

# Epigenetics, noncoding RNAs, and cell signaling – crossroads in the regulation of cell fate decisions

Editorial overview

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For a complete overview see the [Issue](#)

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**Robert Blelloch** received a MD and PhD from the University of Wisconsin – Madison in 2001. He did clinical and postdoctoral training at Brigham and Women's Hospital and the Whitehead Institute for Biomedical Research respectively. In 2006, he joined the faculty of the UCSF where he holds the Peter Carroll Endowed Chair. His lab studies the role of post-transcriptional regulation and epigenetics in mammalian cell fate decisions and cancer. They have performed seminal work on how microRNAs function to promote and silence the pluripotent stem cell fate. His lab has also uncovered novel classes of small RNAs and has studied their roles in early mammalian development.

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**J. Silvio Gutkind** received his Ph.D. in Pharmacy and Biochemistry from the University of Buenos Aires, Argentina. He was a postdoctoral fellow at the NIMH and NCI, and joined the NIDCR, NIH, where he is currently the Chief of the Oral and Pharyngeal Cancer Branch. His team performed seminal work unraveling the intracellular signaling circuitries by which cell surface receptors and Rho GTPases regulate the nuclear expression of growth promoting genes, thereby promoting normal and cancerous growth. His laboratory studies signaling mechanisms involved in cancer initiation, tumor-induced angiogenesis, and stem cell fate decisions, and his lab is now exploiting the emerging information for the development of novel mechanism-based anticancer therapies.

The development of a multicellular organism is a remarkable feat. During this process a single cell zygote divides and differentiates into the diverse cell types that make up the adult organism. Development is driven by changes in gene expression, which is regulated both by internal and external factors, allowing cells to acquire distinct identities while possessing the same underlying DNA sequence. While there is much to be learned before achieving a systems-wide view of how such factors cooperate to regulate cell fate transitions, significant progress has been made in recent years in understanding the building blocks of such a system and how some of those building blocks interact. This issue focuses on three areas: chromatin structure, noncoding RNAs, and signaling. While it is only possible to provide a limited breadth in a single issue, the examples discussed provide general principles that can be applicable to many other areas of molecular and cell biology.

Epigenetics is the heritable regulation of gene expression that occurs independent of changes in the primary DNA sequence. The best molecularly understood examples of epigenetics are modifications to the nuclear chromatin including covalent modifications to histones and DNA and associated structural changes. [Koh and Rao](#) focus on DNA methylation and the recently discovered Tet family of proteins, which are involved in demethylation of cytosines. The authors summarize recent localization studies of different methylation marks including methyl and hydroxymethyl modifications of cytosines. They make the important point that most changes in methylation do not occur at promoter-associated CpG islands, but rather at distal regulatory elements of low CpG density. Furthermore, transcription factor binding often precedes these changes. [Iglesias-Bartolome et al.](#) extend this discussion in the context of epithelial development describing how epigenetic modifications control the identity and fate of stem cells. They also describe that differentiation is associated with simultaneous methylation of proliferation genes and demethylation of lineage specific genes and cell cycle inhibitors. The authors then discuss concurrent changes in repressive and activating histone marks, along with histone positioning that are critical for stem cell maintenance and differentiation.

The stability of a cell fate is heavily dependent on the dynamic nature of changes in chromatin. A remarkable example of this dynamic nature is the effect of the circadian clock on chromatin changes. [Aguilar-Arnal and Sassone-Corsi](#) describe how the clock genes work in unison with histone modifying enzymes to regulate their downstream targets in constantly changing patterns associated with entrained daily rhythms. They also

discuss how metabolism feeds back on the rhythms both by entraining peripheral clock mechanisms as well as more directly by providing cofactors required for the enzymatic function of the histone modifiers.

In some cases, epigenetic mechanisms can go awry, leading to diseases such as cancer. Hammoud et al. revisit findings made over the past two decades describing how many cancer cells show a combination of global DNA hypomethylation and localized methylation of tumor suppressor genes. They describe recent work showing a direct link between tumor-initiating genetic events and the global decrease in DNA methylation. In colon cancer for example, early mutation of the adenomatous polyposis coli (APC) gene leads to upregulation of factors associated with the activation-induced cytidine deaminase (AID) pathway of demethylation. Suppression of these factors reverses global hypomethylation. The authors argue that these events precede the proliferation normally associated with APC through  $\beta$ -catenin and Wnt pathway activation. Analogous events occur during normal expansion of intestinal stem cells, supporting the notion that cancer can co-opt the normal regulatory pathway of the stem cells. Waldmann and Schneider also describe direct effects of mutations and environmental insults on histone modifying enzymes. For example, mutations at modification sites of histones have been associated with pediatric high-grade glioma. Additionally, nickel has been shown to inhibit histone demethylase activity. Therefore, genetic and environmental factors can have detrimental effects on the normal epigenetic state of a cell.

Many nongenetic intrinsic factors can also affect the activity of epigenetic modifying enzymes. In particular, the exploding field of noncoding RNAs has uncovered novel mechanisms by which cells can regulate their epigenetic state. Two reviews touch on key examples of such regulation. Peng and Lin discuss a class of small noncoding RNAs, the piRNAs, which are defined by their interaction with the Piwi family of proteins. The Piwi-piRNA complexes can direct both histone modifications and DNA methylation. They appear not only to work largely in the germline, but can also function in somatic cells. Interestingly, they can also cooperate with the heat shock protein HSP90 to canalize gene expression. Finally, they have been described to have post-transcriptional regulatory roles. Another class of noncoding RNAs with direct roles in epigenetic regulation is the long noncoding RNAs (lncRNAs), many of which directly interact with epigenetic modifying enzymes. Batista and Chang describe another epigenetic function for lncRNAs, namely the regulation of nuclear architecture. Transcription of some of these lncRNAs can cause the formation or alteration of nuclear structures including paraspeckles, interchromatin granules, polycomb bodies, and the nucleolus. The lncRNAs can sequester proteins, preventing them from carrying out their normal function. For

example in *S. pombe*, lncRNAs from the *mei* locus promote meiotic entry by sequestering the protein Mmi1, a suppressor of meiotic genes.

Another class of noncoding RNAs is microRNAs, which function post-transcriptionally by binding the 3' untranslated region (3' UTR) of mRNAs and suppressing their translation, ultimately leading to mRNA degradation. MicroRNAs have roles in almost all aspects of metazoan biology. Lamouille et al. discuss how microRNAs regulate the transition of cells from an epithelial to a mesenchymal state, and vice versa while Bao et al. focus on the capacity of microRNAs to promote the transition of an adult somatic cell to an induced pluripotent stem cell. These findings debunk a prevalent hypothesis that microRNAs simply buffer cell states, but shows how they can drive cell fate transitions. Indeed, Sun et al. review how microRNAs can induce the transdifferentiation of a fibroblast to a neuron. All three articles describe the plethora of downstream targets of the microRNAs, emphasizing the global effects these post-transcriptional regulators have on the transcriptome and proteome of a cell. Additionally, Mueller et al. describe how different mRNA isoforms, generated by alternative polyadenylation, are differentially susceptible to regulation by microRNAs. The authors put forth the interesting hypothesis that heterogeneity in expressed 3' UTR isoforms across a population may partly underlie differential responses of these cells to a common signal.

Not to be forgotten is the role of signaling in determining a cell's fate. Blahna and Hata review how signaling influences both the transcription and processing of microRNAs, exemplifying how these different mechanisms are tightly intertwined. Three additional review articles discuss the complexity of untangling the downstream effects of various signaling pathways during cell fate transitions. Dalton describes how manipulation of one signaling pathway influences many other signaling pathways, confounding the ability to connect a downstream effect to a specific signal. For example, changes in the PI3K pathway determine whether human embryonic stem cells self-renew or differentiate in response to FGF signaling. Similarly, Barry and Camargo describe how loss of Yap in colon cells promotes proliferation in the intestine by potentiating Wnt signaling, while the same deletion in the epidermis inhibits proliferation. This establishes an unexpected cell type-specific crosstalk between the Hippo and Wnt pathways in distinct stem cell populations. Holland et al. expand on this theme by describing how multiple intrinsic factors and external cues regulate Wnt/ $\beta$ -catenin signaling determining how activation of this pathway will be interpreted by different stem and cancer cells.

The concept of how context leads to differential response to signals is further exemplified by recent findings

described in a review by Cheng *et al.* They describe how simply passaging cells influences their response to an external signal. An example of this is the directed differentiation of pluripotent stem cells into pancreatic beta-like cells. This process normally produces mostly fetal-like cells, which are unresponsive to glucose. However, the act of expanding the intermediate progenitor cells in culture leads to a more adult-like beta cell. In another review, Klein *et al.* describe how mitogen activated protein kinases (MAPKs) can be directly recruited to chromatin by either binding DNA or associating with other chromatin proteins. The activated MAPKs can then phosphorylate neighboring proteins including transcription factors, polymerase II elongation complexes, and epigenetic modifying enzymes thereby regulating their activity and their regulated gene expression programs.

Together, these excellent reviews emphasize that how a cell responds to a given signal is governed by both the molecular identity of the cell and the external

environment. While intellectually appealing, experimentally tackling this problem remains a huge challenge, even given the remarkable technical advances over the past few years in genomics, epigenomics, proteomics, and metabolomics. However, this challenge must be confronted in order to both improve our understanding of biology and to develop novel therapeutic options that tackle the entire disease process rather than subcomponents that alone have little impact on disease progression.

Finally, we would like to express our gratitude to the authors of the reviews in this issue for their efforts to bring clarity to complex areas of biology and to provide provocative concepts that should lead to further experimentation. We would like to thank members of the Belloch lab including Amy Chen, Jacob Freimer, and Raga Krishnakumar, who graciously edited the initial draft of this overview. Finally, we would like to finish by thanking Jasmin Bakker for patiently working with us to make this issue a reality.