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Editorial

Neuroblastoma by chance

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Abstract

Neuroblastoma is a pediatric cancer of embryonic origin from neural crest cells. Neuroblastoma has a great medical and social impact because it is occurring with major frequency in pre-scholar age with metastatic disease showing less than 40% of survival at 5-years. In children, metastatic neuroblastoma has very few recurrent mutations but several chromosome structural copy variations. The tumorigenesis of neuroblastoma is still largely unknown; however recently, genomic wide association studies have shown that several gene allelic variants are associated with neuroblastoma predisposition. Many of these gene variants are related to maintaining the chromatin and mitosis integrity. In the present report, I suggest that neuroblastoma predisposing alleles may match by chance influencing the chromatin structure already during the early phases of embryonic life and inducing chromosome instability and structural damages.

Key words: neuroblastoma, tumorigenesis, chromosome instability, allelic variance, mutation, SNP

It is widely accepted that pathogenesis of pediatric cancers is very complicated and involves several clinical and biological aspects. However, it is my opinion that tumorigenesis of neuroblastoma, which accounts for 8-10% of all tumors in children, is closely to be solved. Neuroblastoma is one of the most medically and socially devastating pediatric cancers occurring in pre-scholar age [1]. Today, we have accumulated a huge amount of clinical and biological information about this tumor. Neuroblastoma tumor has very few recurrent mutations but shows a high biological and genetic heterogeneity [2, 3]. The origin of this feature is not known but evaluating clinical and biological data we can tentatively suggest the road to tumorigenesis.

It is generally accepted that neuroblastoma origins from the neural crest cells, a group of cells present in early development phases of human embryos just over the closure of neural tube [4, 5]. However, it is still unclear when and in which way the malignant transformation is occurring. Indeed, the neural crest cells are "marathon runner" cells. In the embryo, neural crest cells migrate in dorsolateral way to form melanocytes and in ventromedial direction to form sympathoadrenal ganglia and finally adrenal medulla, one of the sites from which the neuroblastoma grows.

In vivo models show that *MYCN* oncogene is the major actor in the malignant transformation, possibly together with *ALK* gene [6] or *LIN28* gene (Corallo et al.; manuscript submitted). Nevertheless, in human cancer *MYCN* seems to have a role in the tumor progression rather than tumor initiation. Indeed, a great portion of tumors of high-risk patients have *MYCN* single copy [1].

Interestingly, Capasso et al. [7] show a significant association between allelic polymorphisms and neuroblastoma susceptibility. *BARD1* (OMIN: 601593) is one of the first genes of which allelic variants have been found associated to genetic predisposition to neuroblastoma. Genomic wide association studies have shown that other SNPs are associated to neuroblastoma predisposition [8]. Some of these have been found linked to high-risk neuroblastoma predisposition: *BARD1* (OMIN: 601593); *LMO1* (OMIN: 616792); *Nbpf23* (OMIN: 613017); *Lin28B* (OMIN: 611044). *BARD1* together with *BRCA1* has been shown to be involved in

chromatin remodeling and located in critical regulators of DNA repair. *LMO1* has been found involved in the chromatin accessibility [9]. It is also to underline that *LMO1* includes a super enhancer (SE) in the first exon. Zanon and myself [10] have indicated the association between SE position and gene transcription regulation pointing out the possible role of SE in neuroblastoma aggressiveness. *Nbpf23* (613017) is involved in chromosome 1q duplication [11]; a critical function for maintaining the chromosome information. Molenaar et al. [12] reported that LIN28B showed genomic aberrations and extensive overexpression in high-risk neuroblastoma compared to several other tumor entities and normal tissues. Recently, Zhang et al. [13] have shown a strong association between *XRCC1* gene polymorphisms and neuroblastoma. The *XRCC1* is a well-known gene involved in DNA repair. Remarkably, Takagi et al [14] have shown an association between homologous recombination repair system and neuroblastoma susceptibility, and Wang et al. [15] have demonstrated the association between *hOGG1* and risk of neuroblastoma. The *hOGG1* gene is also involved in the DNA repair system and contributes to maintain the DNA cell integrity. Lastly, Cheng et al. [16] have observed the association between three polymorphisms: rs3810366, rs13181 and rs238406 of *XPD* (OMIN: 126340) and neuroblastoma in Chinese children. The *XPD*, also known as *XRCC2* is involved in defective nucleotide excision repair. Most of these allelic variances occur in genes associated to DNA maintaining information, chromosome assembly, chromosome distribution and they are able to perturb the cell mitosis. So, the allelic distribution can influence the chromatin status and can be involved in chromosome instability (CIN) [17]. The match between allelic variants associated to neuroblastoma can generate CIN in neuroblastic cells leading to chromosome chaos and malignant transformation. Indeed, CIN is a feature of neuroblastoma cells [5, 18]. Both numerical and structural copy number variations (CNVs) are virtually present in all neuroblastoma cells. These chromosome variations have been found in neuroblastoma of patients at any clinical stages and at any age: from newborn to adult, suggesting that CIN is already present in the embryonic age.

Taking all together the new discovery concerning allelic variants associated to neuroblastoma we can hazard that two or more alleles associated to neuroblastoma match by chance producing abnormal proteins involved in CIN. This pattern generates chromosome imbalance of neuroblastoma cells in the early phases of embryonic age [19] possible with accumulation of chromosome damage in tumor of children over one year of age [20]. The model explains why the neuroblastoma has very few mutations and why the tumor aggressiveness is strongly dependent on CNV. It is to be left the influence of environmental factors and parental genomes in the expression of neuroblastoma-associated allele genotypes.

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Competing Interests

The authors have declared that no competing interest exists.

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