophy without cardiac dysfunction until 14 days and initially promoted vascular growth in the heart by hypoxia-inducible factor-1 (Hif-1)-dependent induction of angiogenic factors such as VEGF and angiopoietin-1. After 14 days, however, sustained pressure overload induced an accumulation of p53 that inhibited Hif-1 activity and thereby impaired cardiac angiogenesis and systolic function. To elucidate the mechanisms of how p53 is induced in cardiomyocytes by pressure overload, we examined the DNA damage. Pressure overload induced single-strand but not double-strand DNA break in cardiomyocytes leading to DNA damage responses including activation of H2γAX and p53. Accumulation of single-strand DNA break in the heart induced cardiac dysfunction. These results suggest that DNA damage could induce heart failure by activating DNA damage responses.

Erythropoietin has been reported to be beneficial on the heart after myocardial infarction, but the underlying mechanisms are unknown. Treatment of mice with erythropoietin inhibited left ventricular remodeling and improved cardiac function after myocardial infarction, independent of erythropoiesis and the mobilization of bone marrow-derived cells. Erythropoietin prevented cardiomyocyte apoptosis and increased the number of capillaries and mature vessels in infarcted hearts by upregulating the expression of angiogenic cytokines such as VEGF and angiopoietin-1 in cardiomyocytes. Erythropoietin also increased the expression of sonic hedgehog in cardiomyocytes, and inhibition of sonic hedgehog signaling suppressed the erythropoietin-induced increase in angiogenic cytokine expression. Furthermore, the beneficial effects of erythropoietin on infarcted hearts were abolished by cardiomyocyte-specific deletion of sonic hedgehog. These results suggest that erythropoietin protects the heart after myocardial infarction by inducing angiogenesis through sonic hedgehog signaling.