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REVIEW

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EXPRESSION OF GENES INVOLVED IN P53 PATHWAY REGULATION IN NEUROBLASTOMA: A SHORT REVIEW

M. Inomistova, H. Klymniuk, N. Khranovska, S. Pavlyk, E. Shaida, O. Gorbach, O. Skachkova, D. Shymon*

National Cancer Institute, Kyiv 03022, Ukraine

The search for new prognostic and stratification genetic and epigenetic markers in neuroblastoma is an urgent problem in pediatric oncology. The review summarizes recent progress in studying the expression of genes involved in p53 pathway regulation in neuroblastoma. Several markers associated with recurrence risk and poor outcome are considered. Among them are *MYCN* amplification, high *MDM2* and *GSTP1* expression and homozygous mutant allele variant of *GSTP1* gene A313G polymorphism. Prognostic criteria for neuroblastoma based on the analysis of miR-34a, miR-137, miR-380-5p, and miR-885-5p expression involved in regulating p53-mediated pathway are also considered. The authors' research data on the role of the above markers in regulation of this pathway in neuroblastoma are presented. The study of alterations in expression of microRNAs and genes involved in p53 pathway regulation will not only expand our understanding of the mechanisms of neuroblastoma pathogenesis but could substantiate new approaches for delineating risk groups and risk stratification of neuroblastoma patients as well as treatment optimization based on the genetic characteristics of the tumor.

***Key Words*: neuroblastoma, p53 pathway, gene expression, miRNA.**

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Neuroblastoma (NB) is a malignant tumor of the sympathetic nervous system. Characteristic features of NB are its clinical heterogeneity from localized tumors to spread forms and the ability to early hematogenous metastasis, spontaneous differentiation and regression. Such high clinical heterogeneity reflects the complexity of genomic abnormalities inherent in NB cells [1].

NBs with an aggressive course are characterized by multiple chromosomal aberrations and amplifications of individual genes, in particular, *MYCN*. Amplification of *MYCN* gene (MNA) is clearly associated with rapid progression of tumors of all stages and an unfavorable prognosis in patients of all ages. However, MNA is found in only 25% of NB cases and is often absent in chemotherapy-resistant tumors [2–4]. The search for new prognostic and stratification genetic markers in NB is an urgent problem and should cover both genome rearrangements and epigenetic disorders associated with the pathogenesis of NB. Of greatest interest are the genes involved in signaling pathways, apoptosis, cell cycle regulation, differentiation, invasion, and metastasis.

Loss of p53 functional activity causes proliferation of cells with various genetic abnormalities [5]. There are no changes in *TP53* gene characteristic for NB; the frequency of *TP53* mutations does not exceed 1–2% in primary tumors and is up to 15% in recurrent and/or progressive NBs [6]. In about half of human tumors, *TP53* gene remains unaltered, but function of wild-type p53 is often inhibited by hyperactivity and overexpression of *MDM2* [7]. *MYCN* is among the regulators of p53 signaling pathway [8]. The ability of wild-type p53 to activate transcriptionally *GSTP1* gene [9] determines new mechanisms of genome protection and tumor resistance to drugs.

In recent years, new mechanisms for regulating the activity of both *TP53* gene and p53-mediated pathway including those involving microRNAs have been discovered. MicroRNAs are a class of noncoding RNAs that play an important role in regulating mRNA translation and degradation by completely or partially inhibiting gene activity [9–11]. It has been shown that miRNA-34a is involved in p53-mediated apoptosis. The downregulation of miRNA-34a expression in the course of NB treatment could be considered as a significant negative prognostic factor [12, 13]. MicroRNA-380 is involved in the regulation of the activity of *TP53* gene in NB by binding to *TP53* mRNA and thus blocking the synthesis of the protein [14]. MicroRNA-885-5p also exerts tumor suppressive effect through interaction with CDK2. It is involved in p53-dependent and independent regulatory pathways, influencing cell cycle progression and NB cell survival [15]. MicroRNA-137 functions as a tumor suppressor in NB by inhibiting histone demethylase KDM1A, which inhibits p53/*TP53*-mediated transcription activation. Excessive expression of miRNA-137 in NB cell lines reduces cell viability and proliferation, promoting neuronal differentiation [16]. The Figure provides a generalized representation of the key links in regulation of the p53 pathway.

The study of expression changes of microRNAs and genes involved in p53 pathway regulation in NB will not only broaden the understanding of the mechanisms of p53 pathway regulation, but also justify new approaches to predicting disease and risk stratification of patients.

MYCN AMPLIFICATION IS A GENETIC MARKER OF HIGH RISK IN NB

Currently, amplification of MYCN gene remains the main genetic indicator of high-risk disease

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*Correspondence: E-mail: m.inomistova@gmail.com
Abbreviations used: MNA – amplification of *MYCN* gene; NB – neuroblastoma.

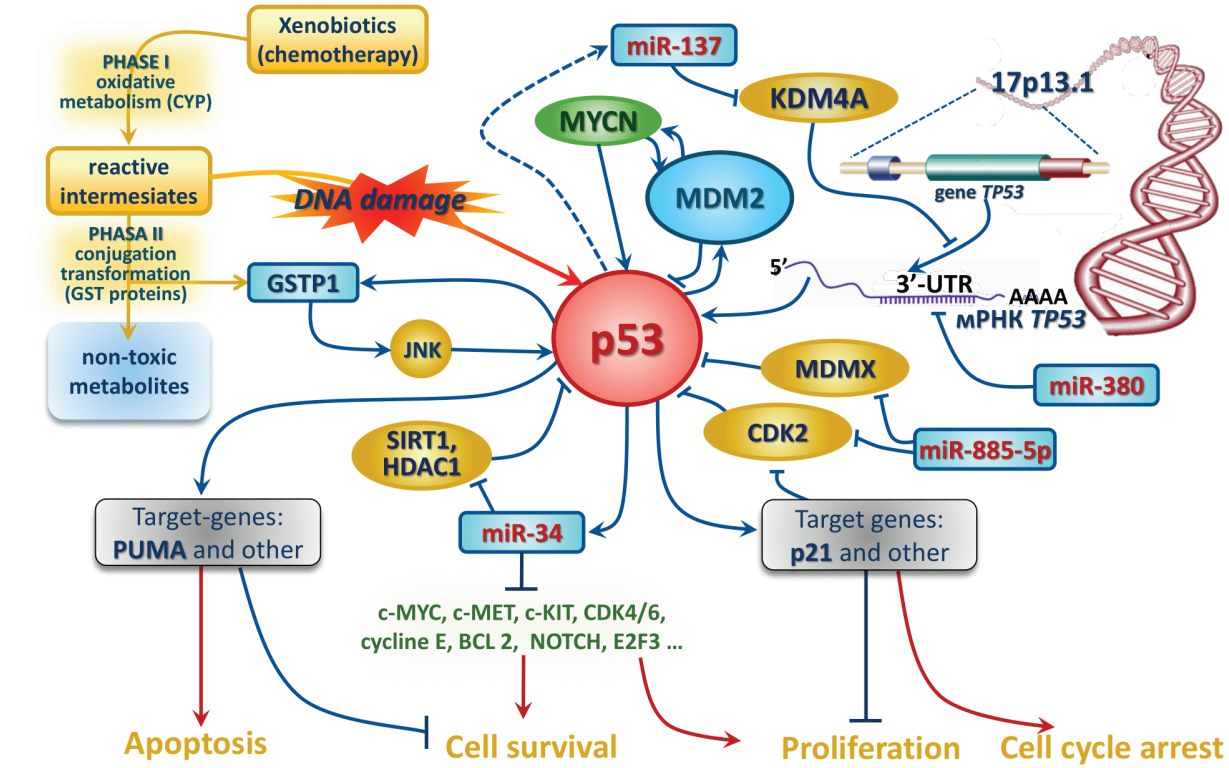

Figure. p53 pathway regulation.

in NB. Amplification of the MYCN gene is found in ~25% of cases and correlates with poor prognosis [2]. Despite the overall positive outlook in infants, a small group of such patients with MNA NB has poor survival rates [17]. In 1999, the International Society of Paediatric Oncology European Neuroblastoma Study Group launched the first multicenter study in Europe for infants designed to recommend treatment based on stage and *MYCN* status, and to collect data prospectively in an attempt to identify the most appropriate therapy [4, 18]. Our own study demonstrated that MNA at ⩾ 9 copies is clinically significant indicating an unfavorable disease course and delineating the high-risk group [19].

ALTERATIONS IN *TP53/MDM2* CO-EXPRESSION MAY PLAY A CRITICAL ROLE IN NB OUTCOME

The p53 protein is usually expressed at low to medium levels in various tissue types. The highest expression levels of *TP53* mRNA are observed in skin tissues, female reproductive organs, gastrointestinal tract, and organs of the immune system, while the lowest expression levels are found in muscle and endocrine cells. There are data on both increased and decreased expression of *TP53* in various cancer types [20]. Thus, in most cases of colorectal, pancreatic, gastric and bladder cancers increased expression of both *TP53* mRNA and p53 protein was observed. At the same time, the decrease and absence of *TP53* expression is observed in lymphomas, prostate, renal, and thyroid cancers [20–22]. It was also established that both a decrease and an increase in the expression of wild-type *TP53* mRNA were observed in various NB cell lines [23]. In general, mutations of the *TP53* gene are not often observed in malignant tumors of the central and peripheral nervous system in children. A possible mechanism of p53 activity reduction in NB may be the loss of chromosomal region 17p, where the *TP53* gene is located [5, 6, 24–26]. In our own studies, the loss of 17 chromosome region was not detected [19].

The expression of *MDM2* oncogene is being studied by researchers all over the world and the amount of the published data is growing exponentially. Most data strongly suggest that increased *MDM2* expression is associated with high probability of distant metastases, as well as a worsening of the response to chemotherapy. *MDM2* is overexpressed in recurrent tumors of various histogenesis [27–32]. *MDM2* may also be associated with resistance to chemotherapy. However, scarce studies have been conducted on changes in the expression of *MDM2*, a direct p53 antagonist, in the NB tissue.

We have found that increased *MDM2* expression in NB was associated with adverse disease characteristics such as recurrence and metastasis ($p = 0.001$), stage IV disease ($p = 0.0002$), and MNA ($p = 0.03$). Also, high levels of *MDM2* gene expression were associated with a decrease in event-free survival [19]. Since the *MYCN* oncogene transactivates *MDM2* [33, 34] in NB tumors with MNA, increased expression of *MDM2* can significantly reduce the activity of p53 that prevents cell cycle arrest and/or apoptosis.

In fact, earlier we have shown that the clinical outcome (relapse-free survival) was by 64% higher in the group with a low level of *MDM2* expression com-

pared to the group with a high level of *MDM2* expression [19]. Low *MDM2* mRNA expression in NB tumors without MNA determines recurrence-free survival. These data suggest that the study of *MDM2* expression may be useful in predicting the course of NB.

As p53 inactivation is more common in recurrent tumors [35, 36], the study of changes in *TP53* gene expression in primary tumors may be the way for understanding the changes that occur during disease development. Our unpublished studies showed a significant decrease in the *TP53* expression in metastatic and recurrent tumors ($p = 0.001$) that was not associated with clinical features of NB. However, in samples with a high level of *MDM2* expression, significant increase in *TP53* expression was found ($p = 0.007$). In the analysis of 3-year event-free survival dependent on *TP53/MDM2* co-expression, in patients with low expression of *MDM2* and high expression of *TP53* (ROC analysis: OC < 0.09 a.u., $p = 0.006$; AUC: 0.84) survival rate was 100%, while in all other groups it was significantly lower (F-Cox criterion: $p < 0.05$ compared to all other groups).

A313G POLYMORPHIC VARIANT AND THE LEVEL OF *GSTP1* EXPRESSION IN NB TISSUE CAN AFFECT THE OUTCOME

The mechanisms underlying the increase of *GSTP1* expression in many human tumors are currently not well understood. *GSTP1* is positively regulated at the early stage of oncogenesis and is overexpressed in many cancers [37]. In addition, high levels of *GSTP1* expression are directly related to drug resistance of the tumor and low patient's survival. This association may be explained by different rates of metabolism of anticancer drugs associated with gene polymorphisms or the role of *GSTP1* in the modulation of apoptosis mechanisms [37–40]. In fact, several anticancer drugs used in the chemotherapy protocol for high-risk NB are potential *GSTP1* substrates (etoposide, adriamycin, and carboplatin). *GSTP1* gene has been shown to be a transcriptional target for p53 [41–43]. It was found that high levels of *GSTP1* expression were associated with a decrease in event-free survival in NB patients [44].

There is evidence that polymorphic variations in glutathione S-transferases are associated with susceptibility to certain cancer types [43, 45, 46]. A polymorphism in codon 105 of *GSTP1* gene (A to G substitution at position 313 of the exon 5 sequence) leads to the substitution of isoleucine to valine, which causes a change in the enzymatic activity of the protein, and is considered as a high-risk genotype in various cancers [45, 46].

Analysis of a frequency of *GSTP1* polymorphic variants in our studies [47] showed no significant differences between the group of patients and the group of practically healthy people ($p = 0.4$) indicating no association between *GSTP1* gene polymorphism and NB risk. Among heterozygous carriers of mutant allele, the majority of patients with stage IV (32%) were found, but this group was characterized by the highest sensitivity to treatment.

We found that the overall survival in patients homozygous by mutant allele was significantly lower compared to other polymorphic variants ($p < 0.04$). To assess the overall prognostic value of *GSTP1* gene, overall survival was also analyzed, taking into account data on its expression and A313G polymorphism. In patients with high *GSTP1* expression, A313G polymorphism did not affect overall survival ($p > 0.05$). However, in patients with low *GSTP1* expression, the presence of the mutant allele determined a favorable prognosis ($p < 0.05$) [47].

CHANGES IN MICRORNA EXPRESSION IN NB REFLECT THE DEVELOPMENT OF THE DISEASE

In recent years, microRNAs have been found to play an important role in regulating p53-mediated pathway. The p53-mediated induction of miRNAs may contribute to the decrease in protein abundance observed after p53 activation [48, 49].

MicroRNAs play the central role in oncogenesis and tumor progression [50–52]. MicroRNA-34a has been identified as a tumor suppressor in several types of cancer, in particular, prostate carcinoma and primary melanoma as well as in several cancer cell lines [53]; a decrease in its expression has been associated with tumor chemoresistance [54]. It is known that miRNA-34a is involved in the processes of p53-mediated apoptosis (Figure). In our study, a decreased expression of miRNA-34a was associated with adverse clinical and biological features of the disease, such as recurrence and metastasis ($p < 0.05$), late age of onset ($p = 0.03$), stage IV ($p < 0.05$), MNA ($p < 0.05$) and overexpression of *MDM2* ($p < 0.05$), and decreased overall survival [55].

MicroRNA-137, which is highly expressed by brain cells, plays an important role in the regulation of neuronal maturation [56]. Overexpression of miRNA-137 inhibits dendrite morphogenesis, phenotypic maturation and development of the spinal cord and brain [57]. On the other hand, reduction of miRNA-137 expression has opposite effects [56]. Taking into account the association of miRNA-137 expression with the main determinants of tumor biology and the clinical course of NB, it can be supposed that this miRNA has a potentially great importance in the biology of NB. The results of the study [16] evidenced that a high level of miRNA-137 expression correlated with a favorable prognosis in patients with NB. It is suggested that miRNA-137 may regulate p53 indirectly mainly due to the degradation of KDM1A [58–60]. MicroRNA-137 functions as a tumor suppressor in NB through indirect activation of p53/*TP53* (Figure). In our study [60], a decreased expression of miRNA-137 was associated with adverse clinical features of NB — older age of NB onset, MNA, stage IV, *MDM2* overexpression, and significantly lower survival rates.

MicroRNA-380-5p is expressed at a high level in most primary NBs. Interestingly, miRNA-380-5p has binding sites in the conserved region of the *TP53* gene in the 3'-UTR. It was found that miRNA-380-5p inhibits p53 function and apoptosis in stem cells without affecting the expression of key elements of the p53-mediated signaling pathway such as p19ARF, MDM2, and Chek2 [14, 49]. The expression of miRNA-380-5p may cause a transient suppression of p53 in stem cells, thus supporting rapid cell proliferation and cell self-renewal without the risk associated with irreversible loss of p53 function, which is often found in cancer cells [14]. Thus, the expression level of miRNA-380-5p can affect the functioning of the p53 pathway, influencing the course of the NB.

In our study, a decreased miRNA-380-5p expression in NB cells was associated with the later stages of the disease, MNA and high level of MDM2 expression [61]. These data may support the hypothesis that miRNA-380-5p is involved in the suppression of p53 at the initial stages of NB development [14]. In patients with MNA, increased expression of miRNA-380-5p correlated with an unfavorable prognosis, which is consistent with the data obtained in experimental model systems and NB cell cultures that showed a link between MYC amplification and inhibition of the p53 pathway in oncogenesis [62].

In NB, several frequently deleted genetic regions were identified. Deletion of the 3p25.3 region is found in ~14% of NB, and this region contains the gene coding for miRNA-885-5p [15]. Afanasyeva *et al*. [15] showed that miRNA-885-5p is a candidate for the role of tumor suppressor in NB. Experimentally increased expression of miRNA-885-5p in NB cell cultures leads to inhibition of growth, aging and apoptosis. MicroRNA-885-5p inhibits proliferation and survival and positively regulates the p53 pathway. This miRNA exerts a tumor suppressor effect on the NB cell cycle through targeting CDK2. It participates in p53-dependent and independent regulatory pathways, influencing the progression of the cell cycle and the survival of NB cells [63].

We have detected the lowest level of microRNA-885-5p expression in recurrent tumors and metastatic foci of patients with stage IV NB and in tumor cells with high *MDM2* expression. Low levels of miRNA-885-5p expression were associated with a significantly decreased event-free survival [64].

Despite the achievements of the last three decades, NB remains a challenge for clinicians and scientists. 20 years ago, it was discovered that MNA occurs in NB. Since then, most research has focused on finding other genetic markers. As it turned out, NB cells, like cells of many other cancer types, often contain considerable, non-accidental damage to many genetic loci. Our results and the works of other researchers revealed the main changes in p53 pathway regulation network that occur during the development and progression of NB, and identified new factors in predicting the course of the disease, namely, expression levels of *MDM2* gene, polymorphism of *GSTP1* gene, altered expression of particular miRNAs (miRNA-34b, -c, miRNA-380-5p, and miRNA-885-5p).

Finding out the exact molecular profile of NB will allow researchers to analyze how specific markers in combination with clinical characteristics can help stratify the high–risk groups of patients and will allow developing new approaches for the prognosis of the disease course.

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ЕКСПРЕСІЯ ГЕНІВ, ЗАЛУЧЕНИХ ДО РЕГУЛЯЦІЇ ШЛЯХУ P53, ПРИ НЕЙРОБЛАСТОМІ: СТИСЛИЙ ОГЛЯД

М. Іномістова, Г. Климнюк, Н. Храновська, С. Павлик, О. Шайда, О. Горбач, О. Скачкова, Д. Шимон

Національний інститут раку, Київ, Україна

Пошук нових прогностичних генетичних та епігенетичних маркерів та маркерів стратифікації у хворих на нейробластому є нагальною проблемою педіатричної онкології. В огляді узагальнено досягнутий на сьогодні прогрес у вивченні експресії генів, задіяних у регуляції шляху передачі сигналу за участю p53 в клітинах нейробластоми. Розглянуто декілька маркерів, асоційованих з ризиком рецидиву та несприятливим прогнозом. Серед них ампліфікація *MYCN*, високий рівень експресії *MDM2* та *GSTP1*, гомозиготність за мутантним варіантом гена *GSTP1* (A313G-поліморфізм). Розглянуто також прогностичні критерії нейробластоми, що базуються на аналізі експресії miR-34a, miR-137, miR-380-5p, та miR-885-5p, які залучені до регуляції шляхів, опосередкованих p53. Представлено власні дані авторів щодо ролі всіх зазначених маркерів у регуляції шляху передачі сигналу за участю p53 в клітинах нейробластоми. Вивчення змін експресії мікроРНКта генів, залучених до регуляції шляхів, опосередкованих p53, не тільки поглиблює розуміння механізмів патогенезу нейробластоми, а й може обґрунтувати нові підходи для визначення груп ризику та стратифікації за ризиком хворих на нейробластому, що буде сприяти оптимізації лікування, виходячи з генетичних характеристик пухлини.

Ключові слова: нейробластома, сигнальний шлях p53, експресія генів, мікроРНК.