Heart and skeletal muscle development are complex events that require a time dependent, coordinated series of protein expression and regulation. Myocyte enhancer factor 2 (MEF2) proteins are key regulators of both cardiac and skeletal muscle lineages that are vital for activation and maintenance of genes representing the structural components of sarcomeric muscle. In mice, MEF2A/C targeted gene ablation results in aberrant heart formation and premature death, whereas in Drosophila melanogaster, D-mef2 loss of function results in complete loss of all muscle tissues. Characterizing the signaling network that controls MEF2 transcription factors is crucial for understanding skeletal and cardiac muscle gene expression. By using different combinations of glycogen synthase kinase 3 beta (GSK3β) and p38 mitogen activated protein kinase (MAPK) inhibitors in immortalized C2C12 myoblasts, we found that GSK3β regulates MEF2 activity through reciprocal regulation of p38. We further investigated this relationship by ectopically expressing constitutively active forms of GSK3β and p38 in myoblasts. Finally, we confirmed this relationship in vivo and in the heart using LacZ-MEF2 transgenic mice, as well as cardiomyocytes from GSK3β(-/-) mice. Understanding cross-talk in the signaling network converging at MEF2 control has therapeutic implications in cardiac and skeletal muscle pathology.

Reference: Dionyssiou MG, Nowacki NB, Hashemi S, Zhao J, Kerr A, Tsushima RG, McDermott JC. Cross-talk between glycogen synthase kinase 3β (GSK3β) and p38MAPK regulates myocyte enhancer factor 2 (MEF2) activity in skeletal and cardiac muscle. J Mol Cell Cardiol. 2013 Jan;54:35-44. doi: 10.1016/j.yjmcc.2012.10.013

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