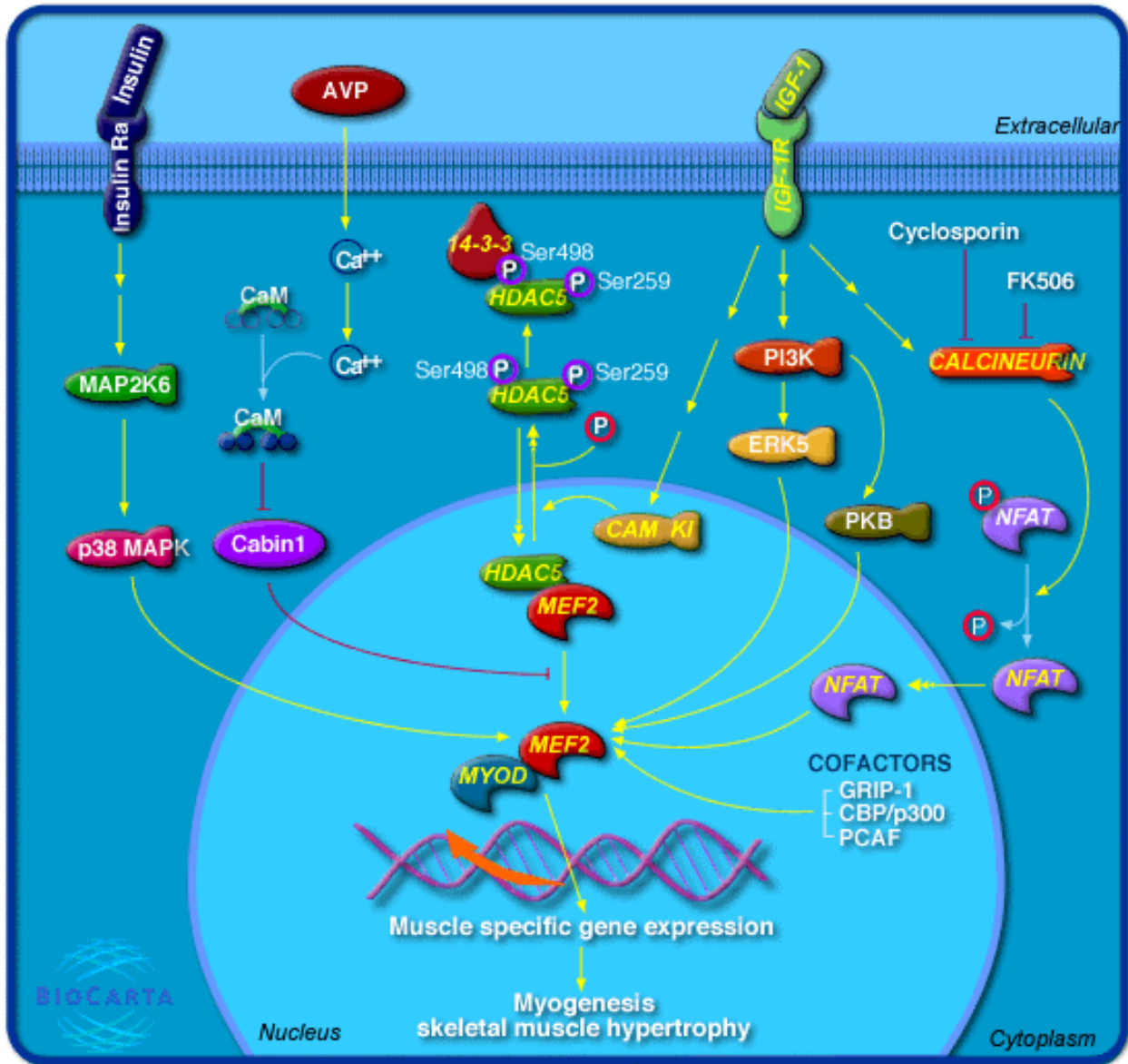


Heart



The differentiation of muscle cells is transcriptionally regulated, in part by the myocyte enhancer factor-2, MEF2. During myogenesis MEF2 binds to MyoD and other basic helix-loop-helix factors to activate transcription of genes involved in muscle cell differentiation. Transcriptional activation by MEF2 is blocked by interaction with HDAC5 and other histone deacetylases. In undifferentiated myoblasts, HDAC5 is present in the nucleus where it binds to MEF2 to block activation of muscle genes. When activated by IGF-1 signaling, CaM kinase phosphorylates HDAC proteins, causing them to be exported from the nucleus, releasing the block on MEF2 transcriptional activation and allowing differentiation to proceed. Transcription cofactors also interact with MEF2 to contribute to gene regulation and myogenesis. The transcriptional regulator NFAT, for example, acts as a cofactor for MEF2

when calcium and calcineurin signaling activate it.

There are four members of the Mef2 gene family, Mef2a-2d. Mef2a is expressed in brain, heart and skeletal muscle. Mef2c is involved in myogenesis in cardiac and skeletal muscle. Mef2d is widely expressed, and may be involved in the regulation of T cell function as well as muscle. (See Mef2Pathway) Several factors regulate Mef2 transcription factors, including Map kinases and histone deacetylase (HDAC) enzymes. Mef2 is phosphorylated by p38 map kinase, and phosphorylation of Mef2c by p38 contributes to skeletal muscle differentiation. BMK-1 (also called Erk5) is another member of the Map kinase family that regulates the activity of Mef2 family members and is unique in that it appears itself to possess a transcriptional activation domain and act as a transcriptional coactivator. Mek3 disruption prevented normal cardiovascular development in mice and appears to signal through p38 and Mef2c in normal cardiovascular development.