Smart Gene Therapy for the Heart

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The ultimate goal in the treatment of myocardial infarction (MI) is the delivery of therapeutic agents in a timely fashion that would be able to protect the heart from the deleterious effects of prolonged ischemia or the effects of repeated bouts of ischemia. The ideal agent would “know” when to become active, specifically in the affected area of the heart to limit side effects, and could be turned “off” after the ischemia is resolved. This “smart” approach would allow for treatment to protect the specific region of the heart most at risk for damage during ischemia while at the same time ending the therapy when the ischemic incident is resolved. This type of approach would foster rapid treatment with minimal outside intervention during the critical early phase of MI.

In this issue of Hypertension, Tang et al describe a novel gene therapy system for ischemic heart injury using an ischemia-sensing biosensor to activate the expression of a therapeutic gene (heme oxygenase-1 [HO-1]), which acts to limit the extent of ischemic injury.1 Because expression of the HO-1 gene is under the control of the ischemia biosensor, its expression is then subsequently turned off after the tissue is adequately oxygenated when proper blood flow is restored to the heart. This permits gene expression to be controlled at an unprecedented level, driven specifically by the pathological stimulus and lasting only as long as the stimulus persists.

The ischemic biosensor developed by Tang et al is composed of an oxygen-sensing transactivator (OST), which is a GAL4 DNA-binding domain fused to the oxygen-dependent degradation domain (ODD) of the hypoxia-inducible factor-1α protein (HIF-1α) along with p65 activation domain.1 Under conditions of hypoxia, the OST is able to activate expression of a therapeutic target gene under the control of a GAL4 upstream activating sequence (UAS) fused to an adenovirus TATA box. The authors express this biosensor under the control of a cardiac-specific promoter to restrict its expression to the heart.

Oxygen-sensing by cells is a basic physiological function and has been an intensive area of research for a number of years.2 Although the mechanism of oxygen-sensing in bacteria has been worked out for some time, only recently has the puzzle of oxygen-sensing in higher organisms been slowly put together.3,4 Most of what we know about the regulation of gene expression by oxygen has come from the study of a group of genes whose expression is regulated by hypoxia, the so-called hypoxia-inducible factors (HIFs). The HIFs are a family of transcription factors that are able to activate a variety of genes whose function varies from angiogenesis to metabolism.5 The HIFs consist of heterodimeric complexes, of which one of the subunits (HIF-α subunit) that makes up the complex is very unstable under normoxic conditions but is stabilized on exposure to hypoxic conditions.

Recent studies have identified the mechanism of stabilization of the HIF-α subunit on exposure to hypoxia.3,4 Under normoxic conditions, the HIF-α subunit is hydroxylated at a conserved proline residue in the ODD by an enzyme of the prolyl-hydroxylase family. This protein modification requires molecular oxygen and iron as cofactors. The hydroxylated HIF-α subunit is then recognized by the von Hippel-Lindau tumor-suppressor protein (pVHL) and targeted for degradation by the ubiquitin pathway. Because the hydroxylation of the HIF-α subunit by the prolyl-hydroxylase is oxygen-dependent, conditions of hypoxia lead to stabilization of the HIF-α subunit, which then serves as a transcription factor to act on its target genes. Interestingly, the von Hippel-Lindau protein was first identified as the cause of von Hippel-Lindau disease, which is a hereditary cancer syndrome characterized by tumors that express high levels of hypoxia-inducible genes such as vascular endothelial growth factor (VEGF).6

One of the exciting aspects of the approach described by Tang et al is the ability to directly link expression of potentially therapeutic genes to the pathological stimulus associated with MI, ischemia.1 By placing the biosensor used in the current study under the control of different cell-specific promoters, a similar approach could be used to limit ischemic damage to the other organs as well. For example, if the ischemia biosensor were placed under the control of a neural or glial cell specific promoter, it would be possible to direct expression of therapeutic genes to limit neural damage associated with stroke. A similar approach could also be developed to protect organs during transplantation, because the protective gene would only be active during the storage of the organ and then switch off once normal blood flow was reestablished. Even more exciting is the potential to create biosensors that could detect alterations in blood flow or shear stress to direct therapeutic gene expression in other pathological conditions such as atherosclerosis and hypertension.

A limitation of the approach described in the study by Tang et al is the transient nature of expression of the sensor and

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The use of biosensors will allow us to move beyond conventional methodologies for gene therapy in which therapeutic genes are expressed in a constitutive fashion to a system in which the expression of a therapeutic gene is controlled by the specific pathological stimulus itself. As we learn more about the specific signals, physical and chemical, that drive the most common pathological conditions of the heart, this approach could be extended to help fight other pathologies of the heart such as hypertrophy and arrhythmias. Ultimately, this area of research will pave the way for development of “smart” therapies for the heart that will allow for early and rapid treatment of a wide variety of cardiac ailments.

References
5. Huang LE, Bunn HF. Hypoxia-inducible factor and its biomedical relevance. *J Biol Chem.* 2003;278:19575–19578.
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