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Neuroblastoma in Children and the Potential Involvement of Viruses in Its Pathogenesis

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Abstract : Neuroblastoma (NBL) has epitomized for at least 40 years our understanding of cancer cellular and molecular biology and its potential applications to novel therapeutic strategies. This includes the discovery of the very first oncogene aberrations and tumorigenesis suppression by differentiation in the 80s; the potential role of suppressor genes in the 90s; the relevance of immunotherapy in the millennium first, and the discovery of additional mutations by NGS technology in the millennium second decade. Similar discoveries were achieved in the majority of human cancers, and similar therapeutic interventions were obtained subsequently to NBL discoveries. Unfortunately, targeted therapies suggested by specific mutations (such as MYCN amplification –MNA- present in ¼ or 1/5 of cases) have not elicited therapeutic successes in aggressive NBL, where the prognosis is still dismal. The reasons appear to be linked to Tumor Heterogeneity, which is particularly evident in NBL but also a clear hallmark of aggressive human cancers generally. The new avenue of cancer immunotherapy (CIT) provided new hopes for cancer patients, but we still ignore the cellular or molecular targets. CIT is emblematic of high-risk disease (HR-NBL) since the mentioned GD2 passive immunotherapy is still providing better survival. We recently critically reviewed and evaluated the literature depicting the genomic landscapes of HR-NBL, coming to the qualified conclusion that among hundreds of affected genes, potential targets, or chromosomal sites, none correlated with anti-GD2 sensitivity. A better explanation is provided by the Micro-Foci inducing Virus (MFV) model, which predicts that neuroblasts infection with the MFV, an RNA virus isolated from a cancer-cluster (space-time association) of HR-NBL cases, elicits the appearance of MNA and additional genomic aberrations with mechanisms resembling chromothripsis. Neuroblasts infected with low titers of MFV amplified MYCN up to 100 folds and became highly transformed and malignant, thus causing neuroblastoma in young rat pups of strains SD and Fisher-344 and larger tumor masses in nu/nu mice. An association was discovered with GD2 since this glycosphingolipid is also the receptor for the family of MFV virus (dsRNA viruses). It is concluded that a dsRNA virus, MFV, appears to provide better explicatory mechanisms for the genesis of i) specific genomic aberrations such as MNA; ii) extensive tumor heterogeneity and chromothripsis; iii) the effects of passive immunotherapy with anti-GD2 monoclonals and that this and similar models should be further investigated in both pediatric and adult cancers.

Keywords : neuroblastoma, MYCN, amplification, viruses, GD2
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