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ROLE OF miRNAs IN NEUROBLASTOMA PATHOGENESIS (review)

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Neuroblastoma is a sympathetic nervous system malignant tumor which is derived from the neural crest cells and constitutes 7–11% of the total number of childhood malignant tumors. Despite the comparatively low level of the disease, about 15% of pediatric cancer deaths are associated with neuroblastoma. As genetically complex cancer, neuroblastoma displays significant genetic heterogeneity. That is why strikingly different outcomes are observed across tumor subtypes — from spontaneous regression without therapy to rapid progression and death due to disease. Genomic amplification of the *MYCN* oncogene is used to predict the neuroblastoma disease outcome for over 30 years, however, recent methodological advances including microRNA and mRNA profiling, comparative genomic hybridization and whole genome sequencing allow to conduct a deeper neuroblastoma genome analysis leading to the identification of new prognostic markers and better patient stratification. In this review, we describe the major epigenetic factors responsible for these diverse clinical neuroblastoma phenotypes.

INTRODUCTION

Neuroblastoma is a sympathetic nervous system malignant tumor which is derived from the neural crest cells and constitutes 7–11% of the total number of childhood malignant tumors, taking fourth place in the structure of cancer morbidity after acute leukemia, central nervous system tumors and malignant lymphomas. The incidence of neuroblastoma constitutes 0,85–1,1 on 100 000 children under 15 years [16]. The disease age distribution is heterogeneous, frequency of tumor detection decreases with age. 90% of patients are newborns and children up to 6 years. In children older than 14 years neuroblastoma occurs rarely. Despite the comparatively low level of the disease, about 15% of pediatric cancer deaths are associated with neuroblastoma [30].

A characteristic feature of neuroblastoma is its clinical heterogeneity — from localized tumors to widespread forms and early hematogenous metastasing. This high clinical heterogeneity reflects the complexity of genomic abnormalities characterized neuroblastoma tumors [19]. As genetically complex cancer, neuroblastoma displays significant genetic heterogeneity. That is why strikingly different outcomes are observed across tumor subtypes — from spontaneous regression without therapy to rapid progression and death due to disease [7].

The role of *MYCN* gene amplification in neuroblastoma pathogenesis was first established in the early 1980s due to its association with high risk tumors and low patients survival [8]. Since then, several other genetic abnormalities were associated with neuroblastoma, including gains of whole chromosomes and a large number of large-scale chromosomal imbalances, such as loss of heterozygosity (LOH) at chromosome arms 1p, 3p, 14q and 11q, unbalanced gain of 1q, 11p and 17q and numerous mutations in key genes such as *ALK*, *PHOX2B* and *PTPRD* [16, 31].

Despite extensive knowledge of somatically acquired genomic rearrangements in neuroblastoma and their correlation with the clinical tumor phenotype, very few is known about the factors leading to these genetic events. Some changes in early embryogenesis or germ line are probably necessary for the development of neuroblastoma. Recently become known significant opportunities of epigenetic factors to promote carcinogenesis, especially in cases of childhood tumors with embryonic origin [14].

Epigenetics is defined as the study of heritable changes in the genes functioning that occur without changes in DNA sequence. Epigenetic modifications consist mainly of DNA methylation, histone modification, chromatin reorganization and expression of non-coding RNA. Epigenetic modifications are well known as regulators of tissue-specific gene expression, genomic imprinting and X-chromosome inactivation [4, 26]. In addition, the key role of epigenetic modifications during cellular differentiation, development and organogenesis has been highlighted by the identification of many epigenetic biomarkers in human diseases, such as neuroblastic tumors [18].

The occurrence of many cancers is the result of the accumulation of genetic and epigenetic changes. While genetic alterations are nearly impossible to reverse, epigenetic changes can dynamically respond to signals from the physical, biological and social environments [5]. This characteristic confers the importance of epigenetic research in various cellular processes, particularly in gene expression regulation. Although epidemiological data provide evidence that there is a direct

interaction between epigenetic modifications and environmental influence on gene expression, the mechanism of epigenetic induced modulations of gene expression is still poorly understood [16].

Numerous studies have demonstrated that genomic and transcriptomic profiles can be predictive clinical disease course, so that the combination of mRNA, miRNA and comparative genomic hybridization are now being used to better define prognostic markers that could provide insight into the molecular basis of clinical heterogeneity in neuroblastoma [8]. This is reflected in the International Neuroblastoma Risk Group (INRG) Staging System, which takes into account both clinical characteristics and tumor biology to identify clinical risk groups with statistically different survival rates [9]. Independently prognostic baseline characteristics of this system included patient age, stage of disease, histology, grade of differentiation, DNA index, *MYCN* gene amplification and presence of chromosome 11q copy number aberrations [2, 19].

NON-CODING RNAS

MicroRNAs (miRNA, miR) are evolutionarily conserved, endogenous, small non-coding RNA molecules, about 22 nucleotides in length. They function as post-transcriptional gene regulators through targeting regions of partial sequence complementarity mainly at the 3'UTR (untranslated region) of the target mRNA resulting in the degradation of the mRNA or inhibition of protein translation [21]. This partial complementarity allows miRNAs to regulate multiple mRNA sequences. At the same time, one mRNA can be regulated by several different miRNAs, resulting in a complex genetic network [24]. MiRNAs are known to regulate oncogenes, tumor suppressor genes, genes involved in cell cycle regulation, cell migration, apoptosis and angiogenesis. Subsequently, altered miRNAs expression profiles are found in several human diseases and in many cancer forms. In fact, certain miRNAs patterns can classify some cancer forms more accurately than data from ~16,000 mRNA [22].

In 2007 Chen and Stallings [14] found that many miRNAs are differentially expressed in different genomic neuroblastoma subtypes and that these miRNA profiles correlate with prognosis, differentiation and apoptosis. Continuation of this work was published in 2009, when a large group of tumors were analyzed to detect expression of 450 miRNA loci [16]. This study highlighted that over-expression of transcription factor *MYCN*, and large-scale chromosomal imbalances had contributed to the widespread dysregulation of miRNA expression in neuroblastoma tumors. Importantly, a miRNA expression signature predictive of clinical outcome was identified, emphasizing the potential of miRNA-mediated diagnostics and therapeutics. In accordance with these results, Schulte et al. reported that seven miRNAs (miR-92, miR-106th, miR-let7b, miR-17–5p, miR-93, miR-99 and miR-221) are regulated by *MYCN* in neuroblastoma, and showed that miR-221 is directly induced by *MYCN in vitro* [28].

New functional studies suggest that miRNAs regulate important genes involved in the neuroblastoma pathogenesis. For example, increased expression of miR-17–5p-92 cluster promotes tumor development by regulating pro-apoptotic gene *BIM*, cell cycle regulator p21, a transcription factor TGF-b and tumor suppressor *Dickkopf* [25]. Other miRNAs may act as tumor suppressor miRNA, such as let-7 and miR-101, which directly regulate the expression of *MYCN*, some miRNAs may have antitumor effects, such as pro-apoptotic miR-34a, anti-invasive miR-335, newest tumor suppressor miR-542–5p and several differentiation related miRNAs (miR-125b, miR-10a and miR-10b) [32, 35]. Other miRNAs have been shown associated with sensitivity to drugs in neuroblastoma, such as miR-204. But still the question remains about the mechanisms that underlie their deregulation in neuroblastoma [27].

REGULATION MECHANISMS OF miRNA EXPRESSION

Altered expression of miRNAs can be caused by several mechanisms, including DNA copy number aberrations, altered transcriptional activators/repressors, aberrant DNA methylation or defective proteins that are involved in the mechanism of miRNA biogenesis and posttranscriptional regulation of miRNA expression. Elucidation of the mechanisms involved in miRNA deregulation needed not only to better understand the role played by miRNAs in the development of the disease, it can also help to identify new therapeutic targets.

Copy number gain and loss

As already mentioned, miRNA expression alterations can be caused by gain and loss of DNA. However, in addition to the normal effect of dose, miRNAs imbalance leads to altered expression of their target genes resulting in significant genome dysregulation. miRNAs are often located at fragile sites and genomic regions involved in cancer development further implicates their involvement with malignant diseases [11].

Integrated analysis of miRNA expression profiling and oligonucleotide comparative genomic hybridization revealed that many of large-scale chromosomal imbalances in neuroblastoma, including loss of 1p, 3p, 11q and 14q, along with 1q and 17q gain, have a major impact upon miRNA expression. The same study identified predictive signature of 15-miRNA for neuroblastoma survival [16]. In a subsequent study it was demonstrated that tumors with 11q LOH can be divided into different subtypes using miRNA signature that differs significantly in clinical outcomes and overall frequency of large-scale genomic imbalances, with the poor survival group having more imbalances. However, this study also found cases where miRNA expression inversely related to genomic imbalance; miRNAs were underexpressed inspite of mapping to a region of DNA copy number gain. This strongly suggests that alternative mechanisms in some instances can counteract the effects of DNA dosage [10].

1p LOH in neuroblastoma is often associated with *MYCN* amplification and poor prognosis [2]. One of the first tumor suppressor miRNA, which was defined as the mapping to the shortest region of overlap, was miRNA-34a. Initial studies have shown that miRNA-34a can induce apoptosis in neuroblastoma cells, due to the fact that miRNA-34a is directly induced by p53 and soon after, *MYCN* was also identified as a direct target of miRNA-34a. MiRNA-34a functions as a tumor suppressor miRNA, inducing apoptosis in neuroblastoma. The multi gene targeting nature of miR-34a is well documented, with target transcripts including *MYCN*, *BCL2*, *SIRT1*, *NOTCH1*, *JAG1*, *CCND1*, *CDK6*, and *E2F3* [35]. Further studies revealed the therapeutic potential of miRNA-3 a in neuroblastoma. Targeted delivery of a miR-34a encapsulated anti-GD(2)-nanoparticles was accomplished in a neuroblastoma mouse model and confirmed miR-34a as an effective inhibitor of neuroblastoma tumor growth *in vivo* [6, 32, 34].

ACTIVATORS AND REPRESSORS OF miRNA TRANSCRIPTION

Transcription factor MYCN

MYCN has a regulating effect on the activation or repression of a large number of oncogenic and tumor suppressing miRNAs in neuroblastoma [16]. Activation or repression of miRNA is thought to occur as a result of direct binding of *MYCN* in the proximal regions of miRNA loci. *MYCN* oncogene amplification was shown to contribute to the widespread miRNA deregulation in neuroblastoma in miRNA profiles that correlate with clinical outcome. Two independent studies have shown that in most cases activity of miRNAs was reduced in tumors with *MYCN* amplification [23].

p53

p53 is a tumor suppressor protein that plays an important role in maintaining genomic stability and preventing the development of tumors by direct activation of several genes, including miRNAs that promote DNA repair, cell cycle arrest and apoptosis [20]. Direct binding of p53 is responsible for activating miRNA-34 family that act as tumor suppressor miRNAs in neuroblastoma. In addition to the miRNA-34 family, p53 directly regulates transcriptional expression of other miRNAs by direct binding to their promoters, such as miRNA-145, miRNA-107, miRNA-192 and miRNA-215 [12, 17]. Although the role of these miRNAs in neuro-

blastoma still needs clarification, other studies suggest that these miRNAs act as tumor suppressors in other cancers.

Inactivating mutations or deletions of the p53 gene are found in 50% of adult cancer in humans. However, in neuroblastoma, mutations of this gene are rare, in <2% of cases at diagnosis, and ~15% at relapse. However, inactivation of p53 can occur by an alternative mechanism in neuroblastoma tumors, for example, MDM2 functions as a negative regulator of p53 expression [12, 17, 29]. Although *MYCN* expression can promote p53 expression, over-expression of MDM2, which is observed in 29% of neuroblastoma, may counteract this effect, leading to inactivation of p53 and abnormal expression of p53-regulated genes [13]. These data indicate that inactivation of p53 in neuroblastoma may lead to deregulation protein-coding genes and miRNAs.

DNA methylation

DNA methylation consist in the addition of a methyl group 5 of the cytosine within the dinucleotide CpG. Gene silencing occurs when aberrant CpG islands are hypermethylated, which are dense clusters of CpG dinucleotides and are often present in genes promoters. Neuroblastoma genome displays different patterns of DNA methylation, which may be associated with different risk groups. The first of the studied genes that is differentially methylated in neuroblastoma, tumor suppressor RASSF1A [3], located at 3p21.3. Inactivation of RASSF1A is observed in 55% among a group of 67 patients with neuroblastoma, suggesting the silencing of this tumor suppressor gene may be associated with neuroblastoma. Another example of a commonly methylated and inactivated gene in neuroblastoma is *CASP8*. *CASP8* gene plays an important role in TNF-associated (Tumor Necrosis Factor) apoptosis pathway. An investigation of a cohort of 70 neuroblastoma tumor samples displayed 56% hypermethylation which was correlated with poor prognosis in neuroblastoma. In other study, involving clustering of a limited number of hypermethylated genes, *CASP8* gene was methylated in 77% of neuroblastoma cell lines [33]. Nowadays, it was described more than 75 genes methylated in neuroblastoma, and more importantly, the methylation status of a number of genes have been shown to be associated with the patients survival or risk factors in neuroblastoma, such as *MYCN* gene amplification, patient's age and disease stage.

Similar to protein coding genes, miRNAs are also susceptible to epigenetic regulation. A recent study with methylation data of several different tumors showed that comparing to the protein-coding genes, miRNAs have a higher level of methylation, about 11,6% of all known miRNAs are methylated [1]. However, very few studies in this area have been reported in relation to neuroblastoma disease. Recently, Das et al. attempted to explore DNA methylation as a possible mechanism of miRNA expression deregulation in neuroblastoma [16]. In-depth analysis of DNA methylation patterns in conjunction with the profile of miRNA and mRNA expression in neuroblastoma, clinical samples allowed the identification of a large set of epigenetically regulated miRNAs, significantly rich in targeted sites in the genes 3'-UTR over-expressed in unfavorable tumor subtypes. It should be noted that a high proportion of both methylated miRNAs (42%) and their associated mRNA targets (56% of targeted mRNA) was associated with poor clinical outcome when under and over-expressed in tumors, respectively. Potential epigenetically regulated miRNAs induced tumor suppressor miRNAs, well-characterized in neuroblastoma, such as let-7miRNA, miR-29c, miR-101, miR-335 and miR-184 [15]. It is important to note that many of miRNAs panel target genes are known to play a key role in neuroblastoma oncogenesis, such as AKT2, LIN28B, and CDK6, suggesting that epigenetic miRNAs silencing may contribute to the over-expression of oncogenes in neuroblastoma [16].

RNA-binding proteins: LIN28B

Several proteins that regulate miRNA processing have been described as key elements in determining the specific miRNA expression patterns in different cells or in the development of diseases. RNA-binding proteins (RBP) can bind to primary or precursor miRNAs and regulate their expression. It was found that 14% of all human pre-miRNAs have terminal loops that are evolutionarily conserved and can act as docks for RBP to regulate miRNA biogenesis [16, 25].

More recently, two independent studies related LIN28B over-expression to neuroblastoma pathogenesis. Diskin et al. reported that SNPs in LIN28B gene had contributed to the over-expression LIN28B in neuroblastoma tumors [25]. The mechanism by which LIN28B exerts its oncogenic effect is explained in the Molenaar et al. study. Consistent with the role LIN28B negative expression regulator of let-7,silencing of LIN28B in neuroblastoma cells leads to over-expression of let-7. Over-expression of LIN28B leads to increased levels of MYCN protein, which was explained by the fact that the let-7 is a direct post-transcriptional MYCN expression regulator. This study demonstrated that MYCN is LIN28-mediated target and LIN28B silencing leads to cell viability decrease and cell differentiation markers increase [16]. As a result of these studies, LIN28B has emerged as a new oncogene in neuroblastoma and a novel therapeutic target.

CONCLUSION

Since the 1980s, there has been significant progress in the diagnostic, stratification and treatment of neuroblastoma patients. Risk classification continues to be optimized and clearly future approaches will need to integrate profiling of mRNA and miRNA, epigenetic modification, whole genome copy number variations with the current INRG system. Thanks to advances in technology, it will allow to screen patients in time-effective, more economic and efficient way. Simultaneously novel therapeutics are being developed to target key regulators of neuroblastoma genome and more refined treatment regimens are based on increasing knowledge of the disease pathogenesis. This progress was induced by increase understanding of fundamental genetic changes associated with tumor behavior and clinical patient outcome.

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Роль микроРНК в патогенезе нейробластомы (обзор литературы)

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Резюме. Нейробластома — злокачественная опухоль симпатической нервной системы, происходит из клеток нервного гребня и составляет 7–11% общего количества злокачественных новообразований у детей. Несмотря на относительно низкий уровень возникновения данного заболевания, около 15% детской смертности, вызванной онкологическими заболеваниями, связаны с нейробластомой. Как генетически сложная форма рака нейробластома характеризуется значительной генетической гетерогенностью. Вот почему разительно отличается течение и тяжесть заболевания в разных подтипах опухоли — от спонтанной регрессии без терапии к быстрому прогрессированию и смерти в результате болезни. Геномная амплификация онкогена *MYCN* используется для прогнозирования течения заболевания при нейробластоме на протяжении более 30 лет, однако последние методические достижения, включая микроРНК и мРНК профилирование, сравнительная геномная гибридизация, а также полногеномное секвенирование позволяют проводить более глубокий анализ генома нейробластомы, что привело к выявлению новых прогностических маркеров и лучшей стратификации пациентов. В обзоре мы приводим основные эпигенетические факторы, ответственные за эти разнообразные клинические фенотипы нейробластомы.

Ключевые слова: нейробластома, *MYCN*, микроРНК.

Роль мікроРНК в патогенезі нейробластоми (огляд літератури)

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Резюме. Нейробластома — злоякісна пухлина симпатичної нервової системи, що походить з клітин нервового гребеня та становить 7–11% загальної кількості злоякісних новоутворень у дітей. Незважаючи на відносно низький рівень виникнення даного захворювання, близько 15% дитячої смертності, спричиненої онкологічними захворюваннями, пов'язані з нейробластомою. Як генетично складна форма раку нейробластома характеризується значною генетичною гетерогенністю. Ось чому разюче відрізняються перебіг та тяжкість захворювання в різних підтипах пухлини — від спонтанної регресії без терапії до швидкого прогресування і смерті в результаті хвороби. Геномна ампліфікація онкогена *MYCN* використовується для прогнозування перебігу захворювання при нейробластомі протягом більше 30 років, однак останні методичні досягнення, включаючи мікроРНК і мРНК профілювання, порівняльну геномну гібридизацію, а також повногеномне секвенування дозволяють проводити більш глибокий аналіз генома нейробластоми, що привело до виявлення нових прогностичних маркерів і кращої стратифікації пацієнтів. В огляді ми наводимо основні епігенетичні фактори, відповідальні за ці різноманітні клінічні фенотипи нейробластоми.

Ключові слова: нейробластома, *MYCN*, мікроРНК.