S08-7 Cardiac fibrosis and purine receptor

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Cardiac fibrosis is characterized by excessive deposition of extracellular matrix proteins and accompanied with hypertrophy, which is one of the causes of heart failure and it contributes to the impairment of cardiac function. It is believed that fibrosis of various tissues such as the heart and the liver is regulated by the signaling pathway of angiotensin II (Ang II) and transforming growth factor-β (TGF-β). To examine the role of the heterotrimeric G_{12} family G protein ($G\alpha_{12/13}$) in the heart, we developed transgenic mice that specifically express inhibitory polypeptides of $G\alpha_{12/13}$ in cardiomyocytes. Transgenic expression of the inhibitory polypeptide suppresses pressure overload-induced fibrosis without affecting hypertrophy. The expression of fibrotic genes (TGF-β, connective tissue growth factor, and periostin) and angiotensin-converting enzyme (ACE) is suppressed by the inhibition of $G\alpha_{12/13}$. Using mechanical stretch of cardiomyocytes as a model of pressure overload, we found that mechanical stretch initiates ATP and UDP release and induces fibrotic gene expression through $G\alpha_{12/13}$. Furthermore, inhibition of G-protein-coupled $P2Y_6$ receptors suppresses the expression of ACE, fibrotic genes and cardiac fibrosis. These results indicate that $P2Y_6$ receptor-$G\alpha_{12/13}$ signaling in cardiomyocytes by the extracellular nucleotides-stimulated mediates pressure overload-induced fibrosis, and this signaling cascade works as an upstream of Ang II and TGF-β.