

Association between Notch signaling pathway and cancer

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Background. The components of the Notch signaling pathway are important in maintaining the balance involved in cell proliferation, apoptosis and differentiation. Therefore, dysfunction of the Notch prevents differentiation, ultimately guiding undifferentiated cells toward malignant transformation. The aim of this article is to present recently published data concerning the role of the Notch signaling pathway components in development and prognosis of oncologic diseases, in occurrence of resistance to cytostatic agents and importance in creating of new cancer treatment approaches.

Materials and methods. The Pubmed was the main source of looking for information for this article.

Results. Recent investigations show that disorders of the Notch signaling pathway are associated with development of some human haematological and solid cancers. In different tissues and organs this active pathway can act as a tumor suppressor or an oncogene. Accordingly, the increased or decreased expression of its components is defined.

Most of published data show that the increased expression of Notch pathway components correlates with a worse prognosis of cancer and a shorter survival. Recently, the Notch pathway has been reported to be involved in drug resistance.

The modulation of the Notch signaling pathway could be helpful in treatment of some tumors with abnormal activity of this pathway's components. Therefore changes in the expression of Notch components could become important predictive factors, helpful in selecting the proper treatment method.

Conclusions. The results of recent studies are very important, since the detecting of the prognostic and predictive value of components of the Notch signaling pathway can allow creating new and improving already known methods of cancer diagnostic and treatment.

Key words: Notch signaling pathway, carcinogenesis, cancer

INTRODUCTION

Recently the Notch signaling pathway and its components have become one of the subjects of research in oncology. Nowadays the expression and changes of components of the Notch signaling pathway in normal and cancerous histological samples, as well as in cancer cells lines and animal models, are under investigation.

Notch signaling is an evolutionary conserved pathway. The components of the Notch signaling pathway are important in maintaining the balance involved in cell proliferation, apoptosis and differentiation, which affects the development and function of many organs. Therefore, dysfunction of Notch prevents differentiation, ultimately guiding undifferentiated cells toward malignant transformation. Investigations of two last decades show that those disorders of the Notch signaling pathway are associated with development of some human haematological and solid cancers (1–5).

It is important that in different tissues and organs an active Notch can act as a tumor suppressor or an oncogene. The mechanisms of such effect is yet unknown (6–8). Accordingly, the increased or decreased expression of Notch signaling pathway components is defined in cancer tissues. There are some data about the role of Notch pathway components in tumor angiogenesis and formation of metastases. Besides, Notch signaling pathways can influence the function of normal and malignant stem cells (9).

The aim of this article is to present recently published data concerning the role of Notch signaling pathway components in development and prognosis of oncologic diseases, in occurrence of resistance to cytostatic agents and importance in creating of new cancer treatment approaches.

MATERIALS AND METHODS

The Pubmed was the main source of looking for information for this article; keywords were “Notch signaling pathway”, “carcinogenesis”, “cancer”.

RESULTS AND DISCUSSION

Notch signaling pathway, its components and their role in cancer development

The Notch signaling in mammals is mediated by the transmembrane receptors Notch1, Notch2, Notch3,

Notch4, and the transmembrane ligands Jagged1, Jagged2 and Dll1, Dll3, Dll4. Notch receptors are type I transmembrane proteins that receive signals from ligands located in neighboring cells. A Notch receptor is composed of extracellular and intracellular domains associated noncovalently. Similar to Notch receptors, Notch ligands are single-pass transmembrane proteins. When the ligands bind to the Notch receptors, a two-step proteolysis cleavage process is initiated, resulting in release of the receptor intracellular domain into the cytoplasm and translocation to the nucleus. This is the way how this pathway is activated (1–3, 10, 11).

Numerous studies have demonstrated that aberrance or loss of Notch signaling pathway components is associated with multiple human diseases (12). For example, the loss of the Jag-1 gene is closely related to the Alagille syndrome which is characterized by various pleiotropic developmental disorders with accompanying features of congenital heart defects and cardiovascular abnormalities. A mutation in the Notch3 gene is directly linked to human degenerative vascular disease CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephatopathy).

Notch signaling pathway also plays an important role in cancer. Growth, differentiation and apoptosis are often aberrant in cancer development and genes, involved in these processes. The first evidence for the involvement of the Notch signaling in cancer came from T-ALL (T-cell acute lymphoblastic leukemia). Notch signaling receptors and ligands are frequently deregulated in human malignancies: breast, cervical, lung, colon, head and neck, renal carcinomas and others (6, 12, 13).

An important concept is that the Notch signaling can be both oncogenic and tumor suppressive. Notch may act either as a tumor suppressor or a tumor promoter depending on the cell type and tissue. Altered Notch signal acts as a tumor promoter in tissues where in normal conditions it acts as a stem cell or a cell fate regulator. Notch as a tumor suppressor is observed in the tissues where in normal conditions the Notch signal initiates the final differentiation process (6).

Oncogenic Notch signaling in hematologic malignancies

Notch signaling pathways play an important role in hematopoiesis. Notch signaling is involved in the

maintenance of the pool of lymphoid, myeloid and erythroid precursor populations. This pathway also regulates the development and differentiation of multiple hematopoietic cell types, including T and B cells, monocytes, macrophages, dendritic cells, osteoclasts and natural killer cells (6). Consequently, deregulated expression of Notch pathway elements can lead to the development of hematologic malignancies. It is considered that Notch induces inhibition of apoptosis and induction of proliferation in hematologic malignancies. For example, aberrant Notch1 expression has been identified as a facilitative factor in the development of T-cell acute lymphoblastic leukemia and lymphoma (T-ALL). Notch1 activating mutations have been identified in more than 50% of human T-ALL (14). Deregulated Notch signaling is also involved in the pathogenesis of multiple myeloma. Overexpression of Jagged1, Jagged2, Notch1 and Notch2 proteins are found in samples of human multiple myeloma (15). Acute myelogenous leukemia (AML) is characterized by overexpression of Jagged1 mRNA/protein and Notch1 protein (16). Two recent studies have identified activating Notch1 mutations in chronic lymphocytic leukemia (CLL) (17, 18).

Oncogenic Notch signaling in solid tumors

Similar to hematologic malignancies, the expression of Notch pathway elements has been observed in solid human tumors. Majority of studies demonstrate correlative associations between ligand and/or Notch receptor overexpression and tumor development (19).

Deregulated ligands involved in the Notch signaling expression have been observed in a number of tumors. Overexpression of the Jagged-1 protein has been reported in human cancers of the prostate (20) and brain (21). Upregulation of JAG1 mRNA and overexpression of Jagged-2 has been observed in human pancreatic cancer. JAG2 mRNA is up-regulated and the Jagged-1 expression is increased in human cervical cancer (6).

Deregulated Notch receptor expression has been reported in a number of solid human tumors (22). Oncogenic Notch signaling was detected in renal cell carcinoma, head and neck cancer, neuroblastoma and in case of endometrial cancer (19, 23). For example, the increased Notch1 protein expression has been observed in human cancers of the brain, cervix, colon, lung, pancreas and skin (6, 21, 22, 24,

25). Overexpression of the Notch2 protein is detected in human cancers of the cervix, colon, pancreas, skin and some types of brain cancers (6, 22, 24). Protein overexpression of Notch3 and Notch4 has been reported in human malignant melanoma and pancreatic cancer (6, 22). Increased expression of Notch1 and Notch3 was detected in ovarian cancer (19, 26).

Role for the Notch signaling in solid tumor pathogenesis has been best studied in breast cancer models in mice (6). Expression of either activated Notch1 or activated Notch4 has been shown to induce transformation of mouse mammary epithelial cells *in vitro*. Overexpression of Notch4 in normal human breast epithelial cells induces transformation *in vitro* (27). The recent study has shown that more than 50% of human breast tumors express reduced protein levels of Numb, a negative regulator of the Notch signaling, and a negative correlation exists between the Numb expression and the breast tumor differentiation grade (28).

Notch as a tumor suppressor in hematologic malignancies

Simultaneous activation of Notch1 and inactivation of Notch2 can be important in T-cell lymphomagenesis. Obtained results represent the instance for the involvement of Notch2 inactivation in the development of thymic primary tumors while confirming the role of Notch1 as an activated oncogene (29). There are some investigations about involvement of Notch in B-cell malignancies. Notch signaling has been shown to inhibit proliferation and/or induce apoptosis in malignant B cells (30, 31).

Notch as a tumor suppressor in solid tumors

Notch signaling acts as a suppressor in prostatic and brain tumor cancer cells, in small-cell lung cancer cells, in liver cancer cells (6, 25, 32). There are some data about the tumor suppressive role of the Notch signaling in embryonal carcinomas and in neuroendocrine tumors such as carcinoid or medullary thyroid cancers (19).

Expression of the Notch1 gene is markedly reduced in a panel of cervical carcinoma cells whereas the expression of Notch2 remains elevated, and the Notch1 expression is similarly reduced or absent in invasive cervical cancers. So, the Notch1 expression in early-stage cervical cancer may promote tumor

formation, whereas the expression in late-stage cancer may be tumor suppressive (24).

It was suggested that Notch acts as a tumor suppressor in hepatocellular carcinoma. Patients with better survival showed significantly higher expression of Notch related genes (33). Two recent studies of head and neck squamous cell carcinoma identified mutation affecting Notch receptors. Mutations were nonsense or insertion/deletions therefore predicted to be loss of function, supporting a tumor suppressive function (34, 35).

The role of the Notch signaling in the mammalian skin is less well characterized. Notch1 suppresses the development of skin cancer in mice. When the Notch1 function is inactivated specifically in the mouse skin, the epidermis undergoes hyperproliferation with subsequent development of skin tumors (36). Recent findings suggest that Notch1 may function as a tumor suppressor in human skin as well. In normal differentiated human epidermis, the Notch signaling is activated and functions to promote keratinocyte differentiation. Notch activity is significantly reduced in the two major types of non-melanoma skin cancer, squamous cell carcinomas and basal cell carcinomas. Human basal cell carcinomas lack activated Notch1 signaling (22).

The molecular mechanisms mediating suppression functions of Notch are still not clear. Several studies have highlighted antiproliferative effects of Notch signaling as an important mechanism. Notch signaling can trigger pathways leading to the arrest of cells growth and differentiation. Tumor suppressor activity is thought to be a result of crosstalk with other signaling pathways that govern decreased cell proliferation, increased apoptosis or the promotion of cellular differentiation (6, 25, 36, 37).

Different Notch receptors can have opposite effects in the same tumor type. Notch1 and Notch2 seem to play a crucial role in breast tumor differentiation. Notch1 expression is increased in poorly-differentiated tumors, whereas the Notch2 expression is high in well-differentiated tumors and reduced in breast tumors with poor differentiation. Therefore, Notch1 may possess tumor-promoting functions while Notch2 could play a tumor-suppressive role in human breast cancer. In contrast, in human brain tumors, Notch1 may be tumor suppressive with Notch2 playing an oncogenic role (6, 28, 32).

Taken together, these observations indicate that the role of the Notch signaling in the cancer development is ambiguous. Notch signaling can be both oncogenic and tumor suppressive. Activation of Notch in various cell populations may have different effects on the growth of the tumor as a whole. It is important to identify the cellular factors that determine whether the Notch signaling will be oncogenic or tumor suppressive. Several factors may play a role in determining how Notch acts. Most of cancers express more than one type of Notch ligand and/or receptor, the overall expression profile of these ligands/receptors may ultimately determine whether the Notch signaling will be oncogenic or oncosuppressive. Other factors are cell type, the presence of specific cytokines/growth factors in the cellular microenvironment, the dosage of the Notch signaling, etc. (6). Use of this knowledge in the near future will hopefully lead to the development of clinical therapeutics for the treatment of Notch-related malignancies.

Prognostic value of components of the Notch signaling pathway

There are not much published data concerning the prognostic value of components of the Notch signaling pathway, although most of them show that the increased expression of Notch pathway components correlates with a worse prognosis of cancer and a shorter survival. The increased expression of Notch1 and its ligand Jagged-1 is associated with more aggressive course of breast and prostate cancer (9, 21). Elevated expression of Notch1 and Jagged-1 also correlates with shorter time to breast cancer recurrence (38), raised expression of Jagged-1 correlates with recurrence in lymph node-negative breast cancer (39). It is known that Notch1 and Notch4 receptors can be used as prognostic markers in breast cancer (40).

Jagged-1 is highly expressed in metastatic prostate cancer as compared with localized prostate cancer or benign prostatic tissues. Increased expression of Jagged-1 is associated with a larger rate of prostate cancer recurrence after radical prostatectomy. So Jagged-1 can be a potential prognostic marker which would help to distinguish prostate cancer with an aggressive course (20).

M. Wang et al. (41) investigated the expression of Notch1 in case of ovarian cancer and found out

that it correlates with tumor differentiation status and FIGO (Federation International of Gynecology and Obstetrics) stage of ovarian cancer: expression of Notch1 increased gradually with the poor differentiating of cancer tissues and the increasing of the FIGO stage in ovarian cancer tissues.

The investigation of invasive cervical carcinomas showed that high nuclear Notch3 expression is associated with a shorter overall survival than low nuclear Notch3 expression ($P = 0.041$) (42). It is also known that the expression of nuclear Notch3 in pancreatic adenocarcinomas is associated with clinically more aggressive disease (39).

So, data about the potential prognostic value of components of the Notch signaling pathway are still being collected. Nevertheless, there are evidences that the course of disease in case of various sites of cancer depends on the expression of separate components of the Notch signaling pathway.

The value of components of the Notch signaling pathway in cytostatic drug resistance

There are some data about molecular mechanisms of drug resistance development (7). Recently, Notch pathway has been reported to be involved in drug resistance. Furthermore, studies have demonstrated that Notch regulates the formation of cancer stem cells and contributes to the acquisition of the epithelial-mesenchymal transition phenotype, which are critically associated with drug resistance. Notch signaling could con-

tribute to chemoresistance by protecting the cell from apoptosis, as it activates targets involved in cellular survival (43, 44). It is known that overexpression of Notch1 increases the drug resistance of breast cancers (45), cervical cancers to doxorubicin (46), and lung cancers to cisplatin and paclitaxel (43). So the decrease of activity of the Notch signaling pathway in tumors with the increased Notch expression can improve their sensitivity to cytostatics (Table 1).

The role of the Notch signaling pathway in research of new cancer treatment methods

Recently a lot of various trials and clinical evidences have shown that the Notch signaling pathway can act as an oncogene or a tumor suppressor in many tumors. This finding allowed using of the Notch signaling pathway as a potential cancer treatment target. The modulation of this pathway could be helpful in treatment of some tumors with abnormal (increased or decreased) activity of Notch pathway components. Possible molecular targets are Notch ligands, receptors, ligand and receptor binding, Notch intracellular domain (NICD) release, NICD and transcription complex interaction, etc. (47). So changes in the expression of Notch components could become important predictive factors, helpful in selecting the proper treatment method.

Nowadays there are some data about new effective agents which suppress the activity of the Notch

Table 1. The list of Notch pathway components involved in chemoresistance (adapted by Ref. 7)

Drug	Components of Notch pathway	Cell or tissue
Cisplatin	Notch1 is highly expressed in cisplatin resistance cells	Head and neck squamous cells, colorectal, and ovarian cancer cells
Doxorubicin	Increased Notch3 expression is associated with doxorubicin resistance	Hepatocellular carcinoma cells, myeloma cells
Gemcitabine	Inhibition of Notch3 enhances sensitivity to gemcitabine Notch2 and Jagged-1 are highly up-regulated in gemcitabine resistance	Pancreatic cancer cells
Gefitinib	Increased Notch1 expression is associated with gefitinib resistance	Breast cancer cells
Docetaxel	Down-regulation of Notch1 signaling increased chemosensitivity to docetaxel	Breast and prostate cancer cells

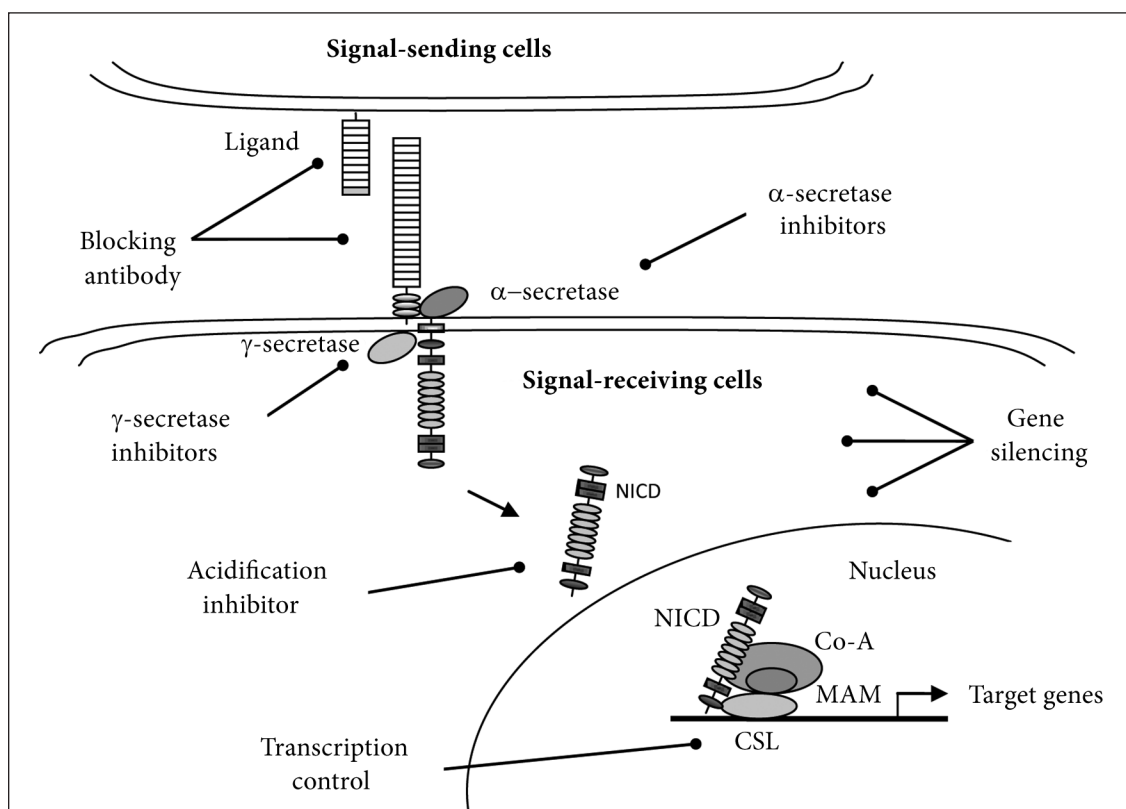


Figure. Potential cancer therapeutics by targeting Notch signaling pathways. NICD – Notch intracellular domain; Co-A – Co activators; CSL – DNA binding protein; MAM – Mastermind-like

signaling pathway and can be useful in treatment of some types of cancer. Among such agents, there are antibodies against Notch proteins: antibodies against Notch1 can be effective for treatment of T-lineage acute lymphoblastic leukemia (T-ALL), colon, breast cancer (47), antibodies against Notch2 for melanoma treatment (48), antibodies against Notch3 effective for non-small cell lung and ovarian cancer (49, 50).

Currently, one of the most promising agents seem to be gamma-secretase inhibitors (gamma-secretase is an enzyme which participates in Notch pathway activation) (51). Gamma-secretase inhibitors (GSIs) were originally developed in the late 1990s to treat Alzheimer disease because gamma-secretase enables amyloid plaques to build up in the brain in Alzheimer disease (52). Notch signaling is activated via the activity of gamma-secretase which makes it a target in cancer therapy. Several forms of gamma-secretase inhibitors have been tested for antitumor effects. For example, IL-X, an original gamma-secretase inhibitor, has been shown to have Notch1-dependent antitumor activity. Re-

cently, the dipeptide gamma-secretase inhibitor DAPT (*N*-(3,5-Difluorophenacetyl-L-alanyl)-*S*-phenylglycine *t*-butyl ester) was reported to suppress medulloblastoma growth and induce G0-G1 cell cycle arrest and apoptosis in a T-ALL animal model (53). Another gamma-secretase inhibitor GSI-XII induces apoptosis of myeloma cells and improves their sensitivity to chemotherapeutic drugs such as doxorubicin (54).

Gamma-secretase inhibitors have been shown to inhibit Notch expression and tumor cell growth of pancreatic cancer cells *in vitro* and Kaposi sarcoma cells *in vitro* and *in vivo* (55). Gamma-secretase inhibitors also suppress prostate cancer cell growth (56). In addition, GSIs have been shown to have an antiangiogenic effect by reducing endothelial cell proliferation and microvessel outgrowths *in vitro* (57). Currently, inhibitors of gamma-secretase are being tested in preclinical and Phase I clinical trials, suggesting that the Notch signaling is an important target in cancer therapy (7, 58).

Figure shows the components of the Notch signaling pathway, which can be affected by various

Table 2. Gamma-secretase inhibitors and Notch signaling pathway

Type of malignancy	Gamma-secretase inhibitors' effect on Notch pathway	References
Medulloblastoma	Inhibit Notch2 activity and growth of medulloblastoma	X. Fan et al., 2004 (32)
Kaposi sarcoma	Inhibit Notch1, -2, -4 activity and induce apoptosis in Kaposi sarcoma cells	CL. Curry et al., 2005 (55)
Pancreatic cancer	Cause mutations in Notch1 and inhibit the growth of pancreatic cancer cells lines	Z. Wang et al., 2006 (59, 60)
Lung cancer	Inhibit Notch3 signaling, growth, and apoptosis of lung cancer cell lines <i>in vitro</i> and <i>in vivo</i> using mouse xenograft models	J. Konishi et al., 2007 (61)
Breast cancer	Inhibit Notch1 activity and growth of breast cancer cells	G. Farnie et al., 2007 (38)
Ovarian cancer	Inhibit Notch1 and cause cell growth inhibition and apoptosis in ovarian cancer cells A2780	M. Wang et al., 2010 (62)

recently developed anticancer agents. Table 2 illustrates the way how gamma-secretase inhibitors influence the Notch pathway.

It was already mentioned that the Notch signaling pathway has been reported to be involved in drug resistance. So targeting Notch could be a novel therapeutic approach for the treatment of cancer by overcoming drug resistance of cancer cells (7). There are some data that gamma-secretase inhibitors treatment can enhance the apoptotic effect of taxanes in colon cancers (63) and of doxorubicin and melphalan in multiple myeloma cells (64). The results of one of the published studies (25) indicated that the viability of colon cancer cells was synergistically decreased by gamma-secretase inhibitors (GSI34) in combination with multiple forms of chemotherapy, including oxaliplatin, fluorouracil (5-FU), etc. So use of GSIs may then present a novel means to both enhance the effects of chemotherapy and to delay chemoresistance in patients with metastatic disease.

It is also known that inhibition of Notch3 enhances sensitivity to gemcitabine in pancreatic cancer (65), and inhibition of Notch by GSIs sensitizes glioma stem cells to radiation at clinically relevant doses (66).

It is important that current gamma-secretase inhibitors have significant acute toxicities, especially to the gastrointestinal tract (9). Their long-term effects are yet to be discovered. Another major chal-

lenge is to understand how to combine Notch inhibitors with other drugs.

The alternative to gamma-secretase inhibitors could be monoclonal antibodies against Notch proteins and ligands which seem to be more selective, still further studies are needed to determine and confirm their selectivity, effectiveness and safety (8).

Trials are ongoing to find less toxic anticancer agents. For example, Z. Wang et al. study has shown that chemopreventive agents such as genistein and curcumin may inhibit Notch1 activation in pancreatic cancer cells leading to apoptotic cell death (59, 60). There some data about other agents (i. e. resveratrol (67)) that have shown to inhibit the Notch pathway.

Further studies are needed to create agents with minimal toxicity which could modulate the activity of components of the Notch signaling pathway.

CONCLUSIONS

Notch signaling pathway and its components have become one of the subjects of research in oncology. Notch signaling can be both oncogenic and tumor suppressive. The exact role of some components of the Notch signaling pathway is still unclear. Nevertheless, the results of recent studies are very important since the detecting of the prognostic and predictive value of components of the

Notch signaling pathway can allow creating new and improving already known methods of cancer diagnosis and treatment.

ACKNOWLEDGEMENTS

This work has been supported by the Research Council of Lithuania, Project MIP-083/2011.

Received 14 September 2012

Accepted 23 November 2012

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NOTCH SIGNALINIO KELIO IR VĖŽIO SĄSAJOS

Santrauka

Įvadas. Notch signalinio kelio komponentai yra svarbūs palaikant pusiausvyrą tarp ląstelių proliferacijos, apoptozės ir diferenciacijos. Pakitus šio kelio aktyvumui, sutrinka ląstelių diferenciacija, galiausiai nediferencijuotos ląstelės transformuojasi į piktybines. Šio straipsnio tikslas – pateikti pastarųjų metų literatūros duomenis apie Notch signalinio kelio komponentų vaidmenį onkologinių ligų vystymuisi, prognozei, jų poveikį atsparumo citostatikams formavimuisi bei reikšmę kuriant naujus vėžio gydymo metodus.

Medžiaga ir metodika. Pagrindinis informacijos šaltinis, ieškant duomenų, buvo *PubMed* duomenų bazė.

Rezultatai. Pastarųjų metų tyrimų rezultatai rodo, kad Notch signalinio kelio sutrikimai yra susiję su kai kurių hematologinių bei solidinių navikų formavimusi. Priklausomai nuo audinio ir organo aktyvus Notch signalinis kelias gali sukelti onkogeninį arba navikus

slopinantį poveikį. Atitinkamai navikuose nustatoma padidėjusi arba sumažėjusi Notch signalinio kelio komponentų raiška.

Dauguma publikuotų duomenų patvirtina, kad padidėjusi Notch signalinio kelio komponentų raiška koreliuoja su blogesne ligos prognoze bei trumpesne gyvenimo trukme. Nustatyta, kad Notch signalinis kelias taip pat svarbus formuojantis atsparumui citostatikams.

Notch signalinio kelio moduliavimas gali praversti gydant piktybinius navikus, kuriuose nustatytas nenormalus Notch signalinio kelio komponentų aktyvumas. Taigi, ateityje Notch signalinio kelio komponentų raiškos pokyčiai galėtų tapti svarbiais predikciniais veiksniais, kurie padėtų parinkti tinkamą gydymo taktiką.

Išvados. Nors atskirų Notch signalinio kelio komponentų vaidmuo kancerogenezėje nėra gerai žinomas, esamų tyrimų rezultatai yra vertingi, nes šio kelio komponentų ir jų pokyčių prognozinės ir predikcinės reikšmės nustatymas leistų sukurti naujus bei patobulinti jau esančius vėžio diagnostikos ir gydymo metodus.

Raktažodžiai: Notch signalinis kelias, kancerogenezė, vėžys