The adult heart enlarges and increases in weight in response to ischemic stress and hypertension, a process termed cardiac hypertrophy. However, the heart also increases in size after regular physiological exercise. Cardiac hypertrophy is recognized as an important process in the development of heart failure. Initial results pointed to a clear signaling pattern of physiological hypertrophy after training versus pathological hypertrophy after damage. Although the signaling mechanisms involved have been studied for more than a decade, there is no clear distinction at the molecular level of physiological and pathological hypertrophy.1 Rather, the balance between signaling pathways preventing deterioration and pathways activated in association with preserving left ventricular function is regarded as critical. Accordingly, the terms adaptive and maladaptive were introduced to reflect these processes, respectively.2 A potential treatment avenue could be to selectively identify pathways involved in maladaptive hypertrophy that could be blocked. Alternatively, enhancing signaling pathways specifically involved in adaptive hypertrophy might allow us to conserve left ventricular function.

Cai et al have identified a new target in cardiac hypertrophy: the receptor-associated late transducer (RALT).3 RALT appears to be a specific antagonist of maladaptive hypertrophy (Figure). Mechanistically, RALT functions as a negative regulator of epidermal growth factor receptor–mediated signaling not only in the heart but in other organs as well. The investigators used angiotensin II and isoproterenol as stimuli for stress-induced, maladaptive left ventricular remodeling in transgenic mice overexpressing RALT under the control of the α-myosin heavy chain (α-MHC) promoter. Cai et al found that RALT protected against maladaptive hypertrophy. The mechanism was identified with in vitro experiments; RALT downregulated several pathways that depend on activation of the epidermal growth factor receptor.

The approach of overexpressing RALT with the α-MHC promoter is accompanied by all the problems involved in overexpressing any protein. However, the lack of a baseline phenotype supports the notion that the mice had only limited overexpression. This state of affairs allowed for conclusive studies regarding the function of RALT. The authors convincingly showed that their transgenic mice were protected against angiotensin II– and isoproterenol-induced hypertrophy by using various end points, including the fetal gene programs (brain natriuretic peptide, atrial natriuretic peptide, and expression of β-MHC). Echocardiography results and cross-sectional area measurements of adult cardiomyocytes were used to monitor hypertrophy. The most surprising finding was that the RALT transgenic mice exhibited preserved left ventricular function and lacked the hypertrophy-induced left ventricular dilation. Further, histological analysis revealed reduced fibrosis and collagen production after RALT overexpression. Finally, Cai et al found that RALT failed to influence cardiomyocyte programmed cell death (apoptosis).

The results reported by Cai et al are reminiscent of the effects described for a nuclear signaling molecule termed the transcriptional repressor (NAB1). Buitrago et al reported that NAB1 is an endogenous regulator of cardiac growth.4 They showed that NAB1 was upregulated in both mouse and human heart failure. NAB1 was highly expressed in mammalian cardiac myocytes and inhibited cardiomyocyte hypertrophy through repression of the transcription factor early growth response. NAB1 overexpression suppressed adrenergically induced and pressure overload–induced maladaptive hypertrophy, whereas physiological growth during development and in response to exercise was not affected.

Nonetheless, the difference between maladaptive and adaptive cardiac hypertrophy at the cellular level remains unclear. Presuming that the α-MHC promoter is only targeting end-differentiated adult cardiomyocytes, these cells can either undergo enlargement and become multinucleated cells (cellular hypertrophy) or undergo apoptosis. The cells cannot undergo cell division. Whatever the interpretation concerning this issue might be, these 2 studies confirm the existence of specific pathways that allow the modulation of cardiac hypertrophy with functional benefits, namely the stabilization or even improvement of left ventricular function despite ongoing stress signals.

For years, α-MHC–driven gene expression or gene targeting has been regarded as specifically targeting adult cardiomyocytes. These end-differentiated cells may undergo cellular hypertrophy, in which the cells enlarge and become multinucleated but do not undergo cell division. These cells are also more prone to undergo apoptosis. The balance between apoptotic and hypertrophy signaling could be crucial in separating maladaptive and adaptive hypertrophy responses. RALT apparently inhibits cardiomyocyte hypertrophy without increasing apoptosis. This state of affairs could in part explain the phenotype observed by Cai et al, including
the protection against secondary fibrosis. To answer the question of the cellular mechanism, it is important to analyze the type of cells affected by α-MHC–driven RALT overexpression.

The α-MHC promoter has been used to drive transgene expression or DNA recombination using the Cre/lox system. Indeed, α-MHC activation itself has an early peak at embryonic day 7.5, only to be silenced at embryonic day 14 in exchange for β-MHC. After birth, the α-MHC promoter is again reactivated to completely replace β-MHC. Therefore, α-MHC promoter activation is used to drive expression of selected transgenes in the adult heart to specifically target differentiated cardiomyocytes, which are believed to be the only cells in the adult heart exhibiting α-MHC promoter activation. The vascular system and fibroblasts do not express α-MHC. Some phenotypes using the α-MHC promoter revealed embryonic phenotypes attributable to the early expression peak.

Yet a new twist to the understanding of cardiac hypertrophy was added recently. A genetic fate-mapping study showed that cardiac regeneration is involved in postinfarct remodeling, at least in the border zone, of an experimental infarct model in rodents. In this border zone area, >20% of the cardiomyocytes were found to have regenerated from an unknown cell source 4 weeks after injury. In addition, our laboratory recently identified a population of resident precursor cells that are affected by α-MHC–driven gene recombination. These cells, which are located near the endocardium and epicardium, are GATA4⁺ but TropT⁻. The cells appear to arise from the left ventricular/first heart field cardiac development program because they were found to be Tbx5⁺ but islet-1⁻. The cells were clearly affected by α-MHC–driven gene recombination. This finding has implications for the results reported by Cai et al. The phenotype might also be attributable to an effect of RALT on the plasticity of cardiac endogenous stem cells. These new data suggest that the amount of endogenous regeneration is of critical importance.

The observed presence of fibrosis (control mice) or cardiac tissue (RALT-transgenic mice) may represent a secondary effect because fibroblasts are negative for α-MHC. Additional studies are needed to address the role of RALT and other targets shown to antagonize maladaptive cardiac hypertrophy in the context of quantitative cardiac endogenous regeneration. It is intriguing that targeting cardiac signaling indeed allows for functional stabilization despite ongoing stress.

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**References**

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