

ИММУНОМОДУЛИРУЮЩИЕ ЭФФЕКТЫ ПРОТИВООПУХОЛЕВЫХ ПРЕПАРАТОВ – ИНГИБИТОРОВ ТИРОЗИНКИНАЗЫ БРУТОНА – И ВОЗМОЖНОСТИ ИХ ИСПОЛЬЗОВАНИЯ ПРИ АЛЛЕРГИЧЕСКИХ И ИНФЕКЦИОННЫХ ЗАБОЛЕВАНИЯХ

Торшина Ю.С.^{1,2}, Серебряная Н.Б.¹, Глазанова Т.В.², Михалёва М.А.²,
Волошин С.В.²

¹ ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург, Россия

² ФГБУ «Российский научно-исследовательский институт гематологии и трансфузиологии Федерального медико-биологического агентства», Санкт-Петербург, Россия

Резюме. Ингибиторы тирозинкиназы Брутона (ВТК) представляют собой класс препаратов, которые показали свою эффективность и безопасность у больных хроническим лимфоцитарным лейкозом и неходжкинскими лимфомами, считавшихся невосприимчивыми к любому ранее применяемому типу терапии. ВТК играет ключевую роль на всех стадиях развития В-лимфоцитов, однако в последние годы появились данные о том, что ВТК также задействована и в активации миелоидных клеток.

Целью данного исследования является анализ и систематизация всех опубликованных материалов об иммуномодулирующих эффектах ингибиторов ВТК (ибрутиниб, акалабрутиниб и др.).

Систематический обзор научной литературы был выполнен с использованием процесса пошагового поиска в электронных базах данных (PubMed, Web of Science, ScienceDirect и Scopus). При поиске в базе данных использовались следующие ключевые слова: “CLL”, “ВТК”, “ibrutinib”, “COVID-19”, “allergy”, “inflammation”. Поиск исследований проводился с момента появления первого препарата ингибитора ВТК (Ибрутиниб) в 2009 г. до декабря 2022 г.

Представлены имеющиеся на сегодняшний день результаты исследования влияния ингибиторов ВТК на функциональное состояние В- и Т-лимфоцитов, нейтрофилов и моноцитов/макрофагов, описаны иммуномодулирующие эффекты ибрутиниба на клетки адаптивной и врожденной иммунной системы, включая CD4⁺ и CD8⁺Т-лимфоциты, НК-клетки. Поскольку ингибиторы ВТК изменяют функциональную активность фагоцитарных клеток и соотношение популяций Т-клеток,

Адрес для переписки:

Торшина Юлия Сергеевна
ФГБУ «Российский научно-исследовательский институт
гематологии и трансфузиологии Федерального медико-
биологического агентства»
191024, Россия, Санкт-Петербург,
ул. 2-я Советская, 16.
Тел.: 8 (904) 510-79-24.
E-mail: torshina.doc18@yandex.ru

Address for correspondence:

Yuliya S. Torshina
Russian Research Institute of Haematology and Transfusiology,
Federal Medical and Biological Agency
16 2nd Sovetskaya St
St. Petersburg
191024 Russian Federation
Phone: +7 (904) 510-79-24.
E-mail: torshina.doc18@yandex.ru

Образец цитирования:

Ю.С. Торшина, Н.Б. Серебряная, Т.В. Глазанова,
М.А. Михалёва, С.В. Волошин «Иммуномодулирующие
эффекты противоопухолевых препаратов –
ингибиторов тирозинкиназы Брутона – и возможности
их использования при аллергических и инфекционных
заболеваниях» // Медицинская иммунология, 2023.
Т. 25, № 5. С. 1253–1258.
doi: 10.15789/1563-0625-IEO-2816

© Торшина Ю.С. и соавт., 2023

Эта статья распространяется по лицензии
Creative Commons Attribution 4.0

For citation:

Yu.S. Torshina, N.B. Serebryanaya, T.V. Glazanova,
M.A. Mikhalyova, S.V. Voloshin “Immunomodulating effects
of antitumor drugs Bruton tyrosine kinase inhibitors and the
possibility of their use in allergic and infectious diseases”,
Medical Immunology (Russia)/Meditsinskaya Immunologiya,
2023, Vol. 25, no. 5, pp. 1253–1258.
doi: 10.15789/1563-0625-IEO-2816

© Torshina Yu.S. et al., 2023

The article can be used under the Creative
Commons Attribution 4.0 License

DOI: 10.15789/1563-0625-IEO-2816

появилось предположение о возможности использования этих препаратов для лечения ряда других нозологических форм, не только В-клеточных злокачественных новообразований, что на данный момент изучается в клинических исследованиях. Суммированы данные о применении ингибиторов БТК для борьбы со сверхострым воспалением, а также с целью подавления аллергических реакций, в том числе анафилаксии. Кроме того, обсуждается целесообразность кратковременного применения ингибиторов БТК для снижения риска побочных эффектов при оральной иммунотерапии, а также для десенсибилизации к лекарственным средствам.

Приведенные данные свидетельствуют, что ингибиторы БТК являются перспективными препаратами с иммуномодулирующим эффектом. Однако ингибиторам БТК следующего поколения предстоит повысить селективность для снижения нецелевого воздействия на другие киназы.

Ключевые слова: тирозинкиназа Брутона, ингибиторы тирозинкиназы Брутона, ибрутиниб, акалабрутиниб, Т-лимфоциты, НК-клетки, нейтрофилы, моноциты/макрофаги

IMMUNOMODULATING EFFECTS OF ANTITUMOR DRUGS BRUTON TYROSINE KINASE INHIBITORS AND THE POSSIBILITY OF THEIR USE IN ALLERGIC AND INFECTIOUS DISEASES

Torshina Yu.S.^{a, b}, Serebryanaya N.B.^a, Glazanova T.V.^b,
Mikhalyova M.A.^b, Voloshin S.V.^b

^a Institute of Experimental Medicine, St. Petersburg, Russian Federation

^b Russian Research Institute of Haematology and Transfusiology, Federal Medical and Biological Agency, St. Petersburg, Russian Federation

Abstract. Bruton's tyrosine kinase (BTK) inhibitors represent a class of drugs that have demonstrated their efficacy and safety in patients with chronic lymphocytic leukemia and non-Hodgkin's lymphomas who were considered refractory to any previously used type of therapy. BTK plays a key role in all stages of B lymphocyte development, but in recent years, there have been data indicating that BTK is also involved in the activation of myeloid cells.

The aim of this study is to analyze and systematize all published materials on the immunomodulatory effects of BTK inhibitors (ibrutinib, acalabrutinib, etc.).

A systematic review of the scientific literature was performed using a step-by-step search process in electronic databases (PubMed, Web of Science, ScienceDirect, and Scopus). The following keywords were used in the database search: "CLL", "BTK", "ibrutinib", "COVID-19", "allergy", "inflammation." The search for studies was conducted from the time of the first BTK inhibitor drug (ibrutinib) appearance in 2009 until December 2022.

The results of the study on the influence of BTK inhibitors on the functional state of B and T lymphocytes, neutrophils, and monocytes/macrophages are presented. The immunomodulatory effects of ibrutinib on adaptive and innate immune system cells, including CD4⁺ and CD8⁺T lymphocytes and NK cells, are described. Since BTK inhibitors alter the functional activity of phagocytic cells and the ratio of T cell populations, there is a suggestion about the possibility of using these drugs for the treatment of other nosological forms, not only B cell malignancies, which is currently being studied in clinical trials. Data on the use of BTK inhibitors to combat hyperacute inflammation and to suppress allergic reactions, including anaphylaxis, are summarized. In addition, the expediency of short-term use of BTK inhibitors to reduce the risk of side effects during oral immunotherapy and for desensitization to drugs is discussed.

The presented data indicate that BTK inhibitors are promising drugs with immunomodulatory effects. However, BTK inhibitors need to increase selectivity to reduce off-target effects on other kinases.

Keywords: Bruton's tyrosine kinase, Bruton's tyrosine kinase inhibitors, ibrutinib, acalabrutinib, T lymphocytes, NK cells, neutrophils, monocytes/macrophages

Introduction

Bruton's tyrosine kinase (BTK) inhibitors are a new class of drugs for the treatment of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma and mantle cell lymphoma. Since their FDA approval, ibrutinib and acalabrutinib have significantly changed the possibilities of CLL and mantle cell lymphoma therapy, increasing progression-free survival time, especially in patients with a high risk of unfavorable disease progression. However, during the use of these drugs, new data emerged that, in addition to their antiproliferative action on malignant B cells, BTK inhibitors also affect other immune system cells such as T lymphocytes, NK cells, granulocytes, monocytes, macrophages, demonstrating immunomodulatory and anti-inflammatory effects. The aim of this study is to analyze and systematize all published materials on the immunomodulatory effects of BTK inhibitors.

Materials and methods

A systematic review of scientific literature was conducted using a step-by-step search process in electronic databases (PubMed, Web of Science, ScienceDirect, and Scopus). The following keywords were used in the database search: "CLL", "BTK", "ibrutinib", "COVID-19", "allergy", "inflammation". The search for studies was conducted from the time of the first BTK inhibitor drug (Ibrutinib) approval in 2009 until December 2022.

Results and discussion

BTK is a cytoplasmic non-receptor tyrosine kinase that is essential for transmitting signals from the BCR and thus plays an important role in the development, survival, proliferation, differentiation, and activation of B cells at different stages of their development [1]. Upon BCR activation, BTK forms a signaling complex together with spleen tyrosine kinase (SYK), VAV protein, phosphoinositide 3-kinase (PI3K), adapter protein SLP65, and phospholipase C γ 2 (PLC γ 2). BTK phosphorylates PLC γ 2, transcriptional nuclear factor κ B (NF- κ B), nuclear factor of activated T cells (NF-AT), as well as extracellular signal-regulated kinase 1 and 2 (ERK1, ERK2), which in turn mediate subsequent functional responses [1]. In addition to BCR, BTK also regulates signaling pathways of chemokine receptors, including CXCR4 and CXCR5, which play a key role in chemotaxis and migration of B lymphocytes. Similarly, BTK plays an important role in regulating the survival, proliferation, and migration of malignant B lymphocytes, significantly affecting the development of malignant B cell neoplasms.

In recent years, BTK inhibitors are increasingly used instead of combined immunochemotherapy regimens (such as FCR, BR), especially in CLL and MCL patients with high risk of unfavorable prognosis. The use of ibrutinib and acalabrutinib has

also been approved for the treatment of refractory and relapsed forms of lymphoplasmacytic lymphoma, marginal zone lymphoma, and Waldenstrom's macroglobulinemia.

Studies on the mechanisms of action of BTK inhibitors have shown that BTK is expressed not only in B lymphocytes but also in myeloid cell populations, including monocytes, macrophages, granulocytes, myeloid-derived suppressor cells (MDSC), dendritic cells (DC), osteoclasts, adipocytes, megakaryocytes, platelets, as well as NK cells and T lymphocytes [1].

Immune Modulatory Effects of Ibrutinib and Acalabrutinib

As BTK is involved in the activation of many immune cell populations, its inhibition by ibrutinib exerts a complex immune modulatory effect on both adaptive and innate immune system cells, including CD4⁺ and CD8⁺T lymphocytes, NK cells, and cells of most (all?) myeloid lineages [2, 3].

Impaired T lymphocyte function has been observed in patients with CLL, manifested by exhaustion of effector T cells, memory T cells, and immunosuppressive Treg. Most of the immune modulatory effects of BTK inhibitors on T cells (shift towards Th1 phenotype, decrease in Th2 cell numbers, alteration of Th17/Treg balance towards Treg dominance, reduction in cytokine production) are mediated by inhibiting ITK in TCR signaling pathways [3]. In response to CD3 and CD28 stimulation, BTK^{-/-} T cells demonstrate reduced expression of activation marker CD69 and defective proliferation, as well as reduced cytokine production [4].

High levels of BTK expression are also characteristic of monocytes and macrophages [4]. In these cells, BTK critically regulates signal transduction from Toll-like receptors (TLRs), directly interacting with their cytoplasmic Toll/IL-1 (TIR) domains. Upon ligand binding, TLRs induce BTK phosphorylation, which promotes activation of transcription factor NF- κ B and interferon regulatory factors (IRFs), necessary for upregulation of inflammatory cytokine, chemokine, and interferon gene expression [5, 6]. In monocytes, macrophages, and dendritic cells, ibrutinib and acalabrutinib inhibit signal transduction from other receptors that recruit BTK, including TREM-1 and Dectin-1, leading to reduced production of inflammatory cytokines and chemokines, as well as impaired phagocytosis of tumor cells and infectious pathogens. It has been shown that treatment with ibrutinib leads to decreased serum levels of various chemokines and inflammatory cytokines in patients with CLL. These changes may contribute to predisposition to infectious diseases and the possibility of cytokine imbalance.

In granulocytes, ibrutinib also inhibits activation and effector functions induced by BTK-dependent mechanisms upon activation of TLR, TREM-1, and NLRP3 inflammasome formation [7]. It has

been shown that ibrutinib suppresses inflammatory processes by blocking NLRP3 inflammasome assembly and subsequent caspase-1 activation, which prevents the maturation of IL-1 β in neutrophils infiltrating the site of injury [7]. Neutrophils isolated from CLL patients treated with ibrutinib had reduced oxidative burst and bactericidal activity, as well as impaired ability to form extracellular traps (NETs) [8]. Treatment with BTK inhibitors in a mouse model of pneumococcal pneumonia led to a reduction in systemic neutrophil activation and their migration to the lungs [9]. In CLL patients in the early stages of treatment with ibrutinib, neutrophils produce less IL-8 (mediated by immune complexes through Fc γ R) and show reduced degranulation in response to opsonized *E. coli*, leading to a decrease in the release of neutrophil elastase, myeloperoxidase, and lactoferrin. In addition, neutrophils with BTK deficiency exhibit increased sensitivity to apoptosis, impaired maturation and differentiation, and decreased production of active oxygen species [8, 9].

Since ibrutinib and acalabrutinib alter the functional activity of phagocytic cells and the ratio of T cell populations, there is a hypothesis about the possibility of using these drugs to treat a number of other pathological conditions, including various malignancies of the hematopoietic and lymphoid systems, solid tumors, autoimmune diseases, atherothrombosis, and autoimmune diseases [8, 9]. The effectiveness of BTK inhibitors in the treatment of diseases in these groups is currently being studied in several clinical trials.

Possible use of BTK inhibitors in allergies

The main effector cells in allergic diseases, including food allergies, drug allergies, allergic rhinitis, asthma, and chronic spontaneous urticaria, are mast cells and basophils. When an allergen cross-links allergen-specific IgE bound to Fc RI on the surface of mast cells and basophils, a powerful activation signal is generated, which triggers rapid degranulation with the release of numerous allergic mediators, including histamine, prostaglandins, leukotrienes, and cytokines, that determine the development of clinical symptoms. Until recently, specific histamine receptor blockers, leukotriene receptor antagonists, and corticosteroids have been mainly used to treat allergic diseases to suppress pathological immune reactions and allergic inflammation. In recent years, target immunobiological agents have emerged to alleviate the symptoms of asthma and urticaria, aimed at reducing the level of circulating immunoglobulin E (IgE) (omalizumab), cytokines IL-4, IL-5 IL-13 or blocking their receptors. However, the use of these drugs does not allow achieving stable positive effects in a number of treated patients.

Recent studies have shown that BTK is involved in signal transduction through high-affinity Fc RI in human mast cells and basophils, and it is a critical

signaling component for inducing histamine secretion, leukotriene C4, and IL-4. BTK inhibitors can prevent IgE-mediated degranulation and production of inflammatory cytokines by human mast cells and basophils [10]. Ibrutinib has inhibitory activity against a number of kinases involved in transmitting signals from Fc RI to ITK (proto-oncogenic tyrosine protein kinase FYN and tyrosine protein kinase LYN). Thus, BTK inhibitors can potentially be used to prevent allergic reactions, including anaphylaxis.

It is noteworthy that in human basophils, IgE-mediated reactions depend so much on the activity of kinases SRC, LYN, SYK, BTK, and PI3-kinase delta that selective inhibition of any of these kinases leads to complete inhibition of the release of all mediators. In 2017, a pilot study by Regan et al. demonstrated that ibrutinib completely eliminates skin prick test reactivity and IgE-mediated basophil activation test response to aeroallergens in CLL patients within 7 days after starting treatment. Data were obtained that only two doses of ibrutinib can reduce or eliminate skin prick test reactivity to food products and aeroallergens in individuals with allergies.

Currently, several new BTK inhibitors are undergoing clinical trials as potential drugs for the treatment of chronic spontaneous urticaria. The efficacy of fenebrutinib in chronic urticaria has been demonstrated during clinical trials, however, in a phase IIa study, a temporary increase in liver enzyme levels was recorded; this hepatotoxicity, not previously considered an effect characteristic of BTK inhibitors, may interfere with further trials of fenebrutinib [11].

In numerous studies, it has been shown that food oral immunotherapy (OIT) can lead to desensitization to food products in patients with food allergies [11]. However, OIT can be complicated by allergic reactions, ranging from minor (hives, upset stomach) to severe (systemic anaphylaxis requiring adrenaline treatment). Most adverse reactions during food OIT occur during the dose escalation phase. Currently, the feasibility of short-term use of BTK inhibitors to reduce the risk of side effects during OIT is being discussed. It is assumed that short courses of BTK inhibitors can reduce the frequency and/or severity of side effects during the escalation phase, allowing patients to safely reach the maintenance dose.

BTK inhibitors can also be used episodically in desensitization to drugs. It should be noted that ibrutinib is unlikely to prevent reactions to drugs that cause IgE-independent allergies, such as non-specific activation of mast cells due to iodine-containing contrast agents, as it is believed that BTK is not involved in the development of these hypersensitivity reactions. Thus, the use of BTK inhibitors is likely to be limited to preventing immediate-type hypersensitivity reactions (ITHRs), which have IgE-mediated mechanisms, particularly to beta-lactam antibiotics or platinum-based chemotherapeutic agents. BTK

inhibitors act quickly and have a short-term effect that wears off after discontinuation of the drug, potentially making episodic use of drugs to prevent ITHRs such as IgE-mediated anaphylaxis possible [11].

Despite the promising prospects for the use of BTK inhibitors to develop new treatment concepts for patients with IgE-dependent allergies, their introduction into allergology practice may be hindered by both their relatively high cost and the lack of clinical trial data on the safety and efficacy of these drugs — none of the BTK inhibitors currently used in clinical practice have been tested in children, and food OIT is typically indicated for children with food allergies.

The use of BTK inhibitors in patients with COVID-19

The presence of certain anti-inflammatory immunomodulatory effects of BTK inhibitors in patients with hematologic and oncologic diseases has led to the suggestion of using these drugs to control the hyperacute inflammation in patients with COVID-19. Positive expectations were supported by experimental studies that showed that the use of BTK inhibitors saved mice infected with influenza virus from lethal acute lung injury. Interesting data were also obtained when observing patients with hematologic malignancies who developed COVID-19 while taking the BTK inhibitor ibrutinib. For example, six patients with Waldenstrom's macroglobulinemia were reported to have only mild upper respiratory tract symptoms with COVID-19.

As of 2022, there are seven clinical trials registered to study the effectiveness of acalabrutinib (four trials) and ibrutinib (three trials) in COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes acute respiratory distress syndrome, often leading to a fatal outcome. In some patients, a hyperactive inflammatory response of macrophages develops, manifested as a cytokine storm, which leads to respiratory failure. Pathological examination of the lungs in patients who died from coronavirus infection revealed extensive cellular infiltration with predominance of macrophages. It is assumed that the recruitment of macrophages in the development of infection may be associated with an increase in the expression of angiotensin-converting enzyme 2 (ACE2), regulated by increased concentrations of locally produced alpha-interferon. Macrophages can perceive the single-stranded RNA of the SARS-CoV-2 virus through TLR-7 with subsequent signal

transmission, leading to NF- κ B activation. In the presence of the virus, NLRP3 inflammasome activates caspases, cleaving pro-IL-1 β protein and releasing mature cytokine into the surrounding environment [7].

Ibrutinib has been shown to have potential anti-inflammatory effects in terms of lowering levels of inflammatory cytokines that are often elevated in severe COVID-19 [12]. Treatment of patients with severe COVID-19 with acalabrutinib also improved oxygenation and reduced IL-6 production by monocytes. In another clinical trial, acalabrutinib was administered to 19 patients hospitalized with severe COVID-19 (11 on non-invasive ventilation, 8 on mechanical ventilation). Patients were found to have improved oxygenation after 10-14 days of treatment with acalabrutinib [13]. These results confirm that BTK inhibition with ibrutinib or acalabrutinib may provide some degree of protection against the development of severe disease. Thus, BTK inhibition is one of the possibilities to reduce excessive inflammation in severe COVID-19.

Conclusion

Bruton tyrosine kinase was discovered as a key factor in the development of B lymphocytes, which determined the possibility of using BTK inhibitors in B lymphoproliferative diseases. The emergence of a new class of therapeutic agents has led to a significant improvement in treatment outcomes in patients who were considered refractory to any previously used type of therapy. Initially, only B cells were considered to be targets of these medicinal products, but subsequently a significant role of BTK in the activation of myeloid cells became clear, since it enhances signals transduced not only from BCR, but also from other activating receptors. Due to the discovery of the mechanism of BTK activity in myeloid cells during the COVID-19 pandemic, new opportunities have opened for the use of BTK inhibitors in the suppression of hyperacute inflammation. In addition, the possibility of using this class of drugs for the control of allergic inflammation has been shown. However, it is important to consider that the currently marketed BTK inhibitors are not selective enough and have off-target effects also on several other TEC family kinases. Further research is needed to more accurately determine the possible areas of their use.

References

1. Chattopadhyay S., Sen G.C. Tyrosine phosphorylation in Toll-like receptor signaling. *Cytokine Growth Factor Rev.*, 2014, Vol. 25, no. 5, pp. 533-541.
2. Dispenza M.C. The use of Bruton's tyrosine kinase inhibitors to treat allergic disorders. *Curr. Treat. Options Allergy*, 2021, Vol. 8, no. 3, pp. 261-273.

3. Fiedler K., Sindrilaru A., Terszowski G., Kokai E., Feyerabend T.B., Bullinger L., Rodewald H.R., Brunner C. Neutrophil development and function critically depend on Bruton tyrosine kinase in a mouse model of X-linked agammaglobulinemia. *Blood*, 2011, Vol. 117, 1329-1339.
4. Mhibik M., Wiestner A., Sun C. Harnessing the Effects of BTKi on T cells for effective immunotherapy against CLL. *Int. J. Mol. Sci.*, 2019, Vol. 21, no. 1, 68. doi: 10.3390/ijms21010068.
5. Page T.H., Urbaniak A.M., Espirito Santo A.I., Danks L., Smallie T., Williams L.M., Horwood N.J. Bruton's tyrosine kinase regulates TLR7/8-induced TNF transcription via nuclear factor- κ B recruitment. *Biochem. Biophys. Res. Commun.*, 2018, Vol. 499, no. 2, pp. 260-266.
6. Pal Singh S., Dammeijer F., Hendriks R.W. Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol. Cancer*, 2018, Vol. 17, no. 1, 57. doi: 10.1186/s12943-018-0779-z.
7. Pleyer C., Wiestner A., Sun C. Immunological changes with kinase inhibitor therapy for chronic lymphocytic leukemia. *Leuk. Lymphoma*, 2018, Vol. 59, no. 12, pp. 2792-2800.
8. Prezzo A., Cavaliere F.M., Bilotta C., Pentimalli T.M., Iacobini M., Cesini L., Foà R., Mauro F.R., Quinti I. Ibrutinib-based therapy impaired neutrophils microbicidal activity in patients with chronic lymphocytic leukemia during the early phases of treatment. *Leuk. Res.*, 2019, Vol. 87, 106233. doi: 10.1016/j.leukres.2019.106233.
9. Roschewski M., Lionakis M.S., Sharman J.P., Roswarski J., Goy A., Monticelli M.A., Roshon M., Wrzesinski S.H., Desai J.V., Zarakas M.A., Collen J., Rose K., Hamdy A., Izumi R., Wright G.W., Chung K.K., Baselga J., Staudt L.M., Wilson W.H. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci. Immunol.*, 2020, Vol. 5, no. 48, eabd0110. doi: 10.1126/sciimmunol.abd0110.
10. Smiljkovic D., Blatt K., Stefanzi G., Dorofeeva Y., Skrabbs C., Focke-Tejkl M., Sperr W.R., Jaeger U., Valenta R., Valent P. BTK inhibition is a potent approach to block IgE-mediated histamine release in human basophils. *Allergy*, 2017, Vol. 72, no. 11, pp. 1666-1676.
11. Thibaud S., Tremblay D., Bhalla S., Zimmerman B., Sigel K., Gabrilove J. Protective role of Bruton tyrosine kinase inhibitors in patients with chronic lymphocytic leukaemia and COVID-19. *Br. J. Haematol.*, 2020, Vol. 190, no. 2, pp. e73-e76.
12. Volmering S., Block H., Boras M., Lowell C.A., Zarbock A. The neutrophil Btk Signalosome regulates integrin activation during sterile inflammation. *Immunity*, 2016, Vol. 44, pp. 73-87.
13. Xia S., Liu X., Cao X., Xu S. T-cell expression of Bruton's tyrosine kinase promotes autoreactive T-cell activation and exacerbates aplastic anemia. *Cell. Mol. Immunol.*, 2020, Vol. 17, no. 10, pp. 1042-1052.

Авторы:

Торшина Ю.С. — младший научный сотрудник НИЛ иммунологии, врач КЛД лаборатории клинической иммунологии клиники НИЦКМП ФГБУ «Российский научно-исследовательский институт гематологии и трансфузиологии Федерального медико-биологического агентства»; аспирант отдела иммунологии ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург, Россия

Серебряная Н.Б. — д.м.н., профессор, заведующая лабораторией общей иммунологии, отдел иммунологии ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург, Россия

Глазанова Т.В. — д.м.н., главный научный сотрудник НИЛ иммунологии ФГБУ «Российский научно-исследовательский институт гематологии и трансфузиологии Федерального медико-биологического агентства», Санкт-Петербург, Россия

Михалева М.А. — аспирант ФГБУ «Российский научно-исследовательский институт гематологии и трансфузиологии Федерального медико-биологического агентства», Санкт-Петербург, Россия

Волошин С.В. — к.м.н., руководитель научно-исследовательского отдела химиотерапии гемобластозов, депрессий кроветворения и трансплантации костного мозга ФГБУ «Российский научно-исследовательский институт гематологии и трансфузиологии Федерального медико-биологического агентства», Санкт-Петербург, Россия

Authors:

Torshina Yu.S., Junior Research Associate, Research Laboratory of Immunology, Pathology Doctor, Russian Research Institute of Haematology and Transfusiology, Federal Medical and Biological Agency; Postgraduate Student, Department of Immunology, Institute of Experimental Medicine, St. Petersburg, Russian Federation

Serebryanaya N.B., PhD, MD (Medicine), Professor, Head, Laboratory of General Immunology, Department of Immunology, Institute of Experimental Medicine, St. Petersburg, Russian Federation

Glazanova T.V., PhD, MD (Medicine), Chief Research Associate, Research Laboratory of Immunology, Russian Research Institute of Haematology and Transfusiology, Federal Medical and Biological Agency, St. Petersburg, Russian Federation

Mikhalyova M.A., Postgraduate Student, Russian Research Institute of Haematology and Transfusiology, Federal Medical and Biological Agency, St. Petersburg, Russian Federation

Voloshin S.V., PhD (Medicine), Head, Research Department of Hemoblastosis Chemotherapy, Hematopoiesis Depressions and Bone Marrow Transplantation, Russian Research Institute of Haematology and Transfusiology, Federal Medical and Biological Agency, St. Petersburg, Russian Federation