Regulation of SRF Activity by the ATP-dependent Chromatin Remodeling Enzyme, CHD8

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Rodenberg, Jennifer Marie

Name: Jennifer M Rodenberg ...
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Committee Chair:	Herring, B. Paul
Committee Members:	Gallagher, Patricia J. Pavalko, Fredrick M. Skalnik, David
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Abstract:

Under normal conditions, smooth muscle cells do not replicate, or proliferate, and provide a means of contraction for many internal organs, including blood vessels and the gut. However, under abnormal or disease conditions, such as congenital heart disease and cancer, smooth muscle cells acquire the ability to replicate, to make extracellular matrix proteins and to migrate. Thus, determining how smooth muscle cells regulate these processes is crucial to understanding how the cells can switch between normal and diseased states. Serum response factor (SRF) is a widely expressed protein that plays a key role in the regulation of smooth muscle differentiation, proliferation and migration. It is generally accepted that one way that SRF can distinguish between these functions is through pathway-specific co-factor interactions. A novel SRF co-factor, chromodomain helicase DNA binding protein 8 (CHD8), was originally isolated from a yeast two-hybrid assay. CHD8 is widely expressed in adult tissues including smooth muscle. Data from in vitro binding assays indicate that the N-terminus of CHD8 can interact directly with the MADS domain of SRF. Co-immunoprecipitation assays verified the ability of these two proteins to interact within cells. Adenoviral-mediated shRNA knockdown of CHD8 in smooth muscle

cells resulted in statistically significant 10-20% attenuation of expression of SRF-dependent, smooth muscle-specific genes. Similar experiments revealed that knockdown of CHD8 did not affect the SRF-dependent induction of immediate early genes required to promote proliferation. In contrast, knockdown of CHD8 in A10 vascular smooth muscle cells resulted in a marked induction in of apoptosis, characterized by increases in apoptotic markers such as phospho-H2A.X, cleaved PARP and activated caspase-3. These data suggest that CHD8 may play a specific role in modulating SRF's activity toward anti-apoptotic genes, thereby regulating smooth muscle cell survival.

Description:

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