TITLE: The interplay of cardiac developmental factors T-box transcription factor 20 (Tbx20) and Bone morphogenetic protein 2 (Bmp2) and their cross-talk with miR-101-3p in regulating cardiac homeostasis in rodent cardiomyopathy model

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ABSTRACT

Cardiovascular diseases (CVDs) are currently the leading cause of death worldwide. In mammals, the fetal cardiomyocytes are highly proliferative; however, shortly after birth, they exit the cell cycle. This study primarily aims to understand the transcriptional regulation of cardiac transcription factors in reinitiating cardiac proliferation and identify early biomarkers for effective therapeutic intervention during cardiomyopathy. The Endoplasmic Reticulum (ER) is an organelle that organizes and executes the production and assembly of a myriad of proteins. Any perturbation is this machinery results in the generation of ER stress, which in turn activates the Unfolded Protein Response (UPR). There is a very fine balance between ER stress-induced pro-survival and pro-apoptosis. T-box transcription factor 20 (Tbx20) is a cardiogenic transcription factor that plays an important role in cardiac development and homeostasis. Here, we for the first time show that during ER stress, Activating transcriptionfactor 6 (Atf6) drives the expression of Tbx20, which in turn activates downstream signaling involving Bone morphogenetic protein 2 (Bmp2)-pSmad1/5/8 to augment cardiomyocyte proliferation and limit apoptosis. In addition, ER stress *in vivo* as well as diabetic cardiomyopathy results in an elevation in the expression level of Tbx20 with concomitant upregulation of cardiomyocyte proliferation via Bmp2-pSmad1/5/8. However, prolonging the stress resulted in decreased expression of Tbx20 and Bmp2 in cardiomyocytes, whereas the expression of Bmp2 increased drastically in cardiac fibroblasts. Upon delineating the cause for the decrease of Tbx20 and increase of Bmp2 during prolonged stresses, we unravelled the novel mechanism where miR-101-3p binds to the 3'UTR of the *tbx20* gene in cardiomyocytes, thereby resulting in its suppression and concomitant increase of senescent response in cardiac tissue. We also showed miR-101-3p negatively regulates Noggin expression in cardiac fibroblasts during prolonged stress, thus indirectly augmenting the level of Bmp2 and, in turn, the inflammatory response. By differentially regulating Tbx20 in cardiomyocytes and Bmp2 in cardiac fibroblasts, miR-101-3p exacerbates both the severity and progression of cardiomyopathy. Overall, our study uncovers a novel mechanism involving Tbx20-Bmp2 and their cross-talk with miR-101-3p to regulate cardiac homeostasis during cardiomyopathy.

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