Editorial

Stem Cell INVESTIGATION

Arid1a controls tissue regeneration

Shuai Wu, Rugang Zhang, Benjamin G. Bitler

Gene Expression and Regulation Program, The Wistar Institute, Philadelphia, PA 19104, USA

Correspondence to: Benjamin G. Bitler, PhD. Gene Expression and Regulation Program, The Wistar Institute, Room 312, 3601 Spruce Street, Philadelphia, PA 19104, USA. Email: bbitler@wistar.org.

Received: 27 June 2016; Accepted: 25 July 2016; Published: 09 August 2016.

doi: 10.21037/sci.2016.07.07

View this article at: http://dx.doi.org/10.21037/sci.2016.07.07

Switch/Sucrose non-fermentable (SWI/SNF) chromatin remodeling complexes are crucial for regulating temporal and spatial gene expression during development (1). SWI/SNF disrupts the DNA-histone interaction in an ATPase-dependent manner, alters the chromatin architecture and promotes a "poised" chromatin state (2,3). The poised state of chromatin makes it accessible for specific transcriptional regulators to facilitate tissue-specific gene expression profiles (4-6). SWI/SNF function is highly dependent on its subunit composition. Several SWI/SNF subunits, such as BAF155, BAF250a/b (*ARID1A/B*) and BRG1, are reported to affect self-renewal and differentiation in many tissues and embryonic stem (ES) cells (6-8). SWI/SNF complexes also increase transcriptional reprogramming efficiency during development (9). These studies implicate the SWI/SNF complexes are essential to embryonic development and tissue-specific differentiation.

Tissue regeneration is similar to the embryonic developmental process (10). Both processes undergo reorganization and rearrangement of tissue architecture and have unique gene expression patterns. However, the role of SWI/SNF complexes in tissue regeneration has not been addressed. Sun *et al*. recently reported that loss of a SWI/SNF component, Arid1a, promotes liver and ear hole wound regeneration in mouse models (11). Using different liver injury (surgical and chemical) assays in Arid1a conditional and global knockout (KO) mice, Arid1a depletion greatly enhances regenerative capacity. Conversely, Arid1a overexpression blocked liver regeneration.

During development the subunit composition of the SWI/SNF complex changes to facilitate a tissue-specific gene expression signature (9). These tissue-specific SWI/SNF complexes are important in cellular differentiation. For example, overexpression of embryonic stem SWI/SNF (esBAF) significantly increases reprogramming efficiency (12). Overexpression of neural SWI/SNF (nBAF) can convert human fibroblasts to neurons (9). Sun *et al*. showed that Arid1a expression is absent in neonatal liver and begins to be expressed after 10 days. ES cells are thought to have high capacity of regeneration. The findings indicate it is possible that suppression of Arid1a enhances cellular reprogramming and promotes the capacity of regeneration. An interesting observation is that Arid1a is suppressed after injury. Often injury induces several signaling pathways, such as cAMP, JAK-STAT3 and mTOR (13,14). It will be intriguing to determine how injury regulates Arid1a levels and whether injury affects other SWI/SNF subunits.

Previous studies reported SWI/SNF complexes composed of ARID1B or ARID1A are functionally distinct (15). For example, ARID1A depletion promotes cells to enter the cell cycle, while ARID1B depletion induces cell cycle arrest (16). ARID1A loss does not affect the integrity of SWI/SNF complexes. However, ARID1A loss enhances ARID1B's association with the SWI/SNF in a mutually exclusive manner. Sun *et al*. found that loss of Arid1a leads to activation of repressed E2F4 target genes through reducing E2F4 binding on the promoters. This indicates Arid1b cannot rescue Arid1a's role in the suppression of tissue regeneration.

Arid1a deficiency not only promotes liver regeneration, but also improves regeneration in ear-hole wound. This suggests that improvement of regeneration by Arid1a loss is not tissue-specific. ARID1A is a tumor suppressor, which is frequently mutated in ovarian cancer and other cancers (17,18). So, in transformed tissues increased regenerative capacity by depletion of Arid1a may contribute to cancer regenerative potential (or stemness). In the context of human cancers with ARID1A loss-of-function mutations,

whether surgically removal of tumor induces rapid relapse due to regeneration and proliferation has not been examined. Notably, loss of ARID1A expression in ovarian clear cell carcinoma correlates with late-stage disease and predicts early recurrence (19). Regardless, understanding the mechanism of injury-induced suppression of Arid1a will allow for development of therapies that directly control ARID1A expression.

The SWI/SNF complexs play a critical role in transcription by regulating the chromatin and epigenetic landscape. In normal liver tissue from Arid1a wildtype and KO mice, Sun *et al.* evaluated Arid1a's impact on chromatin and transcription through chromatin immunoprecipitation of Arid1a followed by next generation sequencing (ChIP-seq) and RNA-seq. These data reveal that Arid1a significantly binds DNA with C/ebpα and Hnf4a motifs. Subsequently, C/ebpα ChIP-seq in Arid1a KO liver revealed C/ebpα is depleted at a majority of Arid1a-associated genes. Transcriptional profiles indicate Arid1a inhibits regeneration by promoting differentiation through C/ebpα and inhibiting proliferation through E2F4. As an important subunit of SWI/SNF chromatin remodeler, Arid1a deficiency makes the chromatin less accessible for transcription factors, including activators, such as C/ebpα and Hnf4a, and repressors, such as E2F4. However, the malleable chromatin state conveyed by a loss of Arid1a allows for improved regeneration in response to injury.

SWI/SNF mutations are detected in ~20% of all human cancers based on The Cancer Genome Atlas analysis (9). However, Sun *et al.* did not observe tumorigenesis in Arid1a KO mice, which is consistent with previous studies (20,21). Mutations of SWI/SNF complex subunits (ARID1A, BRG1 and PBRM1) convey synthetic lethality through targeting of the polycomb repressor complex protein, EZH2 (22,23). All these SWI/SNF components are important for the function of the complex. Here, suppression of Arid1a promotes regeneration through altering SWI/SNF function. Analogously, does suppression of BRG1 or EZH2 or other subunits also promote regeneration?

The authors' distinct viewpoint and exciting findings open a new direction to study the SWI/SNF complexes. This is the first report to determine the impact of modulating SWI/SNF complex composition on tissue regeneration. Their findings bring a series of interesting questions, for example, how injury suppresses Arid1a expression and whether suppression of other SWI/SNF subunit affects regeneration. With the deeper understanding of the role of SWI/SNF in tissue regeneration, the insight gained from the mechanistic studies will provide scientific rationale for developing therapeutic strategies to promote tissue regeneration and target SWI/SNF-mutated cancers.

Acknowledgements

Funding: This editorial is supported by US National Institutes of Health/National Cancer Institute grants (R01CA163377 and R01CA202919 to R Zhang), US Department of Defense (OC140632P1 and OC150446 to R Zhang), an Ovarian Cancer Research Fund (OCRF) program project (to R Zhang) and The Jayne Koskinas & Ted Giovanis Breast Cancer Research Consortium at Wistar. BG Bitler is supported by a US National Institute of Health/National Cancer Institute grant (K99CA194318).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Sun X, Chuang JC, Kanchwala M, *et al.* Suppression of the SWI/SNF component Arid1a promotes mammalian regeneration. Cell Stem Cell 2016;18:456-66.

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doi: 10.21037/sci.2016.07.07
Cite this article as: Wu S, Zhang R, Bitler BG. Arid1a controls tissue regeneration. Stem Cell Investig 2016;3:35.

