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In This Issue

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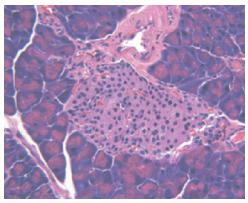
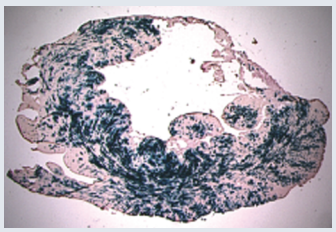
B7-H1 can go both ways The immunomodulator B7-H1 can be inducibly expressed in a variety of tissue types. Several studies have proven B7-H1 is a negative regulator of T cell responses in vitro through antibody inhibition in cell lines and in vivo through B7-H1.Ig fusion protein injection. These observations led researchers to investigate B7-H1 as a clinical target for inhibiting the T cell response in order to generate immune tolerance during transplants and in the treatment of autoimmune diseases. Yang-Xin Fu, Maria-Luisa Alegre, and colleagues now show that in addition to its immunomodulatory effects, B7-H1 can have stimulatory effects on T cell-mediated responses (pages 694–700). The authors generated transgenic mice expressing B7-H1 in pancreatic islet β cells to study the immunomodulatory effects of local expression in nonlymphoid tissues. When B7-H1-expressing islets were transplanted, mice had accelerated allograft rejection, signifying an upregulation of the immune response. Moreover, mice developed T cell-dependent autoimmune diabetes, supporting the notion that B7-H1 can promote rather than inhibit T cell-mediated responses. These findings lead us to question the development of B7-H1 targeted immune response strategies, since B7-H1 can direct positive or negative signals depending on its specific cellular setting.See figure Gene therapy for a broken heart Despite significant advances in the treatment of cardiac disease, chronic heart failure remains a leading cause of morbidity and mortality. […]

B7-H1 can go both ways



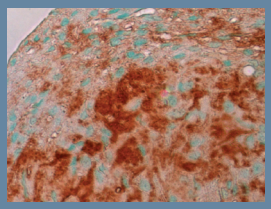
The immunomodulator B7-H1 can be inducibly expressed in a variety of tissue types. Several studies have proven B7-H1 is a negative regulator of T cell responses in vitro through antibody inhibition in cell lines and in vivo through B7-H1.Ig fusion protein injection. These observations led researchers to investigate B7-H1 as a clinical target for inhibiting the T cell response in order to generate immune tolerance during transplants and in the treatment of autoimmune diseases. Yang-Xin Fu, Maria-Luisa Alegre, and colleagues now show that in addition to its immunomodulatory effects, B7-H1 can have stimulatory effects on T cell–mediated responses (pages 694–700). The authors generated transgenic mice expressing B7-H1 in pancreatic islet β cells to study the immunomodulatory effects of local expression in nonlymphoid tissues. When B7-H1–expressing islets were transplanted, mice had accelerated allograft rejection, signifying an upregulation of the immune response. Moreover, mice developed T cell–dependent autoimmune diabetes, supporting the notion that B7-H1 can promote rather than inhibit T cell–mediated responses. These findings lead us to question the development of B7-H1 targeted immune response strategies, since B7-H1 can direct positive or negative signals depending on its specific cellular setting.

Gene therapy for a broken heart



Despite significant advances in the treatment of cardiac disease, chronic heart failure remains a leading cause of morbidity and mortality. Investigators studying the molecular mechanisms of cardiomyocyte dysfunction offer potential new strategies, such as gene therapy, for the treatment of heart failure. John Ross, Jr., and colleagues make promising strides toward this effort by focusing on the SR calcium–ATPase 2 (SERCA2) inhibitor phospholamban (pages 727–736). Gene delivery to express a pseudophosphorylated form of phospholamban (S16EPLN) in chronically failing rat hearts after myocardial infarction exerted beneficial effects on the ailing hearts. The presence of S16EPLN upregulated SERCA2 activity in transduced cells and compensated for defects in calcium uptake during heart failure. Echocardiographic and hemodynamic measurements showed improvements in global function and contractility in the rats that received S16EPLN treatment. Moreover, cardiac remodeling and fibrosis were suppressed in these animals. Although further long-term studies are necessary to clarify the effects of modifying phospholamban on arrhythmias, gene transfer of S16EPLN shows promise as a novel strategy for the treatment of chronic heart failure.

Cartilage reconstruction



Nearly half of the elderly population suffers from osteoarthritis, a degenerative joint disorder characterized by degradation of articular cartilage. Because this disorder is so widespread, finding a regenerative source of cartilaginous tissue would prove invaluable to the orthopedic field. In an effort to regenerate cartilage, Sakae Tanaka and colleagues investigated the signaling mechanisms involved in cartilage-specific gene expression in synovial fibroblasts (SFs) (pages 718–726). A component of the synovial tissue that lines the nonarticular surfaces of joints, SFs are specialized cells that have recently been suggested to have chondrogenic potential. The authors were able to analyze the signaling cascades involved in the differentiation of SF cells into chondrocytes by expressing constitutively active forms of activin receptor–like kinases ($ALK3^{CA}$, $ALK5^{CA}$, and $ALK6^{CA}$) in synovial fibroblasts. Adenovirus-mediated expression of $ALK3^{CA}$ strongly induced chondrocyte-specific marker expression, and $ALK3^{CA}$ virus–infected cultures produced a cartilaginous matrix. Transplantation of these cells into mice induced cartilaginous differentiation and cartilage matrix formation. Further experiments elucidated critical roles for both the Smad and p38 downstream signaling pathways in chondrogenic differentiation of SFs, whereby balance of these two signals will be critical in engineering chondrocytes for cartilage reconstruction.

Vaccines nip breast cancer in the bud

Breast cancer screens are able to identify preneoplastic lesions that can become cancerous. Using the rHER-2/*neu* transgenic mouse model for mammary carcinogenesis, Federica Cavallo and colleagues evaluated vaccine strategies for treating neoplastic lesions (pages 709–717). The authors designed a combined approach consisting of a primary vaccination with plasmids encoding portions of $rp185^{neu}$ and a booster vaccination one week later with cells expressing the protein and engineered to release IFN-γ. Of mice that received the combined vaccine, 48% remained tumor free for the duration of the study, a significant improvement over untreated mice and mice receiving only the primary vaccine. Both morphologic analysis of the lesions and microarray analysis of gene expression in parallel revealed that the immune reaction halted carcinogenesis and reverted neoplastic lesions to an early stage. This study highlights the potential of a combinatorial approach to vaccination for the prevention and suppression of neoplastic lesions.