

Group 3 Medulloblastoma

Subjects: Oncology

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Definition

Medulloblastoma is the most common malignant pediatric brain tumor, which accounts for approximately 20% of all childhood brain tumors.

1. Introduction

Heterogeneity is a main feature of cancer and prevents the development of targeted therapies in the vast majority of cases. The recent molecular characterization of several tumors has greatly contributed to overcome this issue and has provided a new interpretation of each cancer type as a set of individual tumors. Unveiling the molecular basis underlying each tumor subtype is a requisite for instructing personalized cancer treatments. Such deeply molecular analysis has been successfully carried out in Medulloblastoma (MB), the most common malignant pediatric brain tumor ^[1] arising from progenitor cell populations during early brain development. It has been classified into the four molecular subgroups Wingless (WNT), Sonic Hedgehog (SHH), Group 3 (G3) and Group 4 (G4), with defined features both in terms of driver genes and clinical outcomes ^{[2][3]}. The most aggressive MB subgroup is the G3, accounting for 25% of all MBs and associated with the highest rate of metastasis at diagnosis (about 45%) and the worst survival outcome at 5 years (under 60%) ^{[4][5]}. Until now, a G3 common driver pathway has not been identified, which makes this subgroup still enigmatic. However, a c-MYC signature is restricted to G3: it occurs in about 17% of patients whereas it is extremely rare in other MB subgroups, G4 being characterized by n-MYC signature ^{[2][3][6]}. In particular, MYC alteration is due to both gene amplification and aberrant expression and is strictly related to unfavorable outcomes ^{[4][7][8][9]}. Notably, it has been recently demonstrated that the concomitant overexpression of MYC and OTX, another relevant driver gene in G3, is sufficient to induce MB in vivo ^[10].

c-MYC (referred to as MYC hereinafter) is an essential transcriptional factor that orchestrates the gene expression programs necessary for growth, expansion and homeostasis of somatic and stem cells ^[11]. Together with its protein partner MAX, and other cofactors, MYC drives transcription of at least 15% of all genes ^[12], both protein-coding and noncoding genes ^{[13][14][15]}.

While in normal cells the levels of MYC RNA and protein are tightly regulated, in tumor cells they are aberrantly expressed. High levels of MYC have dramatic effects due to the amplification of the ongoing gene expression programs and the activation of previously silent genes implicated in cell cycle progression, proliferation, migration and metastasis ^[16]. For these reasons, MYC has long been considered an ideal cancer target ^[17]. Interfering with MYC expression or function was regarded as potentially detrimental for normal cells for a long time. However, recently the use of small peptides as MYC inhibitors proved to be a safe and effective therapeutic strategy ^[18]. Being deregulated in up to 70% of human cancers ^[19], MYC inhibition can be in principle used against multiple types of tumor.

By contrast, the development of tailored therapies implies a deeper knowledge of tumor-specific genes. The continued efforts in refining MB classification have provided a new challenge for identifying novel, specific tumor drivers beyond the well-known protein coding genes. In this framework, a specific class of noncoding transcripts, the long noncoding RNAs (lncRNAs), are emerging as attractive players in shaping MB features ^[20]. Because of their assessed role as oncogenes or oncosuppressors and their high tissue- and cancer-type specificity, they perfectly meet the criteria for being promising tumor targets and biomarkers. Nevertheless, for G3 MB mainly in silico studies have been carried out to pinpoint lncRNAs potentially involved in tumor biology ^[21].

2. Novel MYC-Regulated Long Noncoding RNAs in Group 3 Medulloblastoma

Cancer is a very complex pathology characterized by high heterogeneity among patients and tumor types [22][23]. It is well established that both coding and non-coding mutations greatly contribute to cancer biology. In particular, the vast majority of known driver mutations affect protein-coding regions and are mainly responsible for aberrant chromatin remodeling and proliferation pathway alterations [24]. Nevertheless, a number of genetic perturbations that affect developmental pathways, such as WNT and NOTCH, are also produced by somatic mutations in non-coding regions as the cis regulatory (promoters) and enhancer sequences or the untranslated regions (5' and 3'UTRs), all of which may have a strong impact on gene expression [24].

Moreover, recent studies that combined DNA- and RNA-based approaches to identify cancer-associated pathways have greatly expanded our knowledge of the multiple mechanisms underlying tumor biology. They revealed that some alterations may occur through changes in RNA, rather than DNA sequence mutations, such as overexpression [25], altered splicing [26] and gene fusion [27].

To add a further layer of complexity, genomic alterations in coding genes that control multiple targets—as chromatin regulators or transcription factors—may in turn affect noncoding genes. This is the case of lncRNAs, noncoding transcripts that are widely implicated in the regulation of gene expression programs underlying relevant biological processes, such as cell differentiation and development. They may act both in cis and in trans and, because of their modular nature, have the unique property to interact with proteins as well as with nucleic acids, both DNA and RNA, with high specificity. Notably, their ability to simultaneously establish such interactions provides them the possibility of targeting specific factors/complexes to a single location [28][29].

In line with their roles, the aberrant expression of lncRNAs may profoundly affect cellular pathways with pathological outcomes. Nowadays, they have been increasingly implicated in tumorigenesis and have been shown to contribute to each of the cancer hallmarks, from cell proliferation and survival to apoptosis, invasion and angiogenesis [30][31]. Such implication arose from the observation that lncRNA expression may be regulated by key oncogenic transcription factors such as MYC, which is involved in the majority of human tumors [19][32]. This suggested the possibility that these transcripts may play a part in the functional output of the oncogenic signal. Notably, while MYC is expressed in a variety of tumors, the lncRNAs are endowed with cell- and cancer type-specific expression which suggests that the same oncogene MYC may influence the expression of distinct sets of lncRNAs, depending on the pathological context. Therefore, while MYC is regarded as a universal target in cancer [18], the identification of MYC-responsive lncRNAs in distinct tumors may represent an alternative strategy for unveiling novel biomarkers as well as driver genes and therapeutic targets. They may be powerful biomarkers not only because many of them are uniquely expressed in distinct cancer types [33], but also because they may be easily detected in body fluids, such as urine, blood and cerebrospinal fluids, making the tumor diagnosis less invasive [34]. Their activity as driver genes is tightly dependent on their role as crucial nodes of regulatory networks. Paradigmatic is their action as microRNA sponges that may derepress gene expression in a pleiotropic manner [35][36] or as scaffolds to deliver transcriptional factors or chromatin remodeling complexes to the chromatin site [37][38].

In the era of precision oncology, researchers decided to unveil the contribution of lncRNAs to MB, the most common pediatric malignant brain tumor, mainly occurring in children under the age of ten [39]. To date, no pharmacological approaches are decisive in the treatment of this tumor, while the secondary effects of chemotherapy, craniospinal radiation or surgical interventions heavily affect the quality of life of pediatric patients, requiring the rapid development of alternative therapies. In particular, G3 MB subgroup sparked our interest for a number of reasons: (i) it is the most aggressive subgroup, being associated with the highest rate of metastasis at diagnosis (40–45%) and the worst survival outcome (under 60% at 5 years) [4][5]; (ii) no any univocal driver pathway has been underscored so far; (iii) the lncRNA landscape has never been thoroughly explored [40].

To unveil the lncRNAs engaged in G3 MB tumorigenesis, researchers exploited a feature of this subgroup, namely the high MYC level, due to both gene copy number increase and aberrant expression [3][10]. Therefore, we looked for MYC-dependent lncRNAs in a cell line, the D283 MED cells, in which MYC is overexpressed [41].

To this aim, researchers inhibited MYC function through the well-characterized dominant-negative OMOMYC [18][42] and analyzed the resultant impact on cell transcriptome. The advantage of using OMOMYC strategy is at least double. On the one hand, by sequestering MYC away from E-boxes on the promoter regions of target genes, OMOMYC blocks the expression of the MYC gene signature, common to tumors with high MYC expression [43]. Additionally, OMOMYC was also proposed to form transcriptionally inactive homodimers to E-boxes, resulting in inhibition of MYC target gene expression [18]. On the other hand, OMOMYC, interfering with the binding of MYC to its partner MAX, leads to ubiquitination and proteasome-dependent degradation of the free MYC monomer [44].

This strategy allowed us to compile the first atlas of MYC-dependent lncRNAs in G3 MB [10]. Through a stringent filtering procedure, researchers selected three candidates, renamed lncMB1, lncMB2 and lncMB3, to be tested for their involvement in G3 MB biology.

By comparing their expression profile in MYC-driven MB-derived cells and G3 primary tumors to normal cerebella, researchers hypothesized a potential oncogenic role for all of them.

By testing the ability of the lncRNAs to influence tumor cell-related features, researchers highlighted a role for lncMB3 in evading programmed cell death. Apoptosis, as a protective mechanism devoted to the maintenance of tissue homeostasis, represents a natural barrier that should be circumvented during tumor development [45]. Accordingly, the acquired resistance towards apoptosis is a hallmark of most, if not all, types of cancer. In this context, the future discovery of lncMB3 target genes will provide a new molecular pathway underlying G3 MB pathogenesis.

Starting from the discovery of the oncogene ZNF703 [46][47][48][49] as a lncMB2 target gene, researchers were able to demonstrate a role for the lncRNA in promoting cell migration and invasion, processes underlying cancer metastasis [50]. However, further studies are needed to realize whether this capability is mediated by ZNF703 and/or by other regulatory circuitries.

References

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