The Potential of Epigenetic Therapy and the Need for Elucidation of Risks

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Epigenetic phenomena are known to be a root cause of many common diseases. To date, the FDA has approved four epigenetic therapies that show promising results for prolonging lives of terminal cancer patients. However, there is a relative lack of knowledge about long-term epigenetic effects, especially those that affect future generations. We propose a heightening of standards for epigenetic therapy: therapies should be targeted to specific genes in specific cells and cannot affect the germline and patients’ epigenomes should be sequenced before and after treatment. Moreover, further research should be performed to answer questions about transgenerational epigenetic effects, to analyze the effects of altered epigenomes in the long term, and to develop superior assays for screening epigenomes. We highlight current research in the field, including the work of the Penn iGEM group.

Epigenetics Background

Introduction. The code of life is more than a sequence of As, Cs, Ts, and Gs. Muscle cells in the human heart contain the same DNA as skin cells in the foot, yet these two cell types behave in radically different ways. Both contain the DNA for over 20,000 human genes but express only the ones needed for their own form and function. These differences in gene expression are modulated by epigenetic controls. Epigenetics refers to any heritable chemical modification of DNA that alters expression without changing genetic sequence. Neurodevelopmental disorders, immunodeficiency, cancer, and other illnesses can result when these mechanisms go awry.

Methylation. In humans, enzymes called methyltransferases add methyl groups to short DNA sequences abundant in the genome called CpG sites. Methyl groups block transcription factors (gene activators) from binding to DNA and performing their normal function. Although epigenetic factors do not change the sequence of DNA, they can affect the phenotype, the observable characteristics of the organism. Specific patterns of methylation are necessary for a cell to modulate the level of expression of each of its genes.

Epigenetic Diseases

Cancer. DNA methylation has been referred to as the “hallmark of cancer” (Szyf 2004). Abnormal methylation patterns throughout the genome that cause blockage of tumor suppressor genes have been linked to many types of cancer. For instance, breast cancer generally exhibits inactivation of the gene BRCA1. In sporadic (i.e. non-familial) cases, this suppression is usually caused by hypermethylation rather than mutation of the gene (Rice 2000). In other cases, hypomethylation causes overexpression of the flap endonuclease 1 gene and lead to breast cancer in some patients (Singh 2008).

Neurological. Methylation abnormalities have been linked to a wide range of diseases. Fragile X syndrome, one of the leading genetic causes of intellectual disability, is characterized by hypermethylation, which disrupts the production of protein necessary for normal brain development. Patients suffering from this disorder are at risk for autism, ADHD, decreased IQ, infertility in females, and distorted facial features (Jacquemont 2011).

Psychological. Epigenetic mechanisms can also impact psychological states. In an animal study, rat pups that received better maternal care in the form of licking, grooming, and arched-back nursing had lower levels of methylation at the glucocorticoid receptor gene. These rats displayed less intense responses to stressful situations than those who received poor maternal care. The researchers were able to eliminate these differences via epigenetic interference (Weaver 2004).

Epigenetic Therapy

Fundamental Advantages. The aforementioned epigenetic roots of disease are attractive targets for therapy. Aberrant DNA methylation patterns are more easily reversible than genetic mutations. In the case of cancer, epigenetic therapy coaxes tumor cells to return to a healthy state, rewiring their methylation patterns so the cells express genes that halt their cancerous uncontrolled growth. Traditional chemotherapy strategies, on the other hand, aim to kill cancer cells and are fundamentally more toxic to patients since healthy cells are also harmed.

Recent Successes. There have been some exciting clinical successes with the first generation of epigenetic
depend on the gravity of the adverse effects—a risk/benefit analysis similar to that performed for any drug approval. Therefore, clinical trials must be designed to take these risks into account. The following researchers are not convinced non-mouse models as most mice can only live for around two years, which may not properly model long-term epigenetic effects. Patients’ epigenomes should be screened, so doctors can be on the lookout for toxicology trials should be performed with adequate supervision. The first two are histone deacetylase inhibitors and prevent histone modifications, one type of epigenetic modification. These agents decrease DNA methylation, as opposed to the way we die. The need for epigenetic therapies is clear and the initial successes are promising for cancer patients, but the model for future developments is not yet set in stone. If doctors want to treat younger patients with non-lethal epigenetic diseases, genome wide epigenetic sequencing in multiple cell types for each patient would reveal potential off-target effects. This kind of personalized medicine could obviate the need for a longitudinal clinical trial. This is difficult and expensive with existing technologies, and these procedural problems must be overcome so that adequate assessment of epigenetic therapies could be performed on patients in need of epigenetic sensitization. The second generation of therapeutic drugs is on the horizon, as epigenetic therapies can be performed (Laird 2010). As more research is conducted, the balance between clinical trials and personal diagnostic tests and the responsibilities of those involved must be reconsidered.

Second Generation Epigenetic Therapies

Higher Standards. Continued development of first generation epigenetic therapies that affect whole genomes and any cell that should be accompanied with open acknowledgement of potential undetectable harm. To date, clinical trials have been conducted with very sick, elderly cancer patients, and research has confirmed epigenetic modifications can affect us on a longer, even transgenerational time-scale (Rothstein 2009). Clinical trials however do not normally track side-effects ten, twenty, or thirty years after treatment. If these trials alleviate disease in the short term but eventually cause unforeseeable epigenetic abnormalities, are they acceptable for younger patients? Little research is available on how epigenetic modifications should be unacceptable. Animal model studies are always carried out before therapies are tested with humans—these must continue to be carried out rigorously before epigenetic therapies are more widely applied. The potential of epigenetic therapy and the need for elucidation of the risks.
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