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Making a mark

High-throughput technologies are enabling epigenetic modifications to be mapped on a genome-wide scale, but whether such knowledge can be rapidly translated into biomedical applications remains unclear.

Despite its inception over 60 years ago, epigenetics is very much in its formative stages. Even the term 'epigenetics' means different things to different people. The best working definition for the field is that it is the study of traits heritable through meiosis or mitosis that are not dependent on the primary DNA sequence. Even so, British geneticist Adrian Bird has commented, "Epigenetics is a useful word if you don't know what's going on—if you do, you use something else."

In the past year, 'what's going on' has become a good deal clearer. The first DNA methylomes for different human cell types have now been worked out; the long-sought mammalian DNA demethylase has been identified; heritable epigenetic marks have been demonstrated to not only depend on genetic variation, but also vary in ways associated with disease predisposition; an expanding group of noncoding RNAs has been shown to interact with the epigenetic machinery; the role of methylation in regulating alternative splicing has been established; and additional evidence has accrued that chromatin modifications are important for neuronal plasticity and protracted changes in brain function. At the same time, efforts to create genome-wide catalogs of covalent modifications of DNA and histones have been spurred by next-generation sequencing and array technologies that offer greater throughput and sensitivity.

The molecular actors participating in what's going on have also become clearer: covalent modifications both to DNA (e.g., methylcytosine and hydroxymethylcytosine nucleotides) and to histones/histone variants (acetylation, methylation, phosphorylation and so on) as well as noncoding RNA molecules (microRNAs, small nucleolar RNAs and large intergenic noncoding RNAs (lincRNAs)), transcription factors, DNA-binding proteins and even cytoplasmic signaling factors.

It is now evident that, unlike changes to DNA sequence, most chromatin states are remarkably reversible and transient. Even DNA methylation—long considered a permanent, gene silencing, epigenetic mark—can be removed in certain instances. These chromatin signatures change during aging and are influenced by environmental factors, such as maternal behavior, physical exercise and diet. And dysregulation of epigenetic silencing is associated with several diseases, including imprinting disorders, Rett syndrome, facioscapulohumeral muscular dystrophy and even autism. But it is in the realm of cancer, particularly leukemias, where epigenetic research has yielded insights into abnormalities in histone marks on promoters, aberrant DNA methylation at CpG islands and microRNAs. For solid tumors, malignancies have been associated with spontaneous defects in tumor suppressor gene silencing and breast cancer invasiveness/metastasis recently has been linked to lincRNA-mediated retargeting of a histone methylase.

Aberrant chromatin remodeling has also been implicated in the process of somatic cell nuclear transfer (SCNT) used to clone animals. Few cloned embryos survive to term and many of the offspring die postnatally or are abnormal. That inappropriate epigenetic signatures are responsible for these defects is evident from the fact that the offspring of these cloned animals—the second generation—are phenotypically normal. In this context, it is sobering that work published in *Nature* (**467**, 280–281, 2010) last month suggests that induced pluripotent stem (iPS) cells show less complete epigenetic reprogramming than embryonic stem cells produced via SCNT.

Of course, if high-throughput technologies can help determine the appropriate signature of epigenetic marks, it may be possible to screen for more fully reprogrammed iPS cells. But given the plasticity of many histone modifications, it remains uncertain whether epigenetic signatures alone will have sufficient predictive or diagnostic value. In most cases, we have no way to tell whether a particular epigenetic signature is a cause of disease or merely a consequence of the pathological state.

From a therapeutic standpoint, there is particular reason for optimism, as four drugs acting on DNA methyltransferase and histone deacetylase enzymes have already been approved. At least in blood cancers, this provides validation that pharmacological alteration of chromatin modifications has tangible clinical benefit, and these successes are spurring industry interest in the development of inhibitors of other epigenetic targets, such as histone methyltransferases.

Currently, however, all epigenetic drugs act in a nonspecific, pangenomic manner and, consequently, are associated with significant dose-limiting toxicities. This is perhaps unsurprising as chromatin-modifying enzymes have no inherent specificity for a particular nucleosome (or its associated gene). Rather, they are recruited by DNA binding proteins or co-factors or RNAs that localize the complex to a specific stretch of sequence. This issue goes beyond simple, drug-related, off-target effects: agents that modify the chromatin state across the genome may also awaken undesirable elements, such as endogenous retroviruses. Thus, if epigenetic therapies are to succeed outside cancer—in neurological indications, for example—their activity needs to be more directed.

We are currently witnessing a renaissance in epigenetics research. Much of the recent growth in the field can be attributed to the technology-enabled ability to survey epigenetic modifications on a genome-wide scale. The success of epigenetic therapy in hematological malignancies has also engendered confidence in the translational potential of the field. But greater emphasis now needs to be placed on elucidating not only the molecular mechanisms by which an expressed or silent state is transmitted through cell division but also the interplay between DNA and/or chromatin modifications and RNAs, transcription factors, nuclear organizing factors and signal transduction pathways in different cells types, at different ages and under different developmental and disease states. With this knowledge in hand, epigenetics has the potential to make an even greater mark on the practice of medicine.

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