Modulation of Cardiac Performance by Motor Protein Gene Transfer

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ABSTRACT: Cardiac muscle performance can be determined by factors intrinsic to each cardiac muscle cell, such as protein isoform expression. One protein whose expression plays a major role in determining cardiac performance is myosin. Myosin is the heart's molecular motor that transduces the chemical energy from ATP hydrolysis into the mechanical energy of each heart beat. Alterations of myosin isoform expression are routinely associated with acquired and inherited cases of cardiomyopathy. For example, human heart failure is consistently associated with increased expression of a slow myosin motor isoform and a concomitant decreased expression of the heart's fast myosin motor isform. Further, mutations of the cardiac myosin gene are the most common cause of inherited hypertrophic cardiomyopathy. Transgenic animal studies have provided insight into cardiac functional effects caused by myosin isoform gene switching (fast to slow myosin or slow to fast myosin) or by expression of a disease-related mutant motor. More direct structure-function analysis using acute gene transfer of myosin motors provides evidence that the inotropic state of cardiac muscle can be affected by motor protein isoform shifting independent of intracellular calcium handling. Because most therapies for the diseased heart target intracellular calcium handling, acute gene transfer of cardiac molecular motors to modulate heart performance offers a novel therapeutic strategy for the compromised heart. Although the development of safe vectors for therapeutic myosin gene delivery are in their infancy, studies focused on acute genetic engineering of the heart's molecular motor will provide a foundation for therapeutic vector development and insight into mechanisms that contribute to cardiomyopathy.

KEYWORDS: **myosin; molecular motor; acute genetic engineering, cardiac performance**

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