

ATF3-dependent cross-talk between cardiomyocytes and macrophages promotes cardiac maladaptive remodeling

Cardiovascular diseases are disorders of the heart and blood vessels which are leading to heart failure. Cardiovascular diseases correspond to 30% of all deaths in the world. The molecular processes that undergone from a healthy heart to a failing heart is called cardiac remodeling. This process initiates as an adaptive response of the heart to un-met capacity, however, turns into a maladaptive response when the un-met capacity becomes chronic leading to heart failure. Cardiac remodeling is associated with an increase in the heart size known as cardiac hypertrophy. The exact molecular mechanisms responsible for cardiac enlargement are not well understood, but understanding them is crucial for the development of novel treatments and prevention of heart failure. Although, cardiac hypertrophy involves primarily the heart resident cells, the cross-talk between the heart cells and other tissues is critical for understanding how adaptive response turns into maladaptive changes.

Cardiac remodeling involves the alteration of gene expression program in the heart and in the related tissues. Transcription factors are the proteins that are responsible to control gene expression in health and disease states. A case in point is the Activating Transcription Factor 3 (ATF3). ATF3 is not expressed in healthy tissues, however, is highly induced following various stress stimuli. ATF3 is considered as an adaptive cellular hub transcription factor in response to stress. Indeed, in the heart, ATF3 is highly expressed in response to multiple heart stressors, however, the role of ATF3 in cardiac remodeling is unknown. In this study, we have generated various modified mice which are unable to express ATF3 in various cells and tissues in the body. Using these mice, we studied the cardiac remodeling response to pressure overload by implanting pumps that release a molecule that mimics high blood pressure leading to maladaptive cardiac remodeling processes in the heart. In this study, we identified ATF3 as a protein responsible for maladaptive remodeling. Ablation of ATF3 specifically in cardiomyocytes (heart contracting cells) or bone marrow derived cells is sufficient to blunt the cardiac remodeling processes in the heart. In the bone marrow, ATF3 expression in macrophages is found to be important for the cardiac remodeling processes. Our model suggests that cardiomyocytes ATF3 expression is necessary for the initial steps in cardiac remodeling. This results in the induction of ATF3 expression in macrophages leading to their recruitment to the heart resulting in cardiac remodeling. This study places ATF3 as a critical transcription factor responsible for the cross-talk between the heart and macrophages leading to maladaptive cardiac remodeling. Thus, ATF3 is a bone fide drug target to suppress maladaptive cardiac remodeling processes to reduce heart failure deaths following chronic pressure overload.

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