

Epigenomic of Aging

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During the last century, advances in health care in conjunction with the cure of many childhood diseases have promoted life expectancy beyond 80 years in most of the western world [1]. As a result, the proportion of elderly in the overall global population has increased dramatically, creating a health care burden due to an exponential growth in the prevalence of age associated diseases. This situation has challenged the science and the health practitioner communities to come up with strategies to decipher the biology that drives aging in order to find ways to both delay aging and support healthy aging [1].

Popular approaches to exploring the aging mechanism and pathways involved in aging included gene scavenging, either through a candidate gene approach or unbiased screening, such as GWAS. Genetic information from these studies on the DNA level has paved the way for the understanding of the aging mechanism, but only scratches the surface in terms of understanding other biological forces behind aging, such as environmental effects, gene expression, translation and regulation, and the interaction between these components [2]. When the ENCODE project led to a revolution in the common scientific notion that assigns most of the genome as “Junk”, understanding these additional forces became the focus of genetic research [3]. For example, DNA sequences that were either at the flanking regions or distal to the gene formerly classified as gene deserts, were identified as crucial elements in the regulation of gene function. Such elements were added to the growing family of epigenetic components (defined as heritable changes in gene function or phenotypes, in the absence of DNA sequence changes).

Epigenetic mechanisms, such as histone modification, DNA methylation and acetylation, miRNA, shRNA, and piRNA are scattered throughout the genome and may serve as a “switch” to turn on or off the target gene. But unlike a simple switch, its components must work in harmony. The outcome depends on many factors, such as their physical location (inter or intra) with reference to the target gene which they either silence or evoke. Disruption of this regulation system often results in deleterious effects in various pathways, such as the cell cycle, apoptosis, detoxification, and cholesterol metabolism [4]. In addition, numerous reports have linked epigenetic perturbation to various types of cancer and many genetic syndromes. The most cited example of the epigenetic effect is in the Agouti mice experiment, where changes in the mother’s diet during pregnancy (different concentrations of folate) resulted in different fur colors. On a pathological level, the offspring with the light color fur indicated a disruption of the agouti gene that resulted in obesity and diabetes [5]. Such phenomenon provides us with three levels of regulation: a) Inheritance of a genetic variant that is sensitive to methylation; b) Environmental effect (diet induce modifier such as folate) that cause methylation changes, and c) The interaction between gene variants and the environment that leads to the early onset of age associated disease (i.e. diabetes).

Since meaningful mutations in the DNA are rare, the flexibility of various adaptations to changes in the environment can be reached instead by epigenetic responses to gene X environmental interactions. Thus, aging, which can be characterized as a slow adaptation to intra-environmental changes, would benefit greatly from excessive epigenetic loci, which would add complexity to gene regulation but more

importantly provide another level of flexibility to allow adaptation to various environments.

These epigenetic mechanisms may be the key to an external intervention in health care for aging and promoting longevity with grace. Instead of invasive treatments, changes in diet or designated supplements or drugs could stimulate epigenetic mechanisms that mediate target gene expression or alteration and could reverse deleterious effects, block/mask/eliminate harmful processes, or promote positive/protective effects. However, such solutions depend upon an individual’s epigenetic blue print and deep understanding of the elements of gene expression regulation. Development of technologies to explore these elements in an efficient way, multi-institutional collaboration efforts to understand the biology at all levels (i.e. transcription, translation, and regulation), and increased data collections of various combinations (tissue, organ, cell, and body) will be the challenge of this era of ENCODE-omics.

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