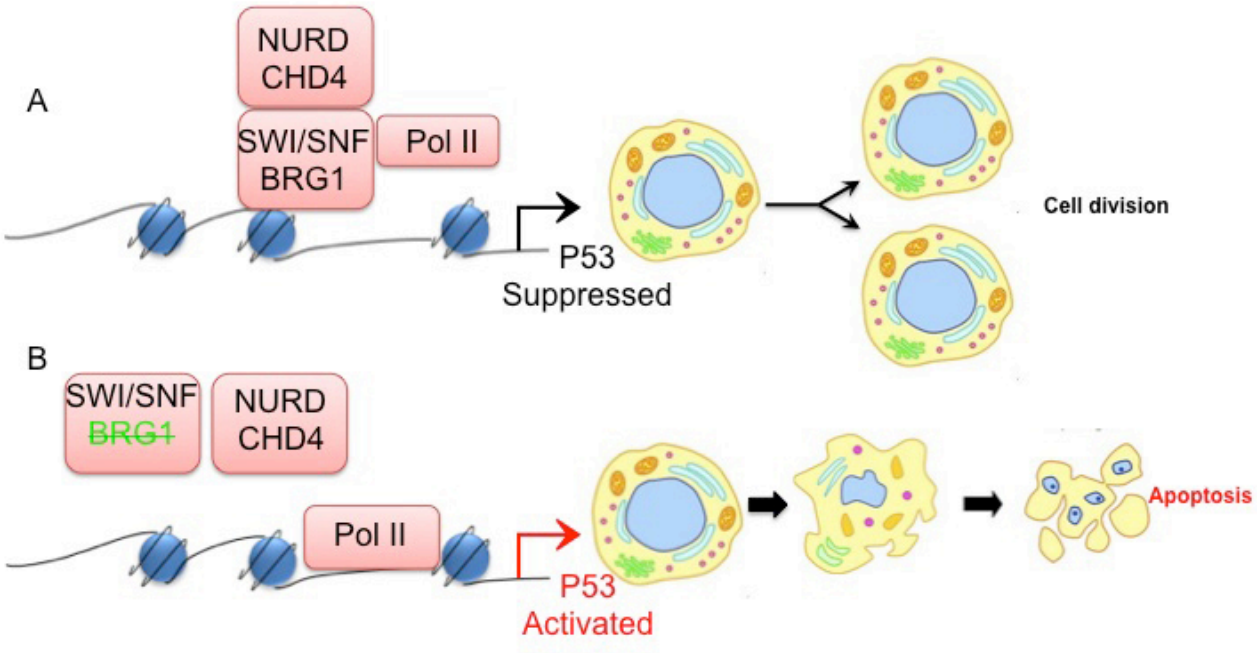
Is chromatin remodeling required to modulate embryonic development?

Chromatin remodeling is active critical process during embryonic development and in cellular malignancies such as cancer. Chromatin is the highly condensed form by which the genomic material (DNA) is packaged in the cell nucleus. The fundamental subunit of chromatin, the nucleosome, is composed of ~146bp DNA wrapped around histone octamers (two copies of each of four core histones, Histon2A, Histone2B, HistoneH3 and HistoneH4). The linker Histone H1 connects nucleosomes to further facilitate the compaction/packaging of genomic materials in cell nucleus. Genes embedded in condensed chromatin require structural conformational changes for activation/repression during specific cellular and developmental processes.



In wild type embryos, basal expression of *p53* is regulated in part be catalytic enzymes of the SWI/SNF and NuRD chromatin remodeling complexes to allow normal cellular growth (A). Ablation of the *Brg1*, the catalytic subunit of the SWI/SNF complex, in embryos lead to increased *p53* expression and the activation of genes downstream of the *p53-pathway* resulting in reduced proliferation and induced apoptosis in development (B).

Mammals possess four major chromatin remodeling complexes SWI/SNF, ISWI, NURD, and INO80 stem. Among these complexes, SWI/SNF complexes are well studied and play vital roles in a variety of physiological functions including development, metabolism, immune function, and

reproduction. The SWI/SNF complex is ~1.5-megadaltons and comprises 10-15 subunits. Brg1 (Brahma related gene 1) and Brm (Brahma) are the mutually alternative catalytic subunits of the SWI/SNF complex, which utilize the energy of ATP hydrolysis to move or exchange nucleosomes. The “complex” that remodels the chromatin structure in specific context has yet to be discovered. One particular area where Dr. Singh in the laboratory of Dr. Trevor Archer at NIEHS/NIH has concentrated over the past several years is identifying specific functions of the SWI/SNF complex that regulates chromatin dynamics and gene expression in development and cancer.

The simultaneous manifestation of rapid processes cell self-renewal, proliferation and differentiation are required for the formation of multicellular organism, and cancer cells acquire similar phenomena. Similarly, programmed cell death is integral aspect of various processes of development and removal of abnormal and overproduced cells. However, abnormal timing, amount or localization of cell death leads to abnormalities or death of embryos. Several transcription factors and signaling pathways regulate cell proliferation and trigger cell death. However, the molecular mechanisms that control cell death in embryos are not well understood.

A recent research study published by Singh et al. showed chromatin remodeling is required during embryogenesis. Using state of the art, genetic loss of function approach in mouse model, temporal deletion of chromatin-remodeling factor *Brg1* in early embryos result developmental arrest and mortality. We observed *Brg1* protein is strongly and ubiquitously express in early embryo and its expression persisted with developmental time that culminates in the form of morphological changes. This finding led us to hypothesize that *Brg1* is a global regulator and might be essential in embryos across development. Then we tested our hypothesis that global deletion of *Brg1*could affects embryonic growth. *Brg1* deletion in embryos caused retarded growth and elevated cell death.

Additionally we observed decreased cellular proliferation, as manifested by diminished expression of proteins regulates cell cycle. Evaluation of BrdU incorporated nuclei demonstrates significantly lower levels of positively stained cells in *Brg1* mutants compare to wild-type control embryos. These observations led us to examine gene expression changes at global level that are potentially responsible for the phenotype of *Brg1* deficient embryos. Global gene expression analysis revealed *p53-signaling* as the top up regulated pathway in *Brg1* mutant embryos. This suggested that aberrant expression of *p53-pathway* induced apoptosis and reduced cell proliferation that intruded rapid processes of development and results in abnormalities, and, ultimately embryonic mortality. Interestingly, cancer cells mimic early embryonic state, *Brg1* silencing in embryonic cancer cell line P19 reduced proliferation and increased expression of *p53-signaling* pathway genes. By performing molecular and biochemical study’s authors provided mechanistic insights on the action of *Brg1*regulating chromatin and gene expression in early developing embryo and cancer cells.

In conclusion, our study suggests that chromatin remodeling is integral in response to the rapid process of early embryonic development. We demonstrated a novel molecular mechanism of Brg1-mediated regulation of gene expression into higher need of cell proliferation and limitation of

inappropriate cell death during development. Finally, the findings of our study of cell death in embryos will help scientists/clinicians understand its function in a variety of diseases including cancer.

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Publication

Brg1 Enables Rapid Growth of the Early Embryo by Suppressing Genes That Regulate Apoptosis and Cell Growth Arrest.
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