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Review

Neuroblastoma and Hippo Signaling Pathway

Nöroblastom ve Hippo Sinyal Yolağı

Selen Kum Özşengezer
Zekiye Altun
Nur Olgun

ABSTRACT

Neuroblastoma (NB) is a malignant tumor often seen in early childhood and originating from the sympathetic nervous system.Hippo signal pathway is a mechanism involved in organ growth, differentiation and plays an important role in stem cells, cancer stem cells and tumorigenesis.YAP,which is the transcription co-activator, is an important part of this mechanism and the inhibition effect of YAP inhibition on cell proliferation highlights the effect of this pathway on cancer. In the diagnosis and prognosis of pediatric tumors, more beneficial clinical applications of YAP and other routes can be considered and further research can be expected.Hippo pathway members, especially YAP, are potential new treatment targets for tumors that show overexpression. Along with the clinical features that affect the progression of the NB, chromosomal abnormalities and both oncogenes and tumor suppressor genes need to be evaluated together to develop new treatment strategies, especially in aggressive NB's. In recent studies, YAP inhibition has been shown to impair tumor growth and NB's cisplatin resistance.This defines YAP as a potential therapeutic target, especially for cisplatin-resistant NB.Hippo is a new glimmer of hope for NB in the signal pathway and open to study and development since all steps cannot be actively determined.

Keywords: *Neuroblastoma, hippo signaling pathway, pediatric oncology*

ÖZ

Nöroblastom (NB) sıklıkla erken çocukluk döneminde görülen ve sempatik sinir sisteminden kaynaklanan malign bir tümördür. Hippo sinyal yolağı, organ büyümesi, farklılaşması ile ilgili bir mekanizmadır ve kök hücreler, kanser kök hücreleri ve tümör oluşumunda önemli bir rol oynar. Transkripsiyon aktivatör olan YAP, bu mekanizmanın önemli bir parçasıdır ve YAP inhibisyonunun hücre çoğalması üzerindeki inhibisyon etkisi, bu yolun kanser üzerindeki etkisini vurgular.Pediatrik tümörlerin tanı ve prognozunda YAP'ın ve diğer yolların daha faydalı klinik uygulamaları düşünülebilir ve daha fazla araştırma beklenebilir. Hippo yolu üyeleri, özellikle YAP, aşırı ekspresyon gösteren tümörler için potansiyel yeni tedavi hedefleridir. NB'nin ilerlemesini etkileyen klinik özelliklerin yanı sıra, özellikle agresif NB'lerde yeni tedavi stratejileri geliştirmek için kromozomal anormalliklerin ve hem onkogenlerin hem de tümör baskılayıcı genlerin birlikte değerlendirilmesi gerekir. Son çalışmalarda YAP inhibisyonunun tümör büyümesini ve NB'nin sisplatin direncini bozduğu gösterilmiştir. YAP'ın özellikle sisplatine dirençli NB için potansiyel bir terapötik hedef olarak tanımlar. Hippo, sinyal yolunda NB için yeni bir umut ışığıdır ve tüm adımlar aktif olarak belirlenemediği için çalışmaya ve gelişmeye açıktır.

Anahtar kelimeler: *Nöroblastom, hippo sinyal yolağı, pediatrik onkoloji*

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Nur Olgun
Dokuz Eylül Üniversitesi,
Onkoloji Enstitüsü, Pediatrik
Onkoloji Anabilim Dalı,
İzmir, Türkiye
nur.olgun@deu.edu.tr
ORCID: 0000-0001-9591-0207

S. Kum Özşengezer 0000-0002-7068-5979
Z. Altun 0000-0002-1558-4534
Dokuz Eylül Üniversitesi,
Onkoloji Enstitüsü, Temel Onkoloji
Anabilim Dalı,
İzmir, Türkiye

Neuroblastoma

Neuroblastoma (NB) is a childhood solid cancer that accounts for about 15% of patient deaths in pediatric oncology. Neuroblastoma originates from the primitive sympathetic neural precursor cells in the peripheral nervous system [1,2]. Although tumors can occur anywhere in the body along the sympathetic nervous system, many of the primary neuroblastoma types can originate in the abdomen, even from the adrenal gland. One of the most common embryonal cancers is neuroblastoma, especially in patients under 5 years of age [3,4]. It is the second most common tumor of solid origin among children under 15 years of age. Prognosis is better in babies less than 18 months old and diagnosed with neuroblastoma not amplified with MYCN. However, children with neuroblastoma may have different clinical, biological, and prognostic features in adrenal, abdominal / retroperitoneal, neck, thoracic, or pelvic regions, depending on the location of their primary tumors in another region [5]. Neuroblastomas can be seen as

different clinical representations ranging from spontaneous regression, metastatic and treatment-resistant disease. Patients are classified by risk groups before treatment as having very low, low, intermediate and high risk. Various stages have been identified using the International Neuroblastoma Staging System (INSS). These stages are classified as 1, 2A, 2B, 3, 4 and 4S. The classification criteria include many factors such as the degree of surgical excision of the primary tumor, lymph node involvement, spread to distant organs, the level of bone marrow involvement, and age [6]. In addition, the International Neuroblastoma Risk Group (INRG), a new classification system, has also been developed [7]. MYCN amplification or 11q heterozygous loss are often found in high-risk neuroblastoma patients which is related to poor prognosis and recurrence of disease. MYCN amplification has been identified as an important poor prognostic factor for survival and remains one of the most important validated biomarkers in neuroblastoma. Inhibition of Aurora A kinase (AURKA) in the treatment of neuroblastoma has been extensively investigated. Aurora A and Aurora kinase B (AURKB) are two important regulators of the cell cycle. AURKA plays an important role in MYCN amplification. AURKA or AURKB expressions are associated with poor prognosis in neuroblastoma and might be targeted with specialized inhibitors. Inhibition of both AURKA and AURKB can be targeted using pan-Aurora kinase (AurK) inhibitors. Tozasertib (a pan-Aurora inhibitor) has been shown to be active in drug-resistant neuroblastomas [8]. High-dose chemotherapy, surgery, radiotherapy and anti-GD2 immunotherapy are used in the treatment of high-risk diseases [9]. NB tumors consist of two types of cells: neuroblastic ganglionic cells and reactive schwannian stromal cells which are divided into four basic morphologic types. These morphologic types include ganglioneuroma, mixed ganglioneuroblastoma, nodular ganglioneuroblastoma and neuroblastoma. These morphological characterizations demonstrate the levels of tumor differentiation in neuroblasts. Neuroblasts die during differentiation and maturation period before they reach the required maturity levels and leave a dominant schwannian stroma. After that, ganglioneuromas express a fully matured and differentiated NB. Although the reason for the assortment and differentiation of Schwann cells is not fully known, retinoic acid treatments are applied to differentiate residual disease with an increase in event - free survival [10].

Neuroblastoma and Development of Neural Crest

The neural crest (NC) forms during the gastrulation and neurulation processes and migrates throughout the embryonal development. Then it harbors a temporary embryonal cell population and differentiates to many various tissues. NC is a temporary embryological tissue originating from neuroectoderm. Development of neural creast involves various stages. During the neural tube formation, a complex and remarkable maturation process occurs. Thus, NC precursors gain the potential for differentiation and form a self-regenerating phenotype reminiscent of embryonic stem cells [11]. With the formation of tissues involved in neural tube development throughout gastrulation, development of neural crest is induced. The primitive neural tube consists of non-neural ectoderm and neural plate (NP) and neural plate border (NPB) tissues. Expression of the NC determining genes is triggered by the induction of genes in NPB. Interconnected signaling pathways of bone morphogenic protein (BMP), Wingless / Int (WNT), Fibroblast growth factor (FGF), and to a lesser extent Notch / Delta signal mediate this induction. This induction chain activates key transcription factors. Cascading signal gradients of BMP, Wnt, Notch and alternative ligands permit differentiation of assorted endothelial elements [12].

Oncogenic and Transcriptional Agents in Neuroblastoma

Although tumorigenesis in neuroblastoma is initiated by the deteriorating development of the neural crest precursors, no single genetic or epigenetic mutation is initiated after DNA and RNA sequencing [13]. There is no common specific-genomic variation

or genetic translocation attributed to all high-risk neuroblastoma tumors, but 1p deletion, MYCN amplification, or 17q gain, neuroblastoma and survival effect can identify subtypes. There are many oncogenic and transcriptional agents effective in neuroblastoma formation. Genes such as MYCN, ALK, and PHOX2B play roles in the pathogenesis of neuroblastoma.

MYCN; oncogene plays an important role in the development of neuroblastoma. The MYCN amplifier is identified by poor prognosis and is found in approximately 20% of cases. In transgenic mouse models, irregular MYCN expression is sufficient for high penetration tumor formation. It activates and suppresses genetic targets (eg mRNA, miRNAs, lncRNAs) by binding directly to DNA. In addition, it activates indirect protein-protein interaction mechanisms. It also has MYCN, anti-p53, proliferative, and pro-epithelial mesenchymal transition (EMT) functions. Throughout the development of embryogenesis and neural crest, MYCN is temporarily expressed in migrating crest cells to become sympathetic ganglion. Therefore, while high levels of MYCN can be found in some aggressive neuroblastomas, in many high-risk cases, minimum MYCN expressions are observed that independently suggest involvement of additional mechanisms in tumorigenesis [14,15].

ALK; Activating mutations of anaplastic lymphoma kinase (ALK) play important roles in the development of neuroblastoma. in all cases of familial neuroblastoma (<1% of total NB cases) and between 6-10% of spontaneous cases. This receptor tyrosine kinase (RTK) is also noted as an oncogene in different types of cancer, where it is typically present as a translocated fusion gene (ALK-NPM). Recent studies have been associated with the necessity of neural crest cells migrating in zebrafish models of ALK for sympathetic neuron development and neurogenesis [16]. This gene is an important regulator of STAT3-dependent stem cell functions. With the latest data from neuroblastoma mouse models, it has been observed that ALK and MYCN cooperate in tumor formation. This kinase suitable for drug targeting, is used in clinical trials for ALK- mutant neuroblastoma [17].

PHOX2B; In a subgroup of familial neuroblastoma and in approximately 4% of sporadic cases, there are mutations of Paired-like Homeobox 2B (PHOX2B). PHOX2B and PHOX2A enables differentiation of neural crest precursors towards sympathetic neurons (18). Recent studies have shown that neuroblastoma differentiation prevents PHOX2B from impairing calcium regulation with resultant loss of function. PHOX2B can also inhibit ALK expression in neuroblastoma [19].

Non-coding RNAs; Non-coding RNAs (microRNA, lncRNAs, piRNAs) are transcriptional regulators in stem cell biology, development, and neural crest differentiation. Many of these microRNAs are released in aggressive neuroblastomas, block p53 activity, activate EMT and metastases. It is reported that the MYCN oncogene can assume tumorigenic effects by regulating miRNAs that are effective for neural cell differentiation and apoptosis. Recent studies have shown that it triggers tumorignesis in neural crest and microRNA by inhibiting Let7a microRNA-mediated tumor suppression of LIN28 regulator expression. In addition, there are many other microRNAs that are directly related to the regulation of metastasis or tumor differentiation [20-22].

Epigenetically, specific structures that differentiate neuroectoderm, neural crest and more mature neural conditions have been demonstrated by different sequencing studies. Especially histone modifications in the crest indicate the presence of t enhancers of various genes. DNA demethylation dependent on DNA-methyltransferase-3-beta (DNMT3B) participates in neural crest maturation, and changes in this process promotes the tumor formation. It activates the differentiation of the neuroblastoma along the programmed neural crest maturation pathway. Alpha-thalassemia mental retardation X-linked (ATRX) factor is an epigenetic factor in NB seen in older children and adolescents. It plays a role in the regulation of telomere length. These mutations occur in 44% of cases of stage IV neuroblastoma in children 12 years of age or older, and only 9% of cases in children under 12 years of age. This gene critically regulates neural crest maturation [23-25].

Neural Crest Induction

Induction of genes within the junction neural plate boundary (NPB) leads to expression of neural crest determining genes. Different signaling mechanisms are involved in neural crest induction [10]. We can evaluate these mechanisms as follows:

Bone morphogenic protein (BMP)

BMP is a protein from the growth factor beta (TGFβ) family and activates the transcription factors of the Smad family which leads to the transcription of genes involved in growth and differentiation. Using an ESC model, there was a reduction in induction with early inhibition (0-2 days) and delayed (3-4 days) inhibition with noggin (BMP antagonist), which led to a decrease in neural crest induction. These studies have shown that BMP expression is required for neural crest induction. In neuroblastoma, BMP has been associated with neuroblastoma differentiation [26].

Wingless / Int (WNT) Signal Pathway

The signaling of WNT / β-catenin has been shown to be effective in neuroblastoma and its developmental pathway. However, WNT / β-catenin signal components have been shown to play a role in neuroblastoma proliferation. Specifically, initiation of the WNT / β-catenin signal pathway in MYCN non-amplified cell lines has been shown to increase MYCN levels. Thus, the 'canonical' ligands (WNT1, WNT6 etc.) support an important role for neuroblastomas. In the SH-SY5Y neuroblastoma cell line, RNAi suppression of WNT1 expression has been shown to significantly reduce cell viability [27].

Fibroblast growth factor (FGF) Pathway

Fibroblast growth factor (FGF) is a cell signaling protein that is secreted by binding to the receptor tyrosine kinase, also known as a fibroblast growth factor receptor (FGRR). Signal activation via FGFR activates many downstream pathways related to proliferation and survival. During induction of neural crest, FGF is released by paraxial mesoderm. In multiple cancer stem cell (CSC) models, including neural tumors such as glioblastoma, it has been indicated that STAT3 induces different transcription factors and contributes to the protection of CSCs [28].

Notch Pathway

Notch proteins are transmembrane signaling molecules that function as intracellular receptors (with Delta / Jagged protein ligands). With the binding of delta ligands, Notch's intracellular space is split, transported to the nucleus and bound to transcription factors. In mice and zebrafish models, Notch pathway has been found to be important in neural crest differentiation and induction. In neural systems, Notch1 is reliable for the regulation of the cell cycle and the protection of neural stem cells. With inhibition of Notch signal components (RBPjs), it can lead to a premature termination of neurogenesis. In neuroblastoma, inhibition of Notchl in the SH-SY5Y human NB cell line has been shown to induce neuronal differentiation via a JNK-CRT (Notch signal blockade) mediated pathway. Treatment of NB xenograft mice with Notch inhibitors (γ -secretase inhibitors, GSI) leads to suppression of tumor progression [29,30].

Hippo Signaling Pathway

The Hippo pathway is a signal pathway that modifies key target genes to control a large number of biological processes including cellular proliferation, survival, differentiation, determination of cell fate, organ size, and tissue homeostasis. The main components of the pathway is serine / threonine kinases, sterile 20-like kinase 1/2 (MST1 / 2) and large tumor suppressor 1/2 (LATS1 / 2). Latest studies have shown that MAP4K and TAOK kinases directly phosphorylate LATS1 / 2, so they demonstrate similar activities with MST1 / 2. These kinases, together with adapter proteins, Salvador homolog 1(SAV1) and MOB kinase activator 1A / B (MOB1A / B), down effector proteins, Yes-associated protein 1 (YAP1) and PDZ, phosphorylate, and inhibit paralo-

gous transcriptional coactivator. The binding motif (TAZ) (also known as WWTR1) sequences them in the cytoplasm by binding to 14-3-3 proteins. Tumour suppressor neurofibromin 2 (also called Merlin) joins these kinases to inhibit YAP and TAZ activity by triggering activation of the pathway. Additional phosphorylation of YAP / TAZ results in facilitation of proteasomal degradation, expedited by attachment to β-TrCP. This regulatory process prevents the build-up of YAP / TAZ within the nucleus and binding to a family of transcription factors known as TEA DNA-binding proteins (TEAD1-4), mediates functions of proliferative and pro-survival genes [31]. The nuclear / cytoplasmic distribution of YAP and TAZ is important in regulating cell polarity. Nuclear localization of YAP and TAZ facilitates tissue regeneration and increases the proliferation of undifferentiated progenitor cells in different organs. Abnormal activation of nuclear TAZ and YAP causes stem cell proliferation. The transition of YAP to cytoplasm ends in cellular differentiation and maturation. Signals activated by YAP and TAZ are also important in determining cell fate. The elements of the Hippo pathway affect mesenchymal stem cells and regulate their differentiation. Hippo pathway involving in embryogenesis and organogenesis is effective in the development of many pediatric cancers. As a diagnostic and prognostic biomarker in oncology, the Hippo pathway plays a role in pediatric malignancies with suggestion to the clinical uses of YAP (Fig.1) [32].

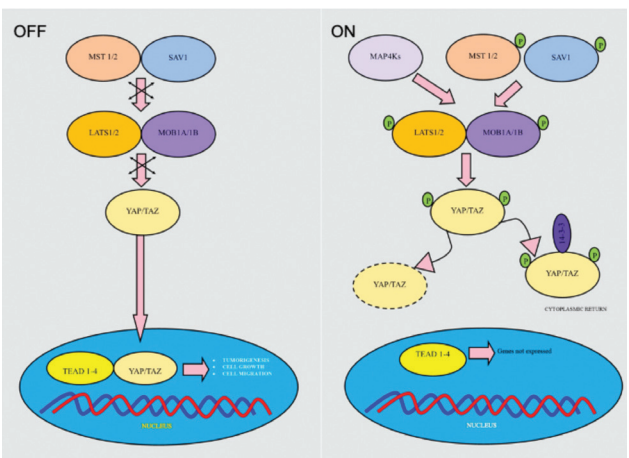

Figure 1. Core components of the Hippo signal path.

Hippo Signaling Pathway and Cancer

The Hippo signaling pathway plays a significant role in the development of stem cells, cancer stem cells and tumorigenesis. The defects in Hippo pathway elements evoke tumor formation in various adult cancers. Hippo core kinases, MST1 / 2 and LATS1 / 2 are often used as tumor suppressors. Other members of the Hippo pathway, for example KIBRA, may also play a role in the improvement of cancers [32,33]. YAP and TAZ principally relate with the TEAD family of transcription factors in cancer pathogenesis. The effective mechanism of YAP in tumorigenesis has not been determined exactly. Previous studies have shoıwn increases in the levels of YAP protein in various types of cancer. That is why YAP is defined as an oncogene. Overexpression of YAP in cancers has been associated with poor prognosis [33]. YAP acts as a tumor suppressor by activating cell apoptosis. In addition, YAP induces apoptosis in various hematological malignancies. Phosphorylation may be related to nuclear and cytoplasmic localization of YAP as an oncogene and tumor suppressor gene. The effective impact of the Hippo pathway in embryonic organogenesis indicates its important role in the development of pediatric cancers. Stopping cellular separation at embryonal level is seen in many pediatric cancers. This is thought that childhood cancers are associated with oncogenesis due to impaired normal embryological development which is associated with development of congenital malformations [34].

Hippo Signaling Pathway and Neuroblastoma

The element of the Hippo signal pathway is expressed in neural crest and regulates phenotype and cell migration. The expression of YAP begins to decrease with the maturation and differentiation of neural crest cells. It is estimated that members of the Hippo pathway originating from neural crest are overexpressed in neuroblastoma. Activation of YAP / TAZ has been demonstrated in neuroblastoma. It has been stated that this activation positively correlates with negative prognostic features. PTPN14

mutations encoding a negative regulator of YAP in recurrence of neuroblastoma have been acknowledged. Neuroblastoma cells being particularly immigrant and invasive have been associated with overexpression of TAZ. TAZ has been proven to support epithelial development to mesenchymal transition and neuroblastoma metastasis. Although studies have shown that YAP and TAZ are therapeutic targets, no experiment has ever been accomplished related to expression levels of these proteins in different subtypes of clinical neuroblastoma cases [35].

The Role of Hippo Signal Pathway and Tumor Immunogenicity

There are several reports related to tumor immunity in the Hippo pathway. Loss of Lats1 / 2 has been shown to inhibit tumor growth in syngeneic mouse tumor models. Lats 1/2 secrete extracellular vesicles rich in nucleic acid that increase tumor immunogenicity and impair activation of T cells in depleted tumor cells [36]. It has also been found that MST1 / 2 mutate in a rare human combined form of immune deficiency (CID), where proliferating T cells increase apoptosis [37]. Further studies are needed in the future to clarify the effects of these findings on cancer. Contrary to the studies, it has been stated that YAP is highly expressed and involves in the formation of directing T cells (Tregs). YAP induces activin expression by regulating TGFβ / SMAD signals. The Hippo pathway has also been shown to regulate the immune checkpoint molecule PD-L1. Reduction of MST1 / 2 or LATS1 / 2 increases the expression of PD-L1 in breast and lung cancer cells. TAZ also plays an important role in increasing PD-L1 expression in cancer cells. Thus, it directs the immune cells to escape which has been shown to be specific to species [38]. PD-L1 expression is also induced by the BRAF inhibitor in resistant melanoma. In a different study, it has been shown that TAZ plays a very important role in the regulation of differentiation of T helper and Treg cells [39].

Conclusion and Suggestions

Alternative treatments that target the Hippo pathway in cancer or immune system cells can cause some confusion.

Further studies are needed to clarify whether the members of the core Hippo pathway have an active role in different immune cells before any clinical or translational relationships are identified. In the diagnosis and prognosis of pediatric tumors, greater number of beneficial clinical applications of YAP and other pathways can be considered and conduction of further research can be expected. Hippo pathway members including especially YAP, are potential new therapeutic targets for tumors showing overexpression. Since YAP and TAZ are exposed to nucleocytoplasmic transport, the identification of small molecules that stop nuclear transport can give another approach to the negative regulation of YAP and TAZ. In addition to the clinical options that have an effect on the progression of the neuroblastoma, chromosomal abnormalities and both oncogenes and tumour suppressor genes should be evaluated so as to develop new treatment strategies, particularly in aggressive neuroblastomas.

In recent studies, inhibition of YAP has been shown to impair tumor growth and NB's resistance to cisplatin treatment which defines YAP as a potential therapeutic target, especially for cisplatin-resistant neuroblastoma. Activation of the Hiippo pathway is rare in human cancers. Therefore, whether inhibition of LATS1 / 2 can increase tumor immunity in many types of cancer should be investigated in future studies. The main goals are to improve the treatment outcomes in cases with advanced stage neuroblastoma and to reduce related side effects. In addition, alternative effective ways are sought in treatment protocols like risk-based national neuroblastoma treatment protocol (TPOG - NBL2009) [2, 40-43]. Hippo signaling pathway is a new glimmer of hope for treatment strategies of neuroblastoma.

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