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Review

The Yin and Yang of Chromatin Dynamics In Stem Cell Fate Selection

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Adult organisms rely on tissue stem cells for maintenance and repair. During homeostasis, the concerted action of local niche signals and epigenetic regulators establish stable gene expression patterns to ensure that stem cells are not lost over time. However, stem cells also provide host tissues with a remarkable plasticity to respond to perturbations. How adult stem cells choose and acquire new fates is unknown, but the genome-wide mapping of epigenetic landscapes suggests a critical role for chromatin remodeling in these processes. Here, we explore the emerging role of chromatin modifiers and pioneer transcription factors in adult stem cell fate decisions and plasticity, which ensure that selective lineage choices are only made when environmentally cued.

Tissue Stem Cells In and Out of Their Niche

One of the fascinating questions in developmental biology is how different cells within a given tissue acquire different properties that allow them to work together as a functional unit. At the heart of this problem are adult stem cells, which are essential building blocks to fuel tissue homeostasis and regeneration. Adult stem cells reside in specialized niches, which profoundly impact their activity and maintenance. Changes in this microenvironment allow stem cells to exit the niche and make tissue and/or repair wounds. However, this poses a dilemma for stem cells: how can they retain their ability to survive outside the stem cell niche (see Glossary), how do they choose appropriate fates and what defines the point of reversibility versus commitment to differentiation? The notion that stem cells acquire greater fate flexibility after injury or transplantation suggests that besides the impact imposed on stem cells by their native niche, additional mechanisms must be in place to govern stem cell identity, fate decisions, and plasticity (Box 1).

While genome-wide chromatin mapping of cultured embryonic stem cells and other cell types have provided new insights into cellular states, *in vitro* mRNA and protein expression profiles have long been known to differ dramatically from their *in vivo* tissue counterparts. Such observations suggest that gene expression, and likely chromatin dynamics, of stem cells will also be highly dependent upon their native niche microenvironment. If so, tackling the mechanisms underlying chromatin dynamics and their physiological relevance will necessitate *in vivo* analyses. This is especially important for adult stem cells, where there are often multiple steps in lineage commitment that cannot be easily understood or recapitulated outside the confines of the tissue. Indeed, even with the handful of recent *in vivo* studies conducted thus far, it is already clear that cell-intrinsic, dynamic chromatin modifications play major roles in adult stem cells, which make lineage choices by integrating changes in niche signals with transcriptional circuitries that determine cell identity.

In this review, we focus on various adult stem cell populations and summarize recent advances on chromatin dynamics that have contributed to the emergence of new concepts in stem cell biology.

Trends

Adult stem cells coordinate niche signals and chromatin states to choose appropriate fates. Upon changes in the local niche environment, stem cells remodel chromatin to survive in transitional states, before undergoing fate selection.

Epigenetic repressors put a brake on precocious lineage commitment. DNA methylation and Polycomb-silencing complexes cooperate to ensure that stem cells are robustly maintained during homeostasis.

Cell identity depends on combinatorial transcription factor complexes on lineage-specific enhancers. Pioneer factors select unique enhancer repertoires by making condensed chromatin accessible for robust gene activation.

Epigenetic memory is achieved by coupling pioneer factors with super-enhancers, allowing stem cells to retain their unique identities in different microenvironments.

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Box 1. Cellular Plasticity – Stem Cells Remain True to Themselves

Adult stem cells are characterized by their ability to self-renew for long term and to produce differentiated cell lineages. As such, they are used sparingly and their main function is to fuel tissue homeostasis. However, it has become increasingly clear that the fate and multilineage potential of adult stem cells can change depending on whether a stem cell exists within its resident niche, whether it is mobilized to repair a wound, or whether it is challenged to *de novo* tissue morphogenesis after expansion in culture and following transplantation [107]. As such, cellular plasticity is the ability of stem cells to adapt to a new microenvironment outside the niche and survive in limbo. Therefore, plasticity is not tested until cells are faced with a new microenvironment.

In most mammals, the epidermis has a dense array of hair follicles, which typically make negligible contribution to epidermal homeostasis. Upon injury, however, hair follicle stem cells efficiently migrate out of their niche and into the epidermis, where they contribute long term to wound repair. In the process, these stem cells lose hair follicle markers and adopt features of epidermal stem cells [108]. Plasticity is not a feature that is limited to stem cells. After ablation of mammalian epithelial stem cells, either by laser or using diphtheria toxin, the empty niche can recruit and induce normally committed cells to proliferate and revert back to a progenitor-like state. Indeed, hair follicle stem cells can be replaced by committed cells above the niche, while hair germ cells can be readily replenished if hair follicle stem cells are intact [93,98]. Similarly in the intestinal crypt, loss of $LGR5^{+}$ stem cells triggers dedifferentiation of committed precursor cells into functional stem cells, which then repopulate the crypt [94,97].

Collectively, these studies have uncovered the dramatic plasticity within mammalian tissues following injury. Stem cells can acquire greater fate flexibility to replenish multiple lineages, whereas upon stem cell loss, their progeny and even differentiated cells may dedifferentiate to repair tissue damage.

DNA Methylation – No Longer Just a Stable Silencing Mark

Although the full complexity of epigenetic regulation is only starting to unveil, DNA methylation is of particular relevance for tissue homeostasis. DNA methylation provides a means for functional variability while maintaining the information content of the nucleotide: In mammals, the fifth carbon of the pyrimidine ring of CpG dinucleotides can become methylated (5mC) [1]. As a result of the spontaneous deamination of 5mC, C→T transitions at CpG dinucleotides account for >30% of all point mutations in human genetic disorders.

During development, CpG methylation is established by *de novo* **DNA methyltransferases** DNMT3A and DNMT3B [2]. The 5mC pattern is then faithfully preserved by DNMT1, which is targeted to hemimethylated DNA by UHRF1 during DNA replication [3]. While the majority of cytosine residues within CpG dinucleotides are methylated, **CpG islands** at promoters remain mostly unmethylated, a feature that has long been surmised to create a permissive environment for transcription initiation [4]. Indeed historically, DNA methylation has been considered a stable silencing mark, ensuring tissue-specific gene expression in a heritable manner throughout development. As such, DNA methylation is critical for control of gene transcription, establishment of cellular identity, silencing of transposon elements, parental imprinting, and X-chromosome inactivation [2].

The presence of 5mC is thought to inhibit transcriptional activation by preventing the binding of many transcription factors to DNA and by recruitment of methyl-binding proteins (e.g., MeCP2 or MDB1) and histone deacetylases, which ultimately generate a repressed chromatin environment [5]. However, recent evidence suggests that DNA methylation is more dynamic than hitherto appreciated. Although 5mC can be lost passively through imperfect maintenance, the discovery of ten eleven translocation (TET) family enzymes provided a compelling means for catalyzed active demethylation [6]. TET enzymes first convert 5mC into 5-hydroxymethylcytosine (5hmC), which can subsequently be reverted to cytosine through iterative oxidation and thymine DNA glycosylase (TDG)-mediated base excision repair [7–9].

Dynamic DNA methylation is achieved by the interplay between DNMT and TET enzymes, and becomes a powerful strategy to regulate gene activity, as was recently found for stem cell lineage progression. Even though global changes are modest, dynamic DNA methylation/demethylation

Glossary

Chromatin remodeling: dynamic modification of nucleosome structure, composition, and positioning to modulate gene expression.
CpG island: short sequence of DNA with over-representation of CG dinucleotides compared with the genomic average; 40–70% of human promoters contain CpG islands.
DNA methyltransferases (DNMTs): catalyze the methylation of DNA on cytosines in CpG dinucleotides. Methylation occurs on the fifth carbon of the pyrimidine ring of cytosines.
Enhancer: regulatory DNA sequence containing multiple transcription factor binding sites. Enhancers activate transcription at a distance and independently of their orientation with regard to the target gene.
Epicenter: short (< 2 kb) active subdomains within super-enhancers, which are particularly enriched for transcription factor binding sites and allow for cooperative binding. Epicenters are cell stage-specific and change dynamically depending on the microenvironment.
Histone modifications: post-translational modifications whereby specific amino acid residues, particularly in histone tails, become chemically modified. These modifications include methylation, acetylation, phosphorylation, ubiquitination, or ADP-ribosylation, and in a combinatorial manner, can affect histone–DNA interactions, histone–histone interactions, and the affinity for other proteins that regulate chromatin function. Specific histone modifications are linked to either an active or silenced chromatin state.
Pioneer factors: a special class of transcription factors able to access their DNA target sites in silent chromatin. As such, pioneer factors establish competence for future gene expression by opening up local chromatin structure and facilitating the subsequent recruitment of additional transcription factors.
Polycomb repressive complexes (PRCs): multiprotein complexes that reversibly modify chromatin structure and silence target genes.
Stem cell niche: local tissue microenvironment that hosts and influences the behaviors or characteristics of stem cells.
Stem cell plasticity: the ability of stem cells to adapt to a new