Inhibition of childhood cancer and evolution.

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Abstract

Cancer is the leading disease-related cause of death in children in developed countries. Arising in the context of actively growing tissues, childhood cancers are fundamentally diseases of deregulated development. Childhood cancers exhibit a lower overall mutational burden than adult cancers, and recent sequencing studies have revealed that the genomic events central to childhood oncogenes is include mutations resulting in broad epigenetic changes or translocations that result in fusion oncoproteins. Here, we will review the developmental origins of childhood cancers, epigenetic deregulation in tissue stem/precursor cells in numerous examples of childhood cancer oncogenes is and emerging therapeutic opportunities aimed at both cell-intrinsic and micro environmental targets together with new insights into the mechanisms underlying long-term squeal of childhood cancer therapy.

Keywords: Childhood Cancer, Cancer, Oncology.

Introduction

Childhood cancers represent the leading cause of disease-related morbidity and mortality in childhood, second only to accidents as a cause of pediatric death1 in the United States and other developed countries. Childhood cancers encompass leukemia's, lymphomas, central nervous system tumors, sarcomas of bone and soft tissue, neuroblastoma, retinoblastoma, rhabdoid tumors, liver tumors, renal tumors, germ cell tumors and additional rare cancers [1].

Revolutionary advances in next-generation sequencing technology together with rapidly increasing progress in chromatin and stem cell biology have ushered in a new molecular understanding of childhood cancer. Recent landmark sequencing studies have demonstrated that the mutational burden in most childhood cancers is substantially lower than that in adult cancers [2].

Furthermore, evidence from genetically engineered mouse models of childhood cancer suggest that many pediatric tumors originate from stem or progenitor cells during particular developmental time windows. It is clear that these cells of origin must provide a transcriptional program permissive for the tumorigenic effects of a first genetic or epigenetic hit, which, as a consequence, distorts further cell divisions toward favoring self-renewal over differentiation [3].

Not only is the rate of mutations and structural variants lower in childhood malignancies compared with adult cancer, but also the types of alterations and particular genes affected differ from adult cancers. Pediatric-cancer-driving point mutations are enriched in genes that encode epigenetic machinery and are largely specific to the diseases in which they arise. Additionally, chromosomal fusion events that juxtapose oncogenes with gene partners that deregulate their proper activation or function are particularly prevalent among many types of childhood cancers other than the multiple genomic events that characterize oncogenes is in many adult cancers, a prominent feature of childhood cancers is epigenetic deregulation, with malignancy attributed to broad deregulation of gene expression [4].

One striking example of this principle is the discovery of point mutations in histone genes that deregulate histone post-translational modifications modulating gene expression. The best-studied example of this is the histone-3 (H3)-K27M mutation that occurs in diffuse midline gliomas, such as diffuse intrinsic pontine glioma and thalamic and spinal cord gliosis of childhood. In DIPG, the H3-K27M (rarely H3-K27I) mutation occurs in both canonical and non-canonical H3 genes encoding H3.3 and H3.1 and is found in ~80% of DIPG cases [5].

Conclusion

In summary, there are mechanistic themes unique to childhood cancer, regardless of the tissue of origin, which warrant distinct therapeutic approaches compared to adult cancer. The genomic landscape of childhood cancer is different, as mutational burden is lower and structural variants are less common in childhood cancer than in adult cancer. Additionally, driver point mutations most frequently occur in epigenetic modifiers, and, together with oncogenic fusion events, tend to be specific to individual cancer types and sometimes even specific to anatomical locations.

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