CARDIAC AND PULMONARY REPLACEMENT

EDITORIAL: GENES PLAY A PART IN PROTECTING THE HEART—A BIT OF POETIC LICENSE

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In this issue of the Journal, Sawa and his colleagues present a well-conceptualized experiment. Using an inactivated viral transmitter, they successfully transfect intact hearts and demonstrate localization of genomic material in the nucleus, cytoplasmic expression of a gene product, and physiologic activity attributable to an overexpressed protein that is presumably the consequence of enhanced transcription (pretranslational control). Several facets of this study are worthy of comment.

The role of molecular biology in cardiac physiology and, more specifically, cardiac surgery has been evolving. Initially, molecular biologic techniques were used for diagnostic purposes to determine the appearance of new or altered gene products in abnormal myocardium. Thus our knowledge of altered proteins in cardiomyopathy, the existence of tiny amounts of neurotransmitters, and the down-regulation or discoordinate regulation of messengers for specific proteins have all been enhanced. Other studies took advantage of modifiers of gene expression to produce abnormal growth in cardiac cells by manipulation of promoters or enhancers (or both) of normally expressed genes. Such studies were most effective in transgenic animals. Other transgenic models have been used to demonstrate the effect of eliminating a gene product or overexpressing a particular product such as the β -receptor to demonstrate the physiologic role of those cellular elements. Such studies may ultimately lead to creating chimeras that may facilitate xenotransplantation through modification of surface antigens.

Real-time modulation of gene expression for a

useful physiologic purpose has been slow in coming, and for good reason. Oligonucleotides capable of serving as the template for subsequent message and protein synthesis have been introduced into cardiac cells by direct injection or by infusion into the coronary circulation, but with such a low expression rate that major transformation of myocytes has been disappointing. Viral vectors introduced into the cardiac circulation have appeared to be the most promising method for achieving high transfection rates. In this study, two unique features have been combined. First, the infective capsule of an inactivated hemagglutinating virus has been coupled mechanically into a liposomal structure. Second, by perfusion of the coronary circulation with this transducing agent, an extraordinarily high level of expression of the protein product resulted. Presumably, alteration of the cell membrane by cold, isolation of the coronary circulation, and structural properties of the viral capsule facilitated transfection. Although the number of animals studied was small, the most exciting aspect of these studies was that a physiologic effect of the overexpressed protein (manganese-superoxide dismutase) could be demonstrated vis-a-vis preservation of ventricular performance after a period of ischemia and reperfusion. The study design was complex, the potential for systematic error was high, and test conditions were difficult. Nonetheless, preserved ventricular function was demonstrated in association with Western block confirmation of increased enzyme levels.

Will these studies lead to any practical therapies? At least two methods of myocardial protection have been linked to enhanced expression of gene products. Heat shock protein appears to be an effective myocardial protective agent when overexpressed in myocytes, and overexpression of protein kinase induced by phorbol esters may play an important role in preconditioning. However, the delay between the genetic stimulus and expression of the protein product retards a practical approach to enhancing myocardial protection. Transfection of myocytes is asso-

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ciated with other concerns as well. Viral vectors mediate inflammatory responses within the myocardium and could prove detrimental in the long term or even incite autoimmune responses. The duration of expression of new gene products may be very short lived. Genomic material in the cytoplasm is rapidly destroyed. Genomic material that migrates into the nucleus of somatic cells is usually not replenished and has an effect that disappears after a few weeks. New genetic material is usually introduced without the benefit of specific regulators of its biochemical function, and normal physiologic mechanisms for controlling expression of these products is absent. Routinely high transfection rates may be difficult to achieve in settings other than those that modify cell membrane integrity.

The next decade will be of great importance in determining the practicality of these interventions.

Exciting potential applications of gene therapy might include normalization of abnormal contractile proteins in cardiomyopathies, rapid induction of cell hypertrophy in association with corrective operations that stress nonhypertrophied cardiac chambers, induction of proteins that could protect against intracellular oxidant stress, and facilitating recovery from ischemic injury by inducing overexpression of important cellular elements down-regulated in association with ischemia and reperfusion. The fantasy of inducing new myocyte growth as the controls in embryogenesis are better understood exists, as does the notion of regenerating cardiac tissue on structural matrices. Surface antigen modification may facilitate transplantation. Such interventions are a long trip from the observations made by Sawa and his colleagues, but the impetus to take the first steps certainly exists.