The role of Brahma-related gene 1 in regulating the expression of microRNAs in colonic smooth muscle cells

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Previous work by our group has shown that mice harboring null mutation of Brahma-related gene 1 (Brg1)-an ATPase subunit of SWI/SNF (SWItch/Sucrose NonFermentable) chromatin remodeling complex have reduced smooth muscle contractility and disorganized smooth muscle cells (SMCs) in colon, which are similar defects to those of microRNA maturation enzyme Dicer-deficient mice. Recently microRNAs (miRs) such as miR-143/145 have been implicated in the regulation of gene expression essential for smooth muscle cell proliferation and differentiation. Thus we aimed to identify the microRNAs that were involved in regulating the phenotypic changes in Brg1-deficient colonic smooth muscle cells and determine how Brg1 regulated them. The microRNA array screens of colonic smooth muscle and quantitative reverse transcription-polymerase chain reaction assays identified 6 miRs were down-regulated and 6 were up-regulated in smooth muscle specific Brg1 knockout tissue compared with control. Inactivation of endogenous Brg1 by introducing dominant negative Brg1 into wild type SMCs in vitro decreased miR-143/145 expression in smooth muscle cells. In Brg1 null SW13 cells, miR-143/145 were dramatically induced by myogenic transcriptional co-factor myocardin only in the presence of Brg1. Chromatin immunoprecipitation assays demonstrated that myocardin together with Brg1 increased the binding of transcription factor serum response factor (SRF) to the promoter region of miR-143/145 gene cluster. In conclusion, Brg1 together with myocardin can induce the transcription of miR-143/145 through enhancing the binding of SRF to the promoter region in SMCs. Together this suggests that SWI/SNF mediated chromatin remodeling regulates the phenotype of colonic smooth muscle by regulating expression of microRNAs that further modulate expression of their targets.

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