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Zhang, Min

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Committee Chair:	Herring, B. Paul
Committee Members:	Firulli, Anthony B. Pavalko, Frederick M. Rhodes, Simon J.
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Abstract:

There are many clinical diseases involving abnormal differentiation of smooth muscle, such as atherosclerosis, hypertension and asthma. In these diseases, one important pathological process is the disruption of the balance between differentiation and proliferation of smooth muscle cells. Serum Response Factor (SRF) has been shown to be a key regulator of smooth muscle differentiation, proliferation and migration through its interaction with various accessory proteins. Myocardin Related Transcrition Factors (MRTFs) are important co-activators of SRF that induce smooth muscle differentiation. Elucidating the mechanism of how MRTFs and SRF discriminate between genes required to regulate smooth muscle differentiation and those regulating proliferation will be a significant step toward finding a cure for these diseases. We hypothesized that SWI/SNF ATPdependent chromatin remodeling complexes, containing Brg1 and Brm, may play a role in this process. Results from western blotting and quantitative reverse transcription - polymerase chain reaction (qRT-PCR) analysis demonstrated that expression of dominant negative Brg1 or knockdown of Brg1 with silence ribonucleic acid

(siRNA) attenuated expression of SRF/MRTF dependent smooth muscle-specific genes in primary cultures of smooth muscle cells. Immunoprecipitation assays revealed that Brg1, SRF and MRTFs form a complex in vivo and that Brg1 directly binds MRTFs, but not SRF, in vitro. Results from chromatin immunoprecipitation assays demonstrated that dominant negative Brg1 significantly attenuated SRF binding and the ability of MRTFs to increase SRF binding to the promoters of smooth muscle-specific genes, but not proliferation-related early response genes. The above data suggest that Brg1/Brm containing SWI/SNF complexes play a critical role in differentially regulating expression of SRF/MRTF-dependent genes through controlling the accessibility of SRF/MRTF to their target gene promoters. To examine the role of SWI/SNF in smooth muscle cells in vivo, we have generated mice harboring a smooth muscle-specific knockout of Brg1. Preliminary analysis of these mice revealed defects in gastrointestinal (GI) development, including a significantly shorter gut in Brg1 knockout mice. These data suggest that Brg1-containing SWI/SNF complexes play an important role in the development of the GI tract.

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