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Perspective

DRUG RESISTANCE, TUMOR CELL HETEROGENEITY AND EPIGENETIC MECHANISMS IN TUMORIGENESIS

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INTRODUCTION

A devastating issue in cancer treatment is cancer cell resistance to new targeted drugs and chemotherapeutics. Increased drug efflux, altered drug metabolism, secondary mutations in drug targets, and activation of downstream or parallel signal transduction pathways are among the numerous mechanisms that contribute to drug resistance. The absence of genetic mutations, the rapid kinetics, and the reversibility of acquired drug resistance all point to an epigenetic cause for drug insensitivity. Through reversible histone modifications and DNA methylation patterns, epigenetic mechanisms produce a variety of transcriptional states, resulting in a dynamic, heterogeneous population of tumor cells—similar to the cellular variation found in the human body. Abnormal transcription of drug transporters, DNA-repair enzymes, and pro-apoptotic factors by epigenomes that favor drug-induced survival render cytotoxic and targeted drugs ineffective and permit the selection of rare drug-resistant tumor cells. Indeed, recent advancements in mapping cancer genomes strongly suggest that epigenetic regulators play a role in driving cancer, which may lead to the acquisition of genetic modifications that result in drug resistance. Because they present an opportunity for "epigenetic drugs" to alter reversible drug-resistance-associated epigenomes in order to either prevent or reverse non-responsiveness to anti-cancer medications, these observations have significant clinical implications.

DISCUSSION

Many diseases, including cancer, face a significant obstacle in the treatment of resistance that develops during drug therapy. As a result of developing resistance to cytotoxic chemotherapeutics and targeted drugs, an estimated 7.5 million cancer patients worldwide die annually. Many of these deaths are the result of unsuccessful anticancer treatments. Therefore, designing therapies to prevent the selection of drug-resistant tumor cells will greatly benefit from an understanding of the mechanisms that cause unresponsiveness to anti-cancer drugs. As a result, these treatments may significantly lower cancer mortality rates. It has become increasingly clear that genetic mutations are a crucial component of acquired drug resistance with the rise of targeted drug therapies. However, genetics are insufficient to explain the relatively quick onset or reversibility of drug-resistant syndrome. A role for non-genetic mechanisms in acquired drug resistance was also suggested by the absence of genetic mutations in drug targets and activated parallel pathways [1-3].

The focus of this review will be on the role of chromatin biology in tumorigenesis and acquired drug resistance that is not genetic. Increased drug efflux, enhanced drug metabolism, inactivation of apoptotic pathways, secondary mutations in drug targets, and activation of downstream or parallel pathways are some of the mechanisms that have been discovered so far to explain acquired drug resistance. Increased genetic instability and an increased rate of mutation in tumor cells have been cited as the foundation for these mechanisms. This genetic diversity makes it possible to select cells that are more likely to survive drug treatment. A number of observations suggest a non-mutational contribution to drug non-responsiveness, despite the fact that a genetic basis for acquired drug resistance contributes to the failure of cancer therapy. To begin, the widespread occurrence of drug resistance suggests that mutational acquisition alone cannot account for this phenomenon. Second, patients receiving retreatment following a drug-free period have been shown to have reversible drug resistance. Thirdly, the majority of tumors that are resistant to drugs do not have mutations in drug targets or activated pathways. Last but not least, there is a great deal of variation in the malignancy and drug resistance of individual cells, despite the idea that tumors are the result of the clonal expansion of cells that have acquired genetic alterations that are advantageous for proliferation, survival, and metastasis. Similar to how transcriptional network states realize a variety of cell types in the body by a single genome, a basis for this variability may be found in the various transcriptional network states produced by the same cancer genome. It has been hypothesized that DNA- and chromatin-modified reversible transcriptional network states contribute to the dynamic heterogeneity necessary for differentiation. Similarly, non-genetic heterogeneity within the tumor cell population and dynamic variation in epigenome configurations are thought to provide a non-genetic variance source for the selection of drug-resistant cells.

Long ignored is the non-genetic cause of acquired drug resistance and tumor cell heterogeneity. Tumor heterogeneity is now appreciated more, and the discovery of "cancer stem cells" or "tumor-initiating cells" has brought up new concerns regarding treatment outcomes. It is now clear that these cells are intrinsically more resistant to various anti-cancer drugs, either by increased drug efflux, inability to execute apoptosis, enhanced DNA repair, different protein dynamics, or by displaying a quiescent cell-cycle state, despite the fact that many questions remain regarding the concept of tumor stem cells and their contribution to tumorigenesis. It has been proposed that DNA and histone modifications may drive non-genetic heterogeneity, resulting in the establishment of tumor-initiating cells and/or drug-resistant cells, given that epigenetics plays a crucial role in determining the fate of cells.

It has been recognized that epigenetics, which is defined as changes in gene expression that occur independently of changes in the DNA sequence and persist over numerous cell divisions, is a significant contributor to the development of non-genetic heterogeneity. Covalent modifications of DNA and histones are at the heart of regulating gene transcription, despite the fact that multiple mechanisms regulate gene expression. By altering the packaging of chromatin, epigenetic changes alter gene transcription and regulate the accessibility of DNA to sequence-specific transcription factors. In addition, transcription complexes contain specialized protein modules that "read" combinations of epigenetic marks and, as a result, "transcribe" them into a biological output like turning on or off transcription [4-6].

CONCLUSION

In the end, the variety of cellular phenotypes that cells with the same genome exhibit is determined by the readout of epigenome variation. Similar to this, a specific combination of epigenetic and genetic marks in a diverse tumor cell population may result in a drug-resistant phenotype. It will be crucial to identify epigenetic marks and their biological consequences in drug-resistant tumor cells in order to design therapies that prevent or reverse drug resistance. We focus on the connection between tumorigenesis and post-translational modifications of DNA and histones, particularly methylation and acetylation, in the first section of this review. The mechanisms that underlie drug resistance will be the focus of our discussion in the second part.

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