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Introduction: Cancer as an epigenetic disease

Jean-Pierre Issa

Fels Institute, Temple University School of Medicine, Philadelphia, PA

“It’s all in the genes” is a common answer to the common question of what causes cancer. But what is all in the genes? The evidence for genetic damage as a cause of cancer is incontrovertible¹ – familial cancers can often be explained by inheritance of mutations, cancer cells carry a considerable load of somatic DNA damage, genetic instability is a feature of many cancers, introducing specific mutations into mice result in cancer formation, and mutagens are generally also carcinogens. But there is also a large body of literature suggesting that cancer is *also* an epigenetic disease².

The term “epigenetic” was coined to describe the phenomenon of cell identity³ – the human body has more than 200 different cell types all dependent on a single genome. This diversity in cellular identities is governed by a network of biochemical modifications to DNA and to the histone proteins that provide structure to DNA. Altogether, these modifications are referred to as the epigenome. Medically, things became even more interesting when it was discovered that variation in the epigenome could also be responsible for phenotypic variation⁴ – for example coat color or susceptibility to obesity in mouse models. There is intense interest currently in decoding the epigenome and relating this code to varied phenotypes and diseases in humans.

That cancer has an epigenetic component is obvious²: Cancer cells have profound defects in cellular identity (most evident by morphology and differentiation states), and the cancer epigenome is very different than the epigenome of normal cells. It has been assumed that these changes are a consequence of genetic damage rather than a cause of neoplastic transformation, but this assumption turns out to be (often) incorrect. It was demonstrated decades ago that reprogramming the cancer epigenome by forcing cells to undergo embryogenesis can reverse the transformed phenotype^{5, 6}. These experiments have been reproduced by modern reprogramming technology such as nuclear transfer or iPS protocols^{7, 8}. These experiments showed that the cancer phenotype cannot be attributed solely to the genetic damage (that persisted through the reprogramming procedures). Furthermore, large scale sequencing studies and laboratory confirmation have shown that cancer-causing genetic damage frequently affects proteins involved in writing, erasing or reading the epigenetic code⁹, demonstrating that epigenetic “errors” are the causative elements in explaining the ultimate cancer phenotype.

Final confirmation of cancer as an epigenetic disease came from five observations that recapitulate the evidence for a genetic etiology of cancer described earlier: (i) Familial cancer can also be due to constitutional epigenetic damage (“epimutations”)¹⁰, (ii) cancer cells carry a considerable load of epigenetic damage⁹, sometimes with no discernible recurrent genetic damage¹¹, (iii) epigenetic instability (e.g. the CpG island methylator

phenotype) is a feature of many cancers¹²; (iv) introducing epimutations is sufficient to promote neoplasia in mice¹³ and (iv) carcinogens are often also epimutagens¹⁴.

What are the translational implications of an epigenetic etiology of cancer? Just like genetic damage, epimutations could be useful as biomarkers for risk assessment, diagnosis, prognosis and treatment selection (precision medicine). In fact, in distinct cases, epimutations appear to perform better than mutations for these tasks and it seems unavoidable that epigenetic profiles will be incorporated into the clinico-pathologic assessments of neoplasia¹⁵. Clinically, the field of epigenetic biomarkers is poised for rapid expansion in the near future. Therapeutically, there are two major difference between genetic damage and epigenetic damage: Genetic activation of oncogene function has provided a very successful strategy for targeting cancer cells and it is unclear whether epigenetic activation of oncogenes provides a similar opportunity. On the other hand, epigenetic damage can be reversed by targeting the writers/erasers/readers of the epigenetic code in a way that cannot be done for genetic damage. This field (“epigenetic therapy”) has markedly expanded recently with more than 30 drugs in clinical trials currently¹⁶. However, there are also many similarities between the therapeutic implications of genetic and epigenetic damage. Synthetic lethality can be arrived at by pathway inactivation through either mutations of epigenetic damage. Immunosenitization can be related to a high genetic load triggering neoantigens, but could also be related to epigenetic damage leading to activation of intracellular inflammatory pathways such as interferon signaling. Finally, there is great interest in combining epigenetic therapy with more conventional therapies, with targeted therapies, and recently with immunotherapies.

This issue explores the translational implications of cancer epigenetics in some detail. The first three articles provide the necessary background to understand the field and discuss the potential of epigenetic information as biomarkers. The next four articles discuss pre-clinical and clinical results of using drugs that target the epigenome to treat patients with cancer. I wish to thank all the authors for their clear and concise reviews and hope this issue will be useful to readers of the Cancer Journal.

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