Investigating Epigenetic Plasticity in Development and in Response to the Environment

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Abstract

Epigenetics is the study of information, heritable during cell division, other than the DNA sequence itself, such as DNA methylation (DNAm), a covalent modification of cytosine. DNAm is an attractive target for study, because it is easily measured in archived samples from pre-existing large patient cohorts. It is now well established from gene-specific studies that epigenetic alterations are important in cancer, and linked to oncogene activation, tumor suppressor gene silencing, and chromosomal instability. We are taking an integrated approach to catalyze the generalization of gene-specific to genomic epigenetics, and to advance the focus in this field from cancer to common disease generally. Doing this requires an integration of new conceptual, technological, epidemiological and statistical approaches.

A recent conceptual shift in my thinking about epigenetic epidemiology has been driven by an assessment of the evolutionary context of epigenetic variation. Neo-Darwinian evolutionary theory is based on exquisite selection of phenotypes caused by small genetic variations, which is the basis of quantitative trait contribution to phenotype and disease. Previous attempts to incorporate epigenetics into evolutionary thinking have focused on Lamarckian inheritance, that is, environmentally directed epigenetic changes. While such environmental effects may play an important role in the short term, I think it unlikely that a given epiallele is stably transmitted over the many generations necessary for a significant selective effect. Rather, I have suggested a non-Lamarckian model for a role of epigenetics in evolution. In this model, genetic variants that do not change the mean phenotype could change the variability of phenotype; and this could be mediated epigenetically. This inherited stochastic variation model would provide a mechanism to explain an epigenetic role of developmental biology in selectable phenotypic variation, as well as the largely unexplained heritable genetic variation underlying common complex disease. I will discuss recent experimental data in support of this model.