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Epigenetic basis of cancer

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In recent years, increasing evidence has demonstrated the role of epigenetic alterations in the etiology of many diseases. Epigenetics -the stable and heritable (or potentially heritable) changes in gene expression that do not entail a change in DNA sequence- are characteristic of different cell types and, in fact, play a key role in defining the transcriptome, which determines the identity of each cell type (1). Two major groups of changes contribute to defining the epigenome of a cell: DNA (cytosine) methylation and histone modifications.

The early onset of epigenetic changes and the growing view that stem cells are the target cells for cancer, together with the idea that epigenetic changes probably distinguish stem cells from somatic cells, make it likely that epigenetic disruption of stem cells is a common unifying theme in cancer etiology (2). Great advances have been made in characterizing epigenetic alterations in cancer. Two major alterations occur concerning DNA methylation patterns. First of all, there is a global loss of 5-methylcytosine or demethylation, in many cases in repetitive sequences. In parallel, CpG islands, CG–rich regions coincident in most cases with the promoter of protein coding genes, suffer from a process of hypermethylation that leads to gene silencing. This mechanism is now considered to be a key event leading to the inactivation of many tumor suppressor genes in a tumor-type specific fashion. More recently, alterations in histone modifications have also been recognized to occur in cancer cells. Histone modification changes are intimately associated with alteration in the DNA methylation pattern. The dependence of histone modifications and DNA methylation pattern can be recognized in a global context of architectural organization. Also, histone deacetylation and specific alterations in the histone methylation profile are specifically associated with transcriptional silencing of many tumor suppressor genes. Finally, it has been demonstrated that histone modification changes can also be detected at a global scale in a cancer cell. In particular, loss of acetylated Lys16 and trimethylated Lys20 residues of histone H4 are a common hallmark of human cancer (3). These changes are associated with the hypomethylation of DNA repetitive sequences, a well-known characteristic of cancer cells that is involved in genomic instability.

External influences on epigenetic processes are seen in the effects of diet on long-term diseases such as cancer (4, 5). On the other hand, it is possible that small defects in transmitting epigenetic information through successive cell divisions, or maintaining it in differentiated cells, accumulate in a process that could be considered as an epigenetic drift. Identification of proteins that mediate these effects has provided insight into this complex process and diseases that occur when it is perturbed (6, 7). Accumulation of epigenetic defects would probably occur at a faster

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rate than that corresponding to genetic mutations as their consequences in survival are probably less dramatic and cells have not developed a comparable number of mechanisms to correct them. Two type of processes could be invoked: first, an accumulation of epigenetic changes or alterations that do not involve cell divisions, in differentiated cells. This could specially affect histone modifications, since these are most likely to occur and be maintained in a DNA replication-indepndent fashion. On the other hand, defects associated to the transmission of epigenetic information throughout cell divisions, and particularly related with DNA replication, could also be taking place.

The study of epigenetic differences in monozygotic twins has provided evidence about the contribution of epigenetic modifications in the establishment of the phenotype (8). These results suggests that external and/or internal factors can have an impact in the phenotype by altering the pattern of epigenetic modifications and allow to evaluate the influence in the importance of the epigenome in shaping up genetic information. A number of epigenomic techniques have been recently made available to identify epigenetic markers in cancer (3, 9, 10). Epigenetic markers are useful in a clinical context for different purposes including diagnosis, prognosis and as predictors to drug-response. Moreover, the reversibility of epigenetic modifications makes it an excellent target in the design of novel therapies aiming to restore the original epigenetic pattern.

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