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NEWSLETTER

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Perspective

Integrating Environmental Signals into the Genome by Epigenetic Modifications

An exploration of recent advances in the field of epigenetics

by Dr. Iñaki Martin-Subero

Epigenetics is rapidly emerging as one of the most exciting scientific fields. After sequencing the human genome, scientists worldwide are beginning to realize that only knowing genetic information is not sufficient to understand phenotypic manifestations. The way the DNA code is translated into function depends not only on its sequence but also on the interaction with environmental factors. Here is where the science of epigenetics comes into play. Epigenetics integrates the different chemical languages that the genome and the environment use to communicate with each other. A common definition of epigenetics is the study of heritable changes that affect gene expression without altering the DNA sequence. However, a more inclusive definition of epigenetic events was recently proposed as “the structural adaptation of chromosomal regions so as to register, signal, or perpetuate altered activity states[1].”

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To date, known epigenetic modifications include DNA methylation, histone modifications, and non-coding RNAs, with DNA methylation being the most studied among them. DNA methylation occurs at cytosines within CpG dinucleotides. These dinucleotides are unevenly distributed throughout the genome and concentrated in specific areas called CpG islands. CpG islands are commonly found in gene promoter regions and repetitive sequences. Hypermethylated CpG islands are associated with gene silencing, whereas lack of DNA methylation allows gene expression.

It is known that DNA methylation plays a key role during embryonic development and the establishment of tissue identities within an organism. However, the epigenetic signature of different tissues is not well defined. The Human Epigenome Project has been launched recently[2] to identify all of the chemical changes and relationships among chromatin constituents, in an effort to further understand normal development, aging, and abnormal gene control in disease as well as the role of the environment in human health. The Human Epigenome Project represents an enormous challenge because epigenomic changes not only show intra- and inter-individual variation, but are subject to modifications throughout

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the life of an organism. The complexity of the epigenome poses both biological and technical challenges. The development of techniques allowing accurate quantification of methylation levels of individual CpG dinucleotides across the genome is a prerequisite for the success of any attempt to characterize the epigenome.

In the last few years, a number of groundbreaking studies have underlined the importance of epigenetics in the life sciences. Nutrition is probably one of the main factors affecting the epigenome. An elegant experimental model to study nutri-epigenomics is the yellow agouti (A^{vy}) mouse, whose phenotype (yellow fur, obesity, and predisposition to various diseases) directly depends on expression of the A^{vy} allele. Studies have shown that maternal supplementation with methyl-donors like folic acid can inactivate the A^{vy} allele by DNA methylation and shift the phenotype of the offspring towards the brown coat color[3]. Factors able to modify the epigenetic pattern of DNA go beyond food intake, and enter the field of psychology. A study published in 2004 highlights the importance of maternal behavior in the establishment of epigenetic marks in the newborn offspring. Increased pup licking and grooming by rat mothers is associated with lower stress responses in the offspring. This effect was observed to be caused by differential methylation of a specific CpG in the glucocorticoid receptor gene[4]. These two reports highlight that experiences in life are potentially able to induce epigenetic modifications. In fact, a recent study provided evidence for epigenetic differences between monozygotic (genetically identical) twins. This study showed that as twins age they accrue a greater number of epigenetic and transcriptional differences. This may account for the phenotypic variation observed in twins leading a different lifestyle, like those separated at birth[5].

Considering the importance of epigenetics in living organisms, it is not surprising to find epigenetic modifications in disease. Tumor-suppressor gene inactivation by promoter hypermethylation is a well-known phenomenon in all types of cancer[6]. However, DNA methylation has deeper implications in cancer biology. Recent studies show that gene promoters becoming de novo methylated in cancer were already repressed at the stem cell stage by histone modifiers of the polycomb group. These findings support the cancer stem theory.

Epigenetics not only plays a role in an individual's health and disease, it can also be transmitted across generations. There is statistical evidence showing that the life circumstances (e.g., food availability) of our ancestors affected the life expectancy of following generations,[7] with this longevity effect being attributed to epigenetic inheritance[8]. Experimental evidence comes from the yellow agouti mouse model, in which the epigenetic benefits of methyl-donor supplementation can be observed in at least two generations[9].

Together, these recent studies on epigenetics have led to the resurrection of old ideas on the evolution of living organisms. Jean-Baptist Lamarck, a French evolutionist of the 18th and early 19th century, postulated the inheritance of acquired traits as a driving force of evolution. Perhaps the new science of epigenetics and the old ideas of Lamarck will find a common place in the 21st century.

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