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Review

Somatic alterations and dysregulation of epigenetic modifiers in cancers

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ABSTRACT

Genomic discovery efforts in patients with cancer have been critical in identifying a recurrent theme of mutations in epigenetic modifiers. A number of novel and exciting basic biological findings have come from this work including the discovery of an enzymatic pathway for DNA cytosine demethylation, a link between cancer metabolism and epigenetics, and the critical importance of post-translational modifications at specific histone residues in malignant transformation. Identification of cancer cell dependency on a number of these mutations has quickly resulted in the development of therapies targeting several of these genetic alterations. This includes, the development of mutant-selective IDH1 and IDH2 inhibitors, DOT1L inhibitors for MLL rearranged leukemias, EZH2 inhibitors for several cancer types, and the development of bromodomain inhibitors for many cancer types—all of which are in early phase clinical trials. In many cases, however, specific genetic targets linked to malignant transformation following mutations in individual epigenetic modifiers are not yet known. In this review we present functional evidence of how alterations in frequently mutated epigenetic modifiers promote malignant transformation and how these alterations are being targeted for cancer therapeutics.

Contents

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1. Introduction

Recent progress in systematic sequencing of human malignancies has identified recurrent mutations in epigenetic modifiers as a consistent theme throughout human cancer. Several of these mutated genes, or classes of genetic alterations, appear to be distinctly associated with specific disease phenotypes which have shed light on new mechanisms of malignant transformation. Moreover, many mutations in epigenetic regulatory genes result in a gain-of-function which is potentially directly targetable. Thus, identification of mutations in epigenetic regulatory genes has provided important information about disease pathogenesis as well as potential new avenues of therapy.

In this review we discuss novel classes of mutated disease alleles in genes encoding epigenetic modifying proteins. These include somatic point mutations and/or translocations in genes directly involved in DNA cytosine methylation modification *(TET2, IDH1/2)*, genes encoding enzymes which modify histone proteins (EZH2, BAP1, MLL1-3, CREBBP, EP300), as well as those required for histone enzyme complexes to function (EED, SUZ12, and ASXL1), and genes encoding histone H3 proteins themselves. This review focuses on the epigenetic aberrations thought to be attributable to these mutations and how these epigenetic alterations might contribute to malignant transformation. In addition, we highlight the potential clinical value of understanding these mutations, as they may be therapeutically targetable in some instances.

2. Mutations in genes affecting DNA methylation

2.1. DNMT3A

The mammalian family of methyltransferases comprises three active DNA methyltransferases that enzymatically add a methyl group to cytosine in CpG dinucleotides in DNA. DNMT1 is a maintenance methyltransferase that methylates the newly synthesized CpG dinucleotides on the hemimethylated DNA during DNA replication. DNMT3A and DNMT3B are primarily responsible for *de novo* DNA methylation, with a high expression level during embryogenesis. The catalytically inactive member of the family, DNMT3L, contributes to the regulation of DNMT3A oligomerization and enhances its methyltransferase activity.

Somatic mutations of *DNMT3A* were first identified in adult AML patients [1,2]. Recurrence studies found *DNMT3A* mutations in ~30% of normal karyotype AML cases, making it one of the most frequently mutated genes in AML [3]. Moreover, it has been demonstrated that mutations in *DNMT3A* confer poor prognosis and decreased overall survival in AML [4]. The rate of *DNMT3A* mutations varies by AML subtype, with the highest rate (20%) seen among cases with monocytic lineage (M4, M5) [5,6]. Mutations occur as a nonsense or frameshift alternation, or missense mutations.

More than 50% of *DNMT3A* mutations in AML are heterozygous missense mutations at the R882 residue within the catalytic domain, most commonly resulting in an Arginine to Histidine amino acid exchange. A murine BMT model with hematopoietic stem/progenitor cells transduced by DNMT3A R882H acquired a chronic myelomonocytic leukemia (CMML)-like disease phenotype, with clinical features reminiscent of human AML with *DNMT3A* mutation [7]. The findings of this study suggest that this mutation alone is capable of initiating leukemia. However, in AML cells, R882 mutations always occur with retention of the wild-type allele, suggesting that the R882 mutant may serve as a dominant-negative regulator of wild-type DNMT3A. To establish this assumption, it has been shown that when exogenously expressed in murine embryonic stem (ES) cells, mouse DNMT3A R878H (corresponding to human R882H) proteins fail to mediate DNA methylation, but interact with wildtype proteins. When the wildtype and mutant forms were coexpressed in the murine ES cells, the wildtype DNA methylation ability was inhibited [8]. Furthermore, in a recent study of this mutation's mechanism, size-exclusion chromatography analysis demonstrated that the mutant enzyme inhibits the ability of the wildtype enzyme to form

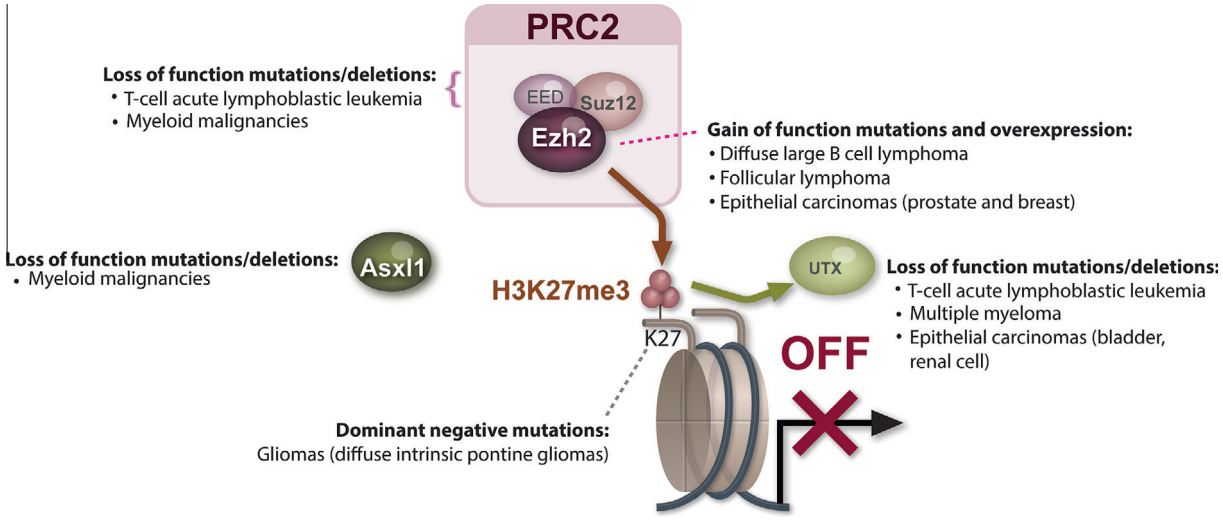

Fig. 1. Cancer associated changes regulating histone H3 lysine 27 (H3K27) methylation. In order to illustrate the wide variety of epigenetic alterations converging on a single epigenetic mechanism in cancer, the genetic alterations associated with alterations in H3K27 methylation are illustrated. Each of the genes portrayed are mutated in cancer and encode proteins which directly or indirectly affect H3K27me3 (in addition to possible additional effects in the cell). For instance, EZH2 is affected by both loss-of-function mutations and deletions in T-cell acute lymphoblastic leukemia (T-ALL) as well as in myeloid malignancies. In contrast, somatic point mutations which confer increased enzymatic activity to EZH2 are found in diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL). SUZ12 and EED, which form an enzymatic complex with EZH2, known as the Polycomb Repressive Complex 2 (PRC2) are also occasionally deleted and/or affected by loss-of-function mutations in myeloid malignancies. The Polycomb associated protein ASXL1 has been found to be associated with global abundance of H3K27 methylation and is frequently deleted and/or affected by loss-of-function mutations in myeloid malignancies as well. UTX, which encodes an enzyme which demethylates di- and trimethyl groups on H3K27 (H3K27me2/3), is frequently deleted and/or affected by loss-of-function mutations in multiple myeloma, T-ALL, and several epithelial carcinomas including renal cell carcinoma and bladder urothelial carcinoma. Finally, as evidence of the importance of H3K27 methylation, this exact residue of histone H3.3 is occasionally mutated in cancer. Histone H3.3 mutations are most enriched in a specific subtype of pediatric gliomas known as diffuse intrinsic pontine gliomas.