Item Number 229 - Transgenic Mouse Model for Congestive Heart Failure

Published date: Feb. 1, 2012

Technology description

Summary

Our researchers have developed five transgenic mouse strains that overexpress human annexin VI protein in heart tissue. This protein is a potent regulator of calcium release and other membrane processes essential to healthy cardiac function. Mice overexpressing annexin VI die from congestive heart failure. Pathological examination indicates that the mice have enlarged hearts, acute diffuse myocarditis, lymphocytic infiltration and moderate to severe fibrosis throughout the heart and around the pulmonary veins.Background
The annexins are a family of calcium-dependent phospholipid binding proteins containing repeated domains of approximately 70 amino acids in length. All of the annexins contain four repeat domains except for annexin VI, which contains eight. Annexin VI is expressed in many tissues including heart, and has been shown to be a potent regulator of the skeletal muscle ryanodine-sensitive calcium release channel, the sodium-calcium exchanger and other membrane processes.
Our transgenic mice were developed by targeting expression of full-length human annexin VI cDNA to heart using the alpha myosin heavy chain gene (àMHC) promoter. At least 10-fold overexpression is exhibited in both atria and ventricles, as determined by Western blot analysis. By immunolocaliza- tion, we have confirmed àMHC promoter-specific overexpression of annexin VI in cardiomyocytes and pulmonary veins. Contractile mechanics of cardiomyocytes isolated from hearts of transgenic mice showed reduced shortening, decreased rates of contraction and increased rates of relaxation compared to controls. Free calcium dynamics monitored during the contraction and relaxation cycle using fura-2 indicated that cardiomyocytes from transgenic animals have lower basal levels of intracellular free calcium, and the same rise in free calcium following depolarization. After stimulation, calcium returns to relative basal levels faster in cell from the transgenic mice than in cells from control mice. These results from completed studies suggest that overexpressing annexin VI in heart disrupts normal calcium homeostasis and suggests that this dysfunction may be due to annexin VI regulation of pumps, channels and/or exchanger in the membranes of cardiomyocytes.

Application area

Our findings suggest that the mice would be useful as animal models for investigating physiological processes associated with congestive heart failure and for screening prospective therapeutic agents.

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