Reuben M. Cherniack Lecture

The Cancer Epigenome

Its Origins, Contributions to Tumorigenesis, and Translational Implications

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Epigenetic abnormalities in lung and other cancers continue to be defined at a rapid pace. We are coming to appreciate that cancers have an "epigenetic landscape" wherein genes vulnerable to abnormalities, such as promoter DNA hypermethylation and associated gene silencing, tend to reside in defined nuclear positions and chromosome domains and relationships to chromatin regulation, which facilitates states of stem cell renewal. These same genes and domains are also vulnerable to epigenetic abnormalities induced by factors to which cells are exposed during cancer risk states, such as chronic inflammation. We can use all of this basic information for translational purposes in terms of deriving biomarkers for cancer risk states and detection and therapeutic strategies.

Keywords: epigenetic; cancer; DNA hypermethylation

The interest in cancer as an epigenetic and as a genetic disease continues to intensify. We now realize that epigenetic abnormalities, or changes in heritable gene expression patterns dictated by other than alterations in the primary base sequence of DNA, may be much more frequent than genetic changes in cancer (1–4). For example, every individual patient's tumor, for all cancer types studied to date, harbors hundreds of genes that are transcriptionally silenced in association with abnormal addition of an epigenetic regulatory modification, DNA methylation, to CpG islands in proximal promoter regions (1–4).

This review briefly discusses the abnormal gene changes that make up what some researchers refer to as "the cancer epigenome" (1–4). Some of these changes involve important tumor suppressor genes for which loss of function can alter each of the key pathways that are fundamental for tumorigenesis (1–4), including those controlling the cell cycle and control of stem cell and progenitor cell regulation (*p16*, *p15*), the Wnt pathway (*APC*, *SOX17*), DNA repair (*MLH1*), cell adhesion and invasion (*E-cadherin*), and apoptosis (*DAP-kinase*). We have entered the era wherein epigenetically altered genes are being randomly screened for in cancers of many types. For example, in The Cancer Genome Atlas Project (TCGA), cancer genomes of gliomas (5) and other cancers, including those of the lung, are being screened not just for genetic alterations but also for epigenetic changes. Several such random screening approaches and results in TCGA reflect the value of adding this

epigenetic focus to genetic changes important to the origins of cancer and the translational implications of the findings.

In terms of random screening procedures, the most complete involve next-generation sequencing of virtually all CpG sites in the genome, which is the context in which cytosines are DNA methylated (6). A recent such study, performed for colon cancers versus normal colon, reveals important features about the occurrence of DNA methylation due to the abnormal gene promoter CpG island (6). First, a large group of the hundreds of hypermethylated colon cancer genes are those that, in embryonic stem cells (ESCs), are located in nuclear domains harboring late replicating genes. Second, a particularly exciting aspect of this finding is that these late replicating genes include those for which promoter region CpG islands have key aspects of chromatin regulation of gene expression, which maintains the state of ESCs/progenitor cells (6). This is consistent with previous studies of several groups for colon cancer linking such genes to a large group that harbors the abnormal DNA methylation in this tumor type (7–9). Importantly, the function of this embryonic chromatin, which is termed "bivalent" (10, 11), is to maintain the involved genes in a low, poised transcription state, which thus prevents stem cells from maturing and maintains their ability to self-renew (10, 11). This is a timely concept when juxtaposed to data linking the properties of cancer "stem/initiating" cells to those for ESCs (12, 13). These findings in the aggregate allow a working hypothesis of how chromatin regulation of key genes may predispose them during tumor progression, and perhaps very early in tumorigenesis, to abnormal, promoter, DNA methylation and a state that helps impede normal lineage commitment and maturation and thereby helps lock in a primitive state of abnormally expanding cells in early cancer evolution (14, 15).

Another recent finding (16) links the predisposition for abnormal, promoter DNA methylation in cancer to inflammation, one of the leading risk states for neoplasia, including in lung (17–19). In this scenario, damage to cells by increasing levels of reactive oxygen species acutely targets a complex of transcriptional repressor proteins and DNA methylating enzymes to CpG islands and predisposes, especially genes with low basal transcription, to abnormal DNA methylation (16). This is an important concept to follow because it suggests that blocking such dynamics during chronic inflammation might constitute a cancer prevention step worthy of pursuing.

Finally, the translational implications of understanding the cancer epigenome are many. Monitoring abnormal gene promoter DNA methylation as a biomarker system is a promising strategy for cancer risk assessment, early cancer diagnosis, molecular staging of tumors, and monitoring of drug sensitivities (1–3). One important example of this is the use of hypermethylation of a four-gene panel, assayed in tumor and chest lymph node DNA, for predicting the early recurrence of stage 1 non-small cell lung cancer (20, 21). Finally, there is also great promise

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for the concept of “epigenetic therapy” for cancer in which reversal of epigenetic gene silencing is being considered as a molecular target strategy. DNA demethylating agents have been approved by the FDA for the treatment of the preleukemia disorder myelodysplasia (22–24). Recently, very promising results have been seen using such a drug, in combination with a histone deacetylase inhibitor, in patients with chemo-refractory, advanced non-small cell lung cancer (21).

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