Acute myeloid leukemia

Acute myeloid leukemia (AML) is a cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal cells that build up in the bone marrow and blood and interfere with normal blood cell production.

In Acute myeloid leukemia, it was determined that mutations of IDH and other genes involving epigenetics regulations are early events, emerging in the pre-leukemic stem cells (pre-LSCs) stage, whereas mutations in genes propagating oncogenic signal are late events in leukemia. IDH mutations are also early events in glioma, occurring before TP53 mutation, 1p/19q deletion etc. Despite these advances in glioma research, studies into other molecular alterations have lagged considerably. In this study, we analyzed currently available databases. We identified EZH2, KMT2C, and CHD4 as important genes in glioma in addition to the known gene IDH1/2. We also showed that genomic alterations of PIK3CA, CDKN2A, CDK4, FIP1L1, or FUBP1 collaborate with IDH mutations to negatively affect patients' survival in LGG. In LGG patients with TP53 mutations or IDH1/2 mutations, additional genomic alterations of EZH2, KMC2C, and CHD4 individually or in combination were associated with a markedly decreased disease-free survival than patients without such alterations. Alterations of EZH2, KMT2C, and CHD4 at genetic level or protein level could perturb epigenetic program, leading to malignant transformation in glioma. By reviewing current literature on both AML and glioma and performing bioinformatics analysis on available datasets, we developed a hypothetical model on the tumorigenesis from pre-malignant stem cells to glioma [1)].

Acute myeloid leukemia (AML) and glioblastoma (GB) are two malignancies associated with high incidence of treatment refractoriness and generally, uniformly poor survival outcomes. While the former is a hematologic (i.e. a “liquid”) malignancy and the latter a solid tumor, the two diseases share both clinical and biochemical characteristics. Both diseases exist predominantly in primary (de novo) forms, with only a small subset of each progressing from precursor disease states like the myelodysplastic syndromes or diffuse glioma. More importantly, the primary and secondary forms of each disease are characterized by common sets of mutations and gene expression abnormalities. The primary versions of AML and GB are characterized by aberrant RAS pathway, matrix metalloproteinase 9, and Bcl-2 expression, and their secondary counterparts share abnormalities in TP53, isocitrate dehydrogenase, ATRX, inhibitor of apoptosis proteins, and survivin that both influence the course of the diseases themselves and their progression from precursor disease. An understanding of these shared features is important, as it can be used to guide both the research about and treatment of each [2)].

Chimeric antigen receptor (CAR) therapy targeting CD19 has yielded remarkable outcomes in patients with acute lymphoblastic leukemia. To identify potential CAR targets in acute myeloid leukemia (AML), we probed the AML surfaceome for overexpressed molecules with tolerable systemic expression. We integrated large transcriptomics and proteomics datasets from malignant and normal tissues, and developed an algorithm to identify potential targets expressed in leukemia stem cells, but not in normal CD34+CD38- hematopoietic cells, T cells, or vital tissues. As these investigations did not uncover candidate targets with a profile as favorable as CD19, we developed a generalizable combinatorial targeting strategy fulfilling stringent efficacy and safety criteria. Our findings indicate that several target pairings hold great promise for CAR therapy of AML [3)].

The gene encoding a human ortholog of rat NUDE1 is transcribed from the reverse strand of this gene, and its 3' end overlaps with that of the latter. The pericentric inversion of chromosome 16 [inv(16)(p13q22)] produces a chimeric transcript that encodes a protein consisting of the first 165 residues from the N-terminus of core-binding factor beta in a fusion with the C-terminal portion of the smooth muscle myosin heavy chain. This chromosomal rearrangement is associated with acute myeloid leukemia of the M4Eo subtype.

Treatment

Allosteric inhibitors of mutant IDH1 or IDH2 induce terminal differentiation of the mutant leukemic blasts and provide durable clinical responses in approximately 40% of acute myeloid leukemia (AML) patients with the mutations. However, primary resistance and acquired resistance to the drugs are major clinical issues. To understand the molecular underpinnings of clinical resistance to IDH inhibitors (IDHi), Wang et al. performed multipronged genomic analyses (DNA sequencing, RNA sequencing, and cytosine methylation profiling) in longitudinally collected specimens from 60 IDH1- or IDH2-mutant AML patients treated with the inhibitors. The analysis reveals that leukemia stemness is a major driver of primary resistance to IDHi, whereas selection of mutations in RUNX1/CEBPA or RAS-RTK pathway genes is the main driver of acquired resistance to IDHi, along with BCOR, homologous IDH gene, and TET2. These data suggest that targeting stemness and certain high-risk co-occurring mutations may overcome resistance to IDHi in AML. [4)]

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