Другие исследования (George et al., 2015) указывают на супрессорную роль генов семейства *Notch* в развитии МКРЛ и их регуляторное значение в дифференцировке нейроэндокринных клеток. Так, в большинстве исследуемых образцов опухолевой ткани высокий уровень экспрессии генов белков-маркеров-нейроэндокринных клеток *CHGA* (хромогранина А) и *GRP* (гастрин-рилизинг пептид) регистрировался на фоне высокой экспрессии гена ингибитора передачи сигналов Notch (гена лиганда *DLK1*) и гена фактора транскрипции *Ascl1*, индуцирующего начальные стадии опухолевой трансформации и необходимого для выживания опухолевых клеток (George et al., 2015).

Одной из потенциальных мишеней таргетной терапии опухолей является лизин-специфическая гистондеметилаза 1 (LSD1), обеспечивающая пролиферацию и метастазирование путем ингибирования опухолевого супрессора p53 (Chen et al., 2012). В эксперименте на мышах и клеточных линиях показано, что подавление активности LSD1, высоко экспрессирующейся при МКРЛ, сопровождается реактивацией передачи сигналов через Notch-1-рецептор и последующим угнетением фактора транскрипции Ascl1 (Augert et al., 2019). На супрессорную роль сигнального пути Notch в онкогенезе при МКРЛ также указывает высокая экспрессия на поверхности опухолевых клеток ингибирующего лиганда DLL3, регулируемая Ascl1 (Leonetti et al., 2019; Owen et al., 2019).

ЗАКЛЮЧЕНИЕ

Результаты представленных исследований подтверждают решающую роль передачи сигналов Notch в эмбриональном развитии легких, дифференцировке бокаловидных клеток и гиперпродукции слизи при ХОБЛ, гиперреактивности и ремоделировании дыхательных путей у больных бронхиальной астмой, инициации и прогрессировании опухолевой трансформации клеток. Плейотропный характер Notch-опосредованных изменений указывает на необходимость дальнейшего изучения молекулярных механизмов, модулирующих сигнальный каскад. Комплексный анализ особенностей Notch-опосредованной индукции или подавления механизмов развития рассмотренных патологий позволит установить потенциальные таргетные мишени, усовершенствовать диагностические методы, а также терапевтические стратегии профилактики и лечения заболеваний органов дыхания.

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СПИСОК ЛИТЕРАТУРЫ

Ишутина О.В. 2021. Сурфактантная система легких. Обзорная статья. Вестник ВГМУ. Т. 20. № 4. С. 7. https://doi.org/ (*Ishutsina O.V.* 2021. The surfactant system of the lungs. A review article. Vestnik VGMU T. 20. № 4. C. 7. https://doi.org/ https://doi.org/10.22263/2312-4156.2021.4.7)

Целуйко С.С., Намаконова В.С., Красавина Н.П., Чжоу С.Д., Ли Ц. 2014. Идентификация и локализация стволовых клеток в органах дыхательной системы (обзор литературы). Бюллетень физиологии и патологии дыхания. № 52. С. 121. (*Tseluyko S.S., Namakonova V.S., Krasavina N.P., Zhou X., Li Q.* 2014. Identification and localization of stem cells in the respiratory system (review). Bulletin Physiology and Pathology of Respiration. V. 52. P. 121).

Agustí A., Vogelmeier C., Faner R. 2020. COPD 2020: changes and challenges. Am. J. Physiol. Lung Cell. Mol. Physiol. V. 319. P. L879. https://doi.org/10.1152/ajplung.00429.2020

Augert A., Eastwood E., Ibrahim A.H., Wu N., Grunblatt E., Basom R., Liggitt D., Eaton K.D., Martins R., Poirier J.T., Rudin C.M., Milletti F., Cheng W.Y., Mack F., MacPherson D. et al. 2019. Targeting NOTCH activation in small cell lung cancer through LSD1 inhibition. Sci. Signal. V. 12. P. 2922. https://doi.org/10.1126/scisignal.aau2922

Bagdonas E., Raudoniute J., Bruzauskaite I., Aldonyte R. 2015. Novel aspects of pathogenesis and regeneration mechanisms in COPD. Int. J. Chron. Obstruct. Pulmon. Dis. V. 10. P. 995. https://doi.org/ d.s82518 https://doi.org/10.2147/cop

Baumgart A., Seidl S., Vlachu P., Michel L., Mitova N., Schatz N., Specht K., Koch I., Schuster T., Grundler R., Kremer M., Fend F., Siweke J.T., Peschel S., Duister J. et al. 2010. ADAM17 regulates the expression of the epidermal growth factor receptor by activating Notch1 extra-small cell lung cancer. Cancer Res. V. 70. P. 5368. https://doi.org/10.1158/0008-5472

Boucherat O., Chakir J., Jeannotte L. 2012. The loss of Hoxa5 function promotes Notch-dependent goblet cell metaplasia in lung airways. Biol. Open. V. 1. P. 677. https://doi.org/10.1242/bio.20121701

Cai W.X., Liang L., Wang L., Han J.T., Zhu X.X., Han H., Hu D.H., Zhang P. 2014. Inhibition of Notch signaling leads to increased intracellular ROS by up-regulating Nox4 expression in primary HUVECs. Cell Immunol. V. 287. P. 129. https://doi.org/10.1016/j.cellimm.2013.12.009

Chen C.Y., Chen Y.Y., Hsieh M.S., Ho C.C., Chen K.Y., Shih J.Y., Yu C.J. 2017. Expression of Notch Gene and Its Impact on Survival of Patients with Resectable Non-small Cell Lung Cancer. J. Cancer. V. 8. P. 1292. https://doi.org/10.7150/jca.17741

Chen Y., Jie V., Yan V., Zhou K., Xiao Y. 2012. Lysine-specific histone demethylase 1 (LSD1): a potential molecular target for tumor therapy. Crit. Rev. Eukaryotic Gene Expression. V. 22. P. 53.
https://doi.org/10.1615/critreveukargeneexpr.v22.i1.40

Galluzzo P., Bocchetta M. 2011. Notch signaling in lung cancer. Expert Rev. Anticancer Ther. V. 11. P. 533.
https://doi.org/10.1586/era.10.158

George J., Lim J.S., Chan S.J., Kun W., Ozretic L., Kong G., Lenders F., Lu H., Fernandez-Cuesta L., Bosco G., Muller S., Damen I., Yahchan N.S., Park K.S., Yang D. et al. 2015. Complex genomic profiles of small cell lung cancer. Nature. V. 524. P. 47.
https://doi.org/10.1038/nature14664

He Z., Wu J., Zeng X., Bao H., Liu X. 2021. Role of the Notch ligands Jagged1 and Delta4 in Th17/Treg immune imbalance in a mouse model of chronic asthma. Exp. Lung Res. V. 47. P. 289.
https://doi.org/10.1080/01902148.2021.1933653

Hua S., Liu F., Wang M. 2019. Emodin Alleviates the Airway Inflammation of Cough Variant Asthma in Mice by Regulating the Notch Pathway. Med. Sci. Monit. V. 25. P. 5621.
https://doi.org/10.12659/MSM.915080

Huang M.T., Chiu C.J., Chiang B.L. 2019. Multi-Faceted Notch in Allergic Airway Inflammation. Int. J. Mol. Sci. V. 20. P. 3508.
https://doi.org/10.3390/ijms20143508

Huang Q., Han L., Lv R., Ling L. 2019. Magnolol exerts antiasthmatic effects by regulating Janus kinase-signal transduction and activation of transcription and Notch signaling pathways and modulating Th1/Th2/Th17 cytokines in ovalbumin-sensitized asthmatic mice. Korean J. Physiol. Pharmacol. V. 23. P. 251.
https://doi.org/10.4196/kjpp.2019.23.4.251

Kared H., Adle-Biassette H., Foïs E., Masson A., Bach J., Chatenoud L. 2006. Jagged2-expressing hematopoietic progenitors promote regulatory T cell expansion in the periphery through notch signaling. Immunity. V. 25. 823.
https://doi.org/10.1016/j.immuni.2006.09.008

Katoh M., Katoh M. 2020. Precision medicine for the treatment of human cancer with impaired regulation of Notch signal transmission (review). Int. J. Mol. Med. V. 45. P. 279.
https://doi.org/10.3892/ijmm.2019.4418

Kiyokawa H., Morimoto M. 2020. Notch signaling in the mammalian respiratory system, specifically the trachea and lungs, in development, homeostasis, regeneration, and disease. Dev. Growth Differ. V. 62. P. 67.
https://doi.org/10.1111/dgd.12628

Lee C.C., Lin C.L., Leu S.J., Lee Y.L. 2018. Overexpression of Notch ligand Delta-like-1 by dendritic cells enhances their immunoregulatory capacity and exerts antiallergic effects on Th2-mediated allergic asthma in mice. Clin. Immunol. V. 187. P. 58.
https://doi.org/10.1016/j.clim.2017.10.005

Leonetti A., Facchinetti F., Minari R., Cortellini A., Rolfo K.D., Giovannetti E., Tiseo M. 2019. The Notch pathway in small cell lung cancer: from preclinical data to therapeutic problems. Cell. Oncol. (Dordr). V. 42. P. 261.
https://doi.org/10.1007/s13402-019-00441-3

Lim J.S., Ibaseta A., Fischer M.M., Cancilla B., O'Young G., Cristea S., Luca V.C., Yang D., Jahchan N.S., Hamard C., Antoine M., Wislez M., Kong C., Cain J., Liu Y.W. et al. 2017. Intratumoural heterogeneity generated by Notch signalling promotes small-cell lung cancer. Nature. V. 545. P. 360.
https://doi.org/10.1038/nature22323

Limbourg F.P., Takeshita K., Radtke F., Bronson R.T., Chin M.T., Liao J.K. 2005. Essential role of endothelial Notch1 in angiogenesis. Circulation. V. 111. P. 1826.
https://doi.org/10.1161/01.CIR.0000160870.93058.DD

Lin C.L., Huang H.M., Hsieh C.L., Fan C.K., Lee Y.L. 2019. Jagged1-expressing adenovirus-infected dendritic cells induce expansion of $Foxp3^{+}$ regulatory T cells and alleviate T helper type 2-mediated allergic asthma in mice. Immunology. V. 156. P. 199.
https://doi.org/10.1111/imm.13021

Luo J., Li L., Hu D., Zhang X. 2020. LINC00612/miR-31-5p/Notch1 Axis Regulates Apoptosis, Inflammation, and Oxidative Stress in Human Pulmonary Microvascular Endothelial Cells Induced by Cigarette Smoke Extract. Int. J. Chron. Obstruct. Pulmon. Dis. V. 15. P. 2049.
https://doi.org/10.2147/COPD.S255696

Ma J., Rubin B.K., Voynow J.A. 2018. Mucins, Mucus, and Goblet Cells. Chest. V. 154. P. 169.
https://doi.org/10.1016/j.chest.2017.11.008

Morianos I., Semitekolou M. 2020. Dendritic Cells: Critical Regulators of Allergic Asthma. Int. J. Mol. Sci. V. 21. P. 7930.
https://doi.org/10.3390/ijms21217930

Morimoto M., Liu Z., Cheng H.T., Winters N., Bader D., Kopan R. 2010. Canonical Notch signaling in the developing lung is required for determination of arterial smooth muscle cells and selection of Clara versus ciliated cell fate. J. Cell. Sci. V. 123. P. 213.
https://doi.org/10.1242/jcs.058669

Motooka Y., Fujino K., Sato Y., Kudoh S., Suzuki M., Ito T. 2017. Pathobiology of Notch2 in lung cancer. Pathology. V. 49. P. 486.
https://doi.org/10.1016/j.pathol.2017.05.005

Nie Y., Yang B., Hu J., Zhang L., Ma Z. 2021. Bruceine D ameliorates the balance of Th1/Th2 in a mouse model of ovalbumin-induced allergic asthma via inhibiting the NOTCH pathway. Allergol. Immunopathol. (Madr). V. 49. P. 73.
https://doi.org/10.15586/aei.v49i6.499

Ostedgaard L.S., Moninger T.O., McMenimen J.D., Sawin N.M., Parker C.P., Thornell I.M., Powers L.S., Gansemer N.D., Bouzek D.C., Cook D.P., Meyerholz D.K., Abou Alaiwa M.H., Stoltz D.A., Welsh M.J. 2017. Gel-forming mucins form distinct morphologic structures in airways. Proc. Natl. Acad. Sc.i USA. V. 114. P. 6842.
https://doi.org/10.1073/pnas.1703228114

Owen D.H., Giffin M.J., Baylis J.M., Smith M.D., Carbone D.P., On K. 2019. DLL3: a new target in small cell lung cancer. J. Hematol. Oncol. V. 12. P. 61.
https://doi.org/10.1186/s13045-019-0745-2

Pancevich-Wojtkiewicz J. 2016. Epidermal growth factor receptor and notch signaling in non-small cell lung cancer. Cancer Med. V. 5. P. 3572. https://doi.org/10.1002/cam4.944

Qin X., Zhang Z., Xu H., Wu Y. 2011. Notch signaling protects retina from nuclear factor-κB- and poly-ADP-ribose-polymerase-mediated apoptosis under high-glucose stimulation. Acta Biochim. Biophys. Sin. (Shanghai). V. 43. P. 703. https://doi.org/10.1093/abbs/gmr069

Sharif A., Shaji A., Chammaa M., Pawlik E., Fernandez-Valdivia R. Sharif A. et al. 2020. Notch Transduction in Non-Small Cell Lung Cancer. Int. J. Mol. Sci. V. 21. P. 5691. https://doi.org/10.3390/ijms21165691

Sinha K., Das J., Pal P.B., Sil P.S. 2013. Oxidative stress: mitochondrial-dependent and mitochondrial-independent pathways of apoptosis. Arch. Toxicol. V. 87. P. 1157. https://doi.org/10.1007/s00204-013-1034-4

Small R. J., Bacmeister J., Bailey D., Baker A., Bishop S., Bryan F., Caron J., Dennis J., Gent P., Hsu H.M., Jochum M., Lawrence D., Muñoz E., diNezio P., Scheitlin T. et al. 2014. A new synoptic scale resolving global climate simulation using the community earth system model. J. Adv. Model. Earth Syst. V. 6. P. 1065. https://doi.org/10.1002/2014MS000363

Sosa Iglesias V., Juranno L., Dubois L.J., Theis J., Voice M. 2018. Drug resistance in non-small cell lung cancer: potential for targeting NOTCH? Front. Oncol. V. 8. P. 267. https://doi.org/10.3389/fonc.2018.00267

Sparaneo A., Fabrizio F.P., Muscarella L.A. 2016. Transmission of Nrf2 and Notch signals in lung cancer: near the intersection. Oxid. Med. Cell. Longev. V. 2016. P. 7316492. https://doi.org/10.1155/2016/7316492

Tindemans I., van Schoonhoven A., KleinJan A., de Bruijn M.J., Lukkes M., van Nimwegen M., van den Branden A., Bergen I.M., Corneth O.B., van IJcken W.F., Stadhouders R., Hendriks R.W. 2020. Notch signaling licenses allergic airway inflammation by promoting Th2 cell lymph node egress. J. Clin. Invest. V. 130. P. 3576. https://doi.org/10.1172/JCI128310

Tsao P., Wei S., Wu M., Huang M., Lin H., Lee M. 2011. Notch signaling prevents mucous metaplasia in mouse conducting airways during postnatal development. Development. V. 138. P. 3533. https://doi.org/10.1242/dev.063727

Wang Y., Xu J., Meng Y., Adcock I.M., Yao X. 2018. Role of inflammatory cells in airway remodeling in COPD. Int. J. Chron. Obstruct. Pulmon. Dis. V. 13. P. 3341. https://doi.org/10.2147/COPD.S176122

Whitsett J.A. 2018. Airway Epithelial Differentiation and Mucociliary Clearance. Ann. Am. Thorac. Soc. V. 15. P. S143. https://doi.org/10.1513/AnnalsATS.201802-128AW

Yu L., Li J. 2022. Punicalagin Alleviates Aged Bronchial Asthma by Inhibiting Th2 Differentiation through IL-4/STAT6 and Jagged1/Notch Pathways. J. Healthc. Eng. V. 2022. P. 1184677. https://doi.org/10.1155/2022/1184677

Zeng Z., Wang L., Ma W., Zheng R., Zhang H., Zeng X., Zhang H., Zhang W. 2019. Inhibiting the Notch signaling pathway suppresses Th17-associated airway hyperresponsiveness in obese asthmatic mice. Lab. Invest. V. 99. P. 1784. https://doi.org/10.1038/s41374-019-0294-x

Zhou B., Lin W., Long Y., Yang Y., Zhang H., Wu K., Chu Q. 2022. Notch signaling pathway: architecture, disease, and therapeutics. Signal Transduct. Target. Ther. V. 7. P. 95. https://doi.org/10.1038/s41392-022-00934-y

Zong D., Ouyang R., Li J., Chen Y., Chen P. 2016. Notch signaling in lung diseases: focus on Notch1 and Notch3. Ther. Adv. Respir. Dis. V. 10. P. 468. https://doi.org/10.1177/1753465816654873

The Role of the Notch Signaling Pathway in the Pathogenesis of Lung Diseases of Non-infectious Etiology

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A review of current literature data on the significance of the Notch signaling pathway in the mechanisms of the development of diseases of the respiratory system – chronic obstructive pulmonary disease (COPD), bronchial asthma (BA) and lung cancer is presented. In studies of lung tissue samples of patients with COPD and lung tissues of mice, it was found that activation of the Notch signaling pathway promotes metaplasia and increases the functional activity of goblet cells, protects epithelial cells from apoptosis and oxidative stress. Suppression of the Notch–Jagged1/Jagged2 pathway is associated with the transdifferentiation of club-shaped cells into ciliated ones. In patients with AD, the Notch signaling pathway promotes differentiation of Th2 lymphocytes. In the ovalbumin-induced bronchial asthma model, the Notch cascade increases the imbalance of Th17/Treg lymphocyte populations, the production of IL-4, IL-5, IL-13, IL-17, the formation of allergen-specific IgE, eosinophilic infiltration and metaplasia of goblet-shaped epithelial cells of the respiratory tract. A decrease in the concentration of IgE, Th2-type cytokines (IL-4, IL-5, IL-13), an increase in the number of Treg cells and the level of TGFß in bronchoalveolar lavage in mice with asthma, mediated by the introduction of dendritic cells expressing the ligands DLL1 and Jagged1, indicates the protective role of the Notch signaling pathway. On samples of tumor tissue and cell lines of non-small cell lung cancer,

it was found that an increase in the expression of Notch-1 and Notch-3 mRNA is associated with increased proliferative activity, malignant cell transformation, a high risk of metastasis to lymph nodes and an unfavorable prognosis of the disease. In the samples of tumor tissue of small cell lung cancer, an increase in the expression of the Notch ligand DLK1 signaling inhibitor gene, the Ascl1 transcription factor gene and lysine-specific histone demethylase 1 (LSD1) was recorded. Suppression of LSD1 activity is accompanied by reactivation of signaling via Notch-1 receptor and subsequent inhibition of the transcription factor Ascl1, which induces the initial stages of tumor transformation.

Keywords: Notch, chronic obstructive pulmonary disease, bronchial asthma, lung cancer