Epigenetic Variability

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Recent studies have discovered significant epigenetic variability among pluripotent stem cell lines, including abnormalities in imprinting and X chromosome inactivation. Aberrant epigenetic regulation is associated with many diseases, including cancer, and thus evidence of epigenetic instability in pluripotent stem cells has raised concerns regarding their potential use in cell transplantation therapy. Certain epigenetic patterns have been associated with specific derivation methods or phenotypic characteristics, including differentiation potential. These results suggest that epigenetic profiling may be a way to assess the quality of a pluripotent stem cell line, in terms of its safety for clinical applications and its utility as an in vitro model for development and disease.

In order for this to be accomplished, several critical areas must be further explored. The mechanistic pathways between epigenetic patterns and cellular phenotype, regulatory interactions among different epigenetic mechanisms, and mechanisms for targeting of epigenetic marks to specific regions of the genome are largely unknown. Perhaps most importantly, we do not yet know how closely the epigenetic marks in pluripotent stem cells and their derivatives reflect those of their cellular counterparts in vivo. I believe that for pluripotent stem cells to reach their full potential as clinical therapeutics, it is critical for us to continue to investigate basic questions in stem cell biology and epigenetics.

lncRNAs and Brain Epigenetics

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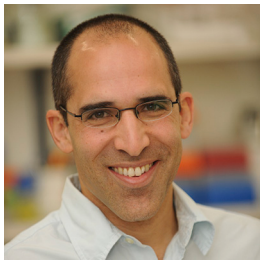
The mammalian genome transcribes many thousands of unique long noncoding RNAs (lncRNAs). Some lncRNAs such as *Xist* have long been known for their role in epigenetics, and more recent studies have revealed additional lncRNAs that interact functionally with chromatin-modifying factors or other epigenetic regulators. lncRNA expression is highly tissue specific. In particular, the expansive set of unique lncRNAs in the brain is even more specific to different brain regions than mRNAs and may also be highly cell-type specific. This exquisite specificity of lncRNAs could be useful for cataloguing the diverse classes of neural cell types, as well as for the molecular diagnosis of neurological diseases.

Emerging evidence also indicates that lncRNAs play key roles in the epigenetics of neural stem cells and brain development. We have obtained only glimpses of the various molecular mechanisms of lncRNAs, and many more novel functions will likely soon be discovered. While epigenetic mechanisms are undoubtedly critical during brain development, it is also clear that some of the molecular mechanisms that underlie the epigenetics of development are also important in postmitotic neurons. For instance, active DNA methylation appears to play a role in memory formation. Given the emerging roles of lncRNAs in neurodevelopmental epigenetics, it will be exciting to learn whether lncRNAs also play key roles in learning, memory, and diseases such as neurodegeneration.

Epigenetics One Stem at a Time



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These are exciting times for the field of stem cell epigenetics. Enhanced abilities to program stem cells and reprogram somatic cells combined with the development of "beyond the primary sequence" methods that feed the sequencing monster are driving this field forward at an increasingly rapid pace. Multilevel maps of chromatin hypersensitivity, DNA methylation, chromatin factors, histone modifications, insulators, chromatin folding, and more are now routinely being generated toward a holistic view of the stem cell epigenome. But while epigenomic maps are insightful, they normally provide correlations, not function. Even at the most fundamental level, we cannot always say for certain if, say, an active chromatin mark is the cause, not the effect, of transcription. Advances in genome editing technologies should enable us to take a step back and test many of the predictions generated over the years. A drawback of current whole-genome methods is that they only reveal population averages, so existing epigenomic profiles fail to explain cell-to-cell variation. Why do some cells differentiate or reprogram better than others? Why do some cells become ectoderm while their neighbors become endoderm under similar conditions? The next challenge will be to take the epigenetic field one step further by relating chromatin plasticity to function at a single-cell, genome-wide level. Once this feat is achieved, the holy grail of programming cells a la carte will become ever more feasible.