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The epigenetic basis of cellular plasticity

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Cellular plasticity is now recognized as a fundamental feature of tissue biology. The steady-state differentiation of stem and progenitor cells into mature cells is, in itself, the index form of cellular plasticity in adult organisms. Following injury, when it is critical to quickly regenerate and restore tissue integrity and function, other types of cellular plasticity may be crucial for organismal survival. In these contexts, alterations in the epigenetic landscape of tissues are likely to occur in order to allow normally restricted cell fate transitions. Epigenetic mechanisms, particularly DNA methylation and histone modifications, have been shown to play an important role in regulating such plasticity. Relevant mechanisms have been well studied in the context of the direct reprograming of somatic cells into induced pluripotent stem cells. Indeed, epigenetic regulation of cell fate is part and parcel of normal embryonic development and is a central regulator of cellular diversity. This is normally thought to involve the establishment of divergent chromatin patterns that culminate in cells with distinct and what were previously thought to be irreversible fates. This brief review aims to put some of these new observations in the larger context of regeneration after injury.

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Cellular plasticity

In multicellular organisms, individual progenitor cells are thought to undergo progressive cell fate restriction on the path to forming fully mature differentiated cells. This concept was promulgated by Conrad Waddington through his conceptualization of an epigenetic landscape for the embryo [1]. However, his diagram did not directly address the restriction of cell identity in adult tissues [2•]. Seminal experimental work in hematopoiesis reinforced his paradigm. This thinking was naturally extended to solid tissues. However, modern experimental evidence has revealed that cell state is remarkably dynamic, especially after injury in epithelia.

It is likely that some forms of adult cellular plasticity are central for organismal survival following injury, particularly when it is critical to quickly restore tissue integrity and function after the loss of cells [3,4]. Plasticity phenomena were initially described on the basis of careful histologic and marking experiments and can now be categorized into a few baskets based on stringent genetic lineage tracing with cell type specific markers: (1) a mature cell can dedifferentiate and revert into a progenitor cell of the same lineage, (2) a mature cell can transdifferentiate into another mature cell, and (3) a progenitor cell can transdetermine and convert into another type of progenitor cell. With regard to dedifferentiation, it is now known that a fully differentiated secretory cell in the mammalian airway can dedifferentiate into a stem cell following ablation of the original stem cell population [5]. Similar examples of dedifferentiation have been reported in fly testis [6,7], and in the stomach and intestine [8–11]. With regard to transdifferentiation, there is evidence that mature δ-cells of the pancreas and the hepatocytes of the liver can convert into insulin producing β-cells and biliary epithelial cells, respectively [12,13]. In the case of transdetermination, work in the fly imaginal disks revealed that progenitor cells could adopt the behavior of related but distinct progenitors [14–16]. The basis of these forms of plasticity is just beginning to be defined. Some of it is likely based on the nature of pre-existing transcriptional networks. But clearly, in the context of injury and environmental perturbation, there must be a rewiring of the epigenetic landscape in the sense that cells of a particular fate can be redirected into another distinct fate, despite the fact that these paths do not normally exist in the embryo or in steady state adult tissues. In emerging new data, epigenetics, in the more restricted modern usage of the term (inheritable, non-genetic histone and DNA alteration), is also clearly at play in regulating plasticity after injury.

There are three major classes of epigenetic modifiers that govern gene expression: (1) DNA methylation, (2) histone marks, and (3) non-coding RNAs. Proteins that read, write, and/or erase DNA and histone modifications are

well described to play key roles in the regulation of cell identity. When promoters and transcription start sites are methylated, activating transcription factors are prevented from binding these regulatory elements or repressive chromatin remodeling complexes are recruited to these regions and result in the repression of gene expression [17–19]. Histone modifications often result in an alteration of the distance between nucleosomes, and have an impact on chromatin compaction and result in the recruitment of histone-modifying complexes that activate or repress gene expression [20]. Genomic imprinting is a prominent example of epigenetic regulation during development. X-chromosome inactivation is regulated by histone modifications and the action of a non-coding RNA, called Xist [21–23].

Polycomb group (PcG) proteins are important epigenetic regulators that act in synergy during development to deposit repressive histone marks that govern tissue-specific gene expression in adulthood [24,25]. The polycomb repressive complex (PRC)-2 mediates the deposition of H3K27me3 via the catalytically active SET-domain-containing proteins Ezh1 and Ezh2, whereas the other two core PRC2 members, Suz12 and Eed, are required for complex stability [26].

The epigenetic basis of cellular plasticity has been very well studied during the direct reprogramming of somatic cells into induced pluripotent stem cells (iPSCs). In addition to alterations of the transcriptional network, ectopic expression of reprogramming transcription factors generates a chromatin landscape that is highly similar to that of embryonic stem cells (ESCs) [27,28,29,30•]. Similarly, open chromatin in ESCs is maintained through the action of chromatin-modifying complexes [31•,32,33]. The INO80 complex, a SWI/SNF family chromatin remodeler, has been shown to play a role in ESC self-renewal and direct reprogramming. INO80 is recruited to pluripotency loci and mediates the maintenance of an accessible chromatin state [31•]. During reprogramming, chromatin alterations are also caused by the induction of locus-specific DNA demethylation [30•,34–36]. Following reprogramming of the female fibroblast cells into iPSCs, the somatic epigenome is globally reversed into an epigenetic state similar to ES cells. In this case, the previously silenced X chromosome is reactivated, indicating that the epigenetic marks can be erased upon reprogramming [30•]. The newly activated X chromosome undergoes random X inactivation upon subsequent differentiation of iPSCs, suggesting that the newly forming epigenetic state can be re-established, independent of the previous epigenetic landscape [30•].

The molecular epigenetic basis of cellular plasticity in adult tissues

In many ways, the index form of adult cellular plasticity is the steady state differentiation of stem and progenitors cells into mature cells [37]. In the case of the intestine, multipotent stem cells possess a broadly permissive chromatin configuration that presumably allows multiple pathways of differentiation to occur (Figure 1) [38••]. During intestinal stem cell differentiation, Notch-mediated lateral inhibition governs the cell fate choice between a secretory and an enterocyte lineage. Interestingly, both secretory and absorptive progenitors showed comparable levels of activating histone marks, H3K4me2 and H3K27ac. Similarly, DNaseI hypersensitivity suggested open chromatin states that allow for either final cell fate choice in both sets of progenitors. The binding of a secretory-specific transcription factor, ATOH1, in intestinal stem cells promotes secretory progenitor cell differentiation. When *Atoh1* is depleted from specified secretory cells, increased enterocyte progenitors are formed (Figure 1) [38••]. This fate acquisition or transdifferentiation is possible because enterocyte-associated chromatin is retained in its open configuration in secretory progenitors. Thus, intestinal progenitors possess broadly open chromatin that allows cell fate switching based on the presence or absence of particular lineage-restricted transcription factors. Presumably, if differentiation was associated with the closing of chromatin linked to alternative lineage-specific genes, plasticity would be restricted.

In the steady state epidermis and hair follicle, the respective stem cells express Klf5 and Sox9, and these lineage-associated transcription factors are required for the maintenance of these stem cells. The expression of these genes is regulated by specific epidermal and hair follicle epicenters within super enhancers (Figure 2a) [39••,40]. During wound repair, both Klf5 and Sox9 are expressed simultaneously. And this dual Klf5 and Sox9 expression in 'wound stem cells' are necessary for repair. In the instance of wound cells, the transient co-expression of Klf5 and Sox9 is associated with (1) a new wound epicenter, (2) the loss of epidermal and hair follicle epicenters, and (3) the expression of activating stress-associated transcription factors (Figure 2b) [39••]. After wound repair, the steady state expression of Klf5 and Sox9 is restored in epidermal and hair follicle stem cells, respectively. In tumors, wound epicenters do occur, but are also associated with new tumor epicenters as well as a sustained expression of Klf5, Sox9, and stress-associated transcription factors (Figure 2C) [39••]. Therefore, while epigenetic plasticity is critical for proper wound repair, it must be tightly regulated to prevent cancer.

The epigenetic regulation of cellular plasticity in lungs

In lung, as in other tissues, epigenetic mechanisms regulating cell plasticity are just beginning to be explored. During development, conditional loss of Ezh2 (a SET-domain-containing subunit of the PRC2 complex, responsible for deposition of H3K27me3 [26]) results in defective branching morphogenesis and impaired