ИТАКОНАТ РЕГУЛИРУЕТ ПРОДУКЦИЮ ЦИТОКИНОВ ЗА СЧЕТ ПОДАВЛЕНИЯ СУКЦИНАТДЕГИДРОГЕНАЗЫ В МОДЕЛИ ЛПС-ИНДУЦИРОВАННОГО ВОСПАЛЕНИЯ

Анисов Д.Э.[1, 2], Друцкая М.С.[1], Носенко М.А.[4], Недоспасов С.А.[1, 2, 3]

[1] *ФГБУН «Институт молекулярной биологии имени В.А. Энгельгардта» Российской академии наук, Москва, Россия*
[2] *ФГБОУ ВО «Московский государственный университет имени М.В. Ломоносова, Москва, Россия*
[3] *Научно-технологический университет «Сириус», Федеральная территория Сириус, Россия*
[4] *Тринити-колледж, Дублин, Ирландия*

Резюме. Итаконат – это иммунорегуляторный метаболит, продуцируемый миелоидными клетками и играющий ключевую роль в регуляции иммунного ответа. Итаконат, с одной стороны, способен подавлять активность сукцинатдегидрогеназы (СДГ), тем самым внося существенный вклад в метаболическое репрограммирование клетки. С другой стороны, итаконат может регулировать активность ряда транскрипционных факторов и регуляторов транскрипции, тем самым влияя на экспрессию генов. В большинстве экспериментальных работ итаконат охарактеризован преимущественно как противовоспалительное вещество. В частности, итаконат, продуцируемый активированными макрофагами, подавляет продукцию цитокинов TNF, IL-1β, IL-6, IL-10. Тем не менее некоторые данные свидетельствуют и о провоспалительной роли итаконата в ряде мышиных моделей заболеваний. Так, делеция гена *Acod1*, ответственного за продукцию итаконата, приводит к подавлению продукции TNF и IL-6 в модели мышиного полимикробного сепсиса, а значит, в контексте воспаления *in vivo* итаконат может выступать как индуктор провоспалительных цитокинов. Механизм регуляции итаконатом продукции цитокинов при системном воспалении остается неизученным. В этой работе мы показали, что инъекция итаконата и его производного диметилитаконата мышам с последующей индукцией воспаления бактериальным липополисахаридом (ЛПС) приводит к изменению содержания цитокинов в крови. Интересно, что системная продукция IL-6 и IL-10 в ответ на итаконат увеличивается, вопреки результатам, ранее полученным на клеточных культурах. При этом продукция IFNγ, наоборот, подавляется. По-видимому, итаконат регулирует продукцию цитокинов *in vivo* за счет подавления активности СДГ. Инъекция ингибитора СДГ, диметилмалоната, с последующей индукцией воспаления у мышей, приводит к аналогичным изменениям содержания цитокинов в крови, наблюдаемым в ответ на итаконат: повышению продукции IL-6, IL-10 и подавлению продукции IFNγ. Наоборот, добавление сукцината, субстрата СДГ и, соответственно, ее активатора, приводит к противоположному эффекту на продукцию цитокинов. Таким образом, можно предположить, что наблюдаемые эффекты

Адрес для переписки:

Анисов Денис Эдуардович
ФГБУН «Институт молекулярной биологии имени В.А. Энгельгардта» Российской академии наук
119991, Россия, Москва, ул. Вавилова, 32.
Тел.: 8 (926) 912-03-50.
E-mail: denis.anisoff@gmail.com

Address for correspondence:

Denis E. Anisov
Engelhardt Institute of Molecular Biology,
Russian Academy of Sciences
32 Vavilov St
Moscow
119991 Russian Federation
Phone: +7 (926) 912-03-50.
E-mail: denis.anisoff@gmail.com

Образец цитирования:

Д.Э. Анисов, М.С. Друцкая, М.А. Носенко, С.А. Недоспасов «Итаконат регулирует продукцию цитокинов за счет подавления сукцинатдегидрогеназы в модели ЛПС-индуцированного воспаления» // Медицинская иммунология, 2023. Т. 25, № 3. С. 477-482.
doi: 10.15789/1563-0625-IMI-2841

For citation:

D.E. Anisov, M.S. Drutskaya, M.A. Nosenko, S.A. Nedospasov "Itaconate-mediated inhibition of succinate dehydrogenase regulates cytokine production in LPS-induced inflammation", Medical Immunology (Russia)/Meditsinskaya Immunologiya, 2023, Vol. 25, no. 3, pp. 477-482.
doi: 10.15789/1563-0625-IMI-2841

DOI: 10.15789/1563-0625-IMI-2841

итаконата на продукцию цитокинов в модели ЛПС-индуцированного воспаления опосредованы его способностью ингибировать СДГ. Эти результаты помогают понять неоднозначную роль итаконата при воспалении и проливают свет на не описанную ранее взаимосвязь работы СДГ и продукции цитокинов в воспалении *in vivo*.

Ключевые слова: иммунометаболизм, врожденный иммунитет, итаконат, макрофаги, воспаление, сукцинатдегидрогеназа

ITACONATE-MEDIATED INHIBITION OF SUCCINATE DEHYDROGENASE REGULATES CYTOKINE PRODUCTION IN LPS-INDUCED INFLAMMATION

Anisov D.E.[a, b], Drutskaya M.S.[a], Nosenko M.A.[d], Nedospasov S.A.[a, b, c]

[a] *Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russian Federation*
[b] *Lomonosov Moscow State University, Moscow, Russian Federation*
[c] *Sirius University of Science and Technology, Federal Territory Sirius, Russian Federation*
[d] *Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland*

Abstract. Itaconate is an immunoregulatory metabolite produced by myeloid cells and plays a key role in the regulation of the immune response. Itaconate, on the one hand, is able to suppress the activity of succinate dehydrogenase (SDH), thereby making a significant contribution to the metabolic reprogramming of the cell. On the other hand, itaconate can regulate the activity of a number of transcription factors and transcription regulators, thereby affecting gene expression. In most experimental studies, itaconate has been characterized predominantly as an anti-inflammatory agent. In particular, itaconate produced by activated macrophages inhibits the production of cytokines TNF, IL-1β, IL-6, IL-10. However, some evidence suggests a pro-inflammatory role for itaconate in a number of mouse disease models. Thus, the deletion of the *Acod1* gene responsible for the production of itaconate leads to the suppression of the production of TNF and IL-6 in the mouse polymicrobial sepsis model, which means that in the context of inflammation *in vivo*, itaconate can act as an inducer of pro-inflammatory cytokines. The mechanism of itaconate regulation of cytokine production in systemic inflammation remains unexplored. In this work, we have shown that injection of itaconate and its derivative dimethyl itaconate into mice, followed by induction of inflammation by bacterial lipopolysaccharide (LPS), leads to changes in the content of cytokines in the blood. Interestingly, the systemic production of IL-6 and IL-10 in response to itaconate is increased, contrary to the results previously obtained in cell cultures. At the same time, IFNγ production, on the contrary, is suppressed. Apparently, itaconate regulates the production of cytokines *in vivo* by suppressing the activity of SDH. Injection of the SDH inhibitor, dimethylmalonate, followed by induction of inflammation in mice, results in similar changes in blood cytokines observed in response to itaconate: increased production of IL-6, IL-10 and suppression of IFNγ production. On the contrary, the addition of succinate, a SDH substrate, leads to the opposite effect on cytokine production. Thus, it can be assumed that the observed effects of itaconate on cytokine production in the model of LPS-induced inflammation are mediated by its ability to inhibit SDH. These results help to understand the controversial role of itaconate in inflammation and shed light on a previously undescribed relationship between SDH and cytokine production in inflammation *in vivo*.

Keywords: immunometabolism, innate immunity, itaconate, macrophages, inflammation, succinate dehydrogenase

This work was supported by RSF grant No. 19-75-30032.

Introduction

Immune cell activation is closely related to alterations in the intensity of metabolic pathways. These alterations lead to accumulation of individual metabolites, which, in addition to their main function in biosynthetic and bioenergetic processes, act as immune effector molecules which strongly affects the phenotype of immune cells. In the light of this paradigm, we can call them immunometabolites [12].

One of such immunometabolites is itaconate. Itaconate is obtained via decarboxylation of cis-aconitate, the Krebs cycle intermediate, by aconitate decarboxylase 1 (also known as Irg1). Itaconate can directly inhibit the enzymatic activity of succinate dehydrogenase (SDH), the key enzyme of the

Krebs cycle, because of its structural similarity with succinate [3]. It is equally important that itaconate can also alkylate cysteine residues on multiple proteins and thereby regulate the activity of a number of enzymes and pathways. Itaconate affects KEAP1-NRF2 axis [5], which regulates the expression of antioxidant proteins and ATF3-IκBζ axis, which coordinates the second wave of the transcriptional response to TLR stimulation [1]. Itaconate can also suppress the work of glycolysis enzymes [7], NLRP3 inflammasome activation [2] and NADPH oxidase functioning [9].

Since the discovery of the immunoregulatory properties of itaconate in LPS-activated bone marrow derived macrophages (BMDM), it has been shown to mediate anti-inflammatory effects. Itaconate administration led to downregulation of inflammatory marker genes and production of inflammatory mediators, including pro-inflammatory cytokines. TNF, IL-1β, IL-6, IL-12p40, IL-18 production was suppressed in macrophage cultures in response to a range of PAMPs/DAMPs. Anti-inflammatory properties of itaconate were also shown in a number of experimental disease models in mice, such as sepsis [4], psoriasis [1], peritonitis [2], pulmonary fibrosis [6].

However, itaconate effects on cytokine production in experimental disease models in mice differ from study to study. Systemic IL-6 production was suppressed in the mouse model of hepatic ischemia-reperfusion injury [11]. At the same time there was also evidence suggesting a pro-inflammatory role for itaconate in inflammation *in vivo*. It was shown that myeloid-specific *Irg1* deletion is sufficient to suppress systemic IL-6 levels in the mouse model of polymicrobial sepsis, which means that itaconate can also enhance IL-6 production [10]. Here we report that itaconate increases systemic production of IL-6 and IL-10 and decreases IFNγ systemic production in the mouse model of LPS-induced inflammation via inhibition of the SDH activity.

Materials and methods

Mice

C57Bl/6 mice (6-8 weeks) were housed in SPF conditions at the Animal Facility of the Center for Precision Genome Editing and Genetic Technologies for Biomedicine, EIMB RAS (under contract No. 075-15-2021-1067 with the Ministry of Science and Higher Education of the Russian Federation). All manipulations with animals were carried out in accordance with the protocol approved by the Bioethics Committee of the EIMB RAS (Protocol No. 3 from 27/10/22).

***In vivo* model of endotoxin-induced sepsis**

Neutral itaconate and succinate solutions were prepared by adding 10 M NaOH to itaconate or succinate solutions (100 mg mL^{-1}) in PBS to neutral pH. Wild type C57Bl/6 mice were treated intraperitoneally (i.p.) with itaconate (1 g kg^{-1}, Sigma), succinate (1 g kg^{-1}, Sigma) or dimethyl itaconate (1 g kg^{-1}, Sigma) and dimethyl malonate (0,3 or 0,5 g kg^{-1}, Sigma) in corn oil (Sigma) or vehicle control for 2 h before stimulation with LPS (*E. coli* O55:B5; 2.5 mg kg^{-1}, Sigma) i.p., 4 h later mice were euthanized, blood and organ samples were collected.

Cytokine detection

Cytokines in blood serum were analyzed by enzyme-linked immunosorbent assay (ELISA) using commercial kits "Mouse IL-6 ELISA Ready-SET-Go", "Mouse IL-10 ELISA Ready-SET-Go", "Mouse IFN gamma ELISA Ready-SET-Go" (ThermoFisher) according to the manufacturer's protocol or measured using Luminex xMAP multiplex technology and MILLIPLEX MAP Mouse Cytokine/Chemokine Magnetic Bead Panel kit according to the manufacturer's standard protocol (Merck).

RNA isolation and real time quantitative PCR

Organ samples were homogenized using PowerLyzer 24 Homogenizer (Qiagen) in ExtractRNA reagent (Evrogen). Reverse transcription and sample preparation were carried out using RevertAid kit according to the manufacturer's recommendations (Thermo Scientific). qPCR was performed using qPCRmix-HS SYBR (Evrogen) according to the manufacturer's instructions. Quantitative PCR was performed using Quant Studio 6 (Applied Biosystems).

Statistical analysis

Data were analyzed using GraphPad Prism 8 software. Data were analyzed using one-way ANOVA test followed by Tukey's post-test analysis for multiple comparisons. Results are displayed as mean ± SEM. Multiplex data are displayed as z-score transformed (heatmap). Differences were considered significant when p values were below 0.05.

Results and discussion

ITA and DI regulate systemic production of IL-6, IL-10 and IFNγ in a mouse model of LPS-induced inflammation

To investigate itaconate effect on cytokine production in inflammation, mice were pre-treated with ITA or DI, and then inflammation was induced with a non-lethal dose of LPS. Blood cytokine screening revealed a similar pattern of changes in the levels of cytokines in the blood (Figure 1A). Despite our expectations, IL-6 and IL-10 levels were significantly increased in the blood in response to itaconate (Figure 2B, C). Itaconate also dramatically decreased IFNγ levels in the blood (Figure 2D). We also observed the similar effects of itaconate on cytokine production at the gene expression level. DI increased *Il6* and

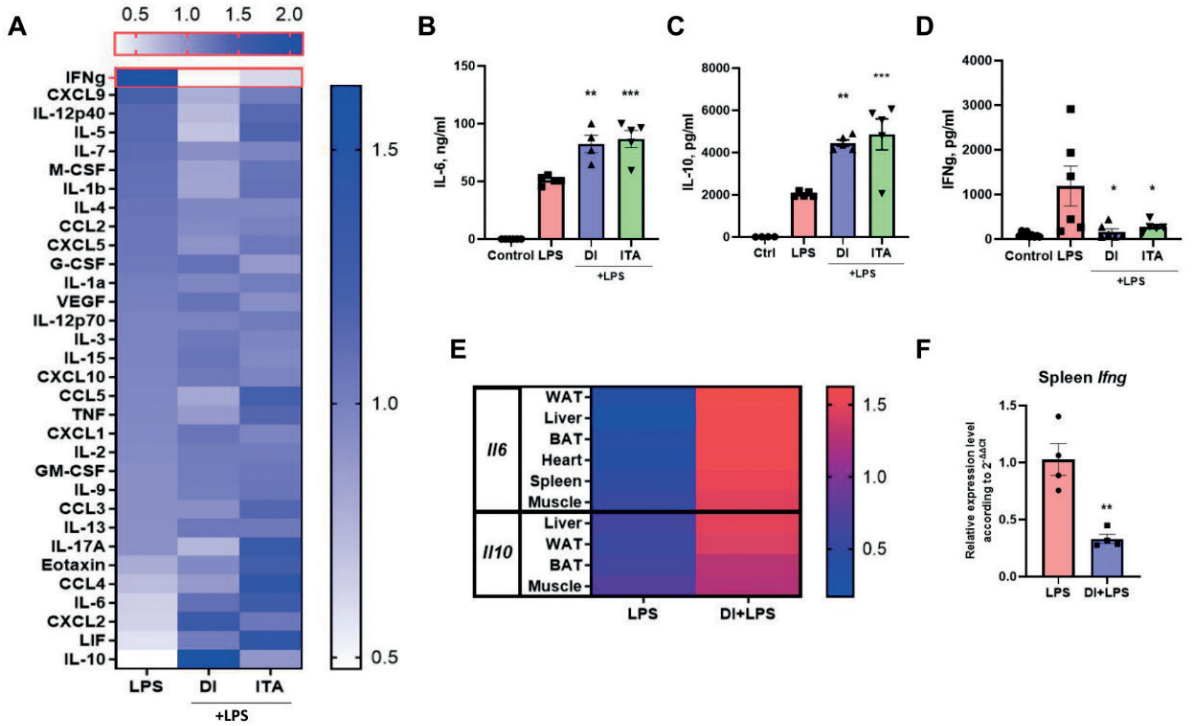

Figure 1. ITA and DI regulate systemic production of IL-6, IL-10 and IFNγ in a mouse model of LPS-induced inflammation

Note. (A) Mice were treated with 50 ug of LPS for 4 h (added at 2 h of 1 g kg^{-1} itaconate (ITA) or dimethyl itaconate (DI) pre-treatment). Blood cytokine levels were measured using multiplex assay. (B-D) Blood IL-6 (B), IL-10 (C) and IFNγ (D) levels were measured by ELISA. (E) *Il6* and *Il10* relative expression in organs. WAT, white adipose tissue; BAT, brown adipose tissue. (F) *Ifng* relative expression in spleen. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Il10 expression in organs actively expressing these genes under LPS-induced inflammation (Figure 1E).

Being a lymphocyte-specific cytokine, *Ifng* expression level was decreased in the spleen in response to DI, which also agrees with blood level changes of IFNγ in our model. Altogether, these data demonstrate that itaconate regulates systemic production of IL-6, IL-10 and IFNγ during inflammation *in vivo* and, at the same time, IL-6 and IL-10 blood levels were changed in a different way than it was initially shown in macrophage cell cultures [1, 8].

Itaconate regulates cytokine production via SDH inhibition

To investigate the mechanism which mediates the observed effects of itaconate on systemic cytokine production in the mouse model of LPS-induced inflammation, we next used dimethyl malonate (DM), a classical SDH-inhibitor. DM pre-treatment leads to the similar pattern of changes in IL-6, IL-10 and IFNγ production: blood IL-6 and IL-10 levels were increased and IFNγ levels were decreased as compared to LPS-control group both after DI and after DM pre-treatment (Figure 2A). The similarity between DI and DM effects on IL-6 levels were also observed in peritoneal lavage (Figure 2B). We observed the same effects of DM at the *Il6* and *Il10* gene expression. In addition, succinate, the SDH substrate and activator, regulated IL-6 and IFNγ levels in the blood in the opposite way to DI and DM: succinate administration suppressed systemic IL-6 levels and enhanced IFNγ production. Altogether, these data suggest that itaconate-mediated changes in IL-6, IL-10 and IFNγ production are due to its ability to inhibit the SDH.

Itaconate has been initially characterized as an important immunoregulatory metabolite. It is synthesized under inflammatory conditions and regulates the production of a number of cytokines, including IL-6. Here we show that both itaconate and dimethyl itaconate increase the systemic levels of IL-6 and IL-10 during inflammation *in vivo*, which does not correlate with their effects previously described in experiments *in vitro* [1, 8]. The role of itaconate in the regulation of cytokine production *in vivo* varies depending on the experimental setting. Itaconate was not studied in the model of LPS-induced inflammation, however, our results agree with Wu et al., which demonstrated that myeloid-specific *Irg1* deletion leads to decreased IL-6 systemic levels in the mouse model of polymicrobial sepsis [10]. At the same time, we for the first time report that itaconate and dimethyl itaconate decrease systemic IFNγ production *in vivo*. This result is in agreement

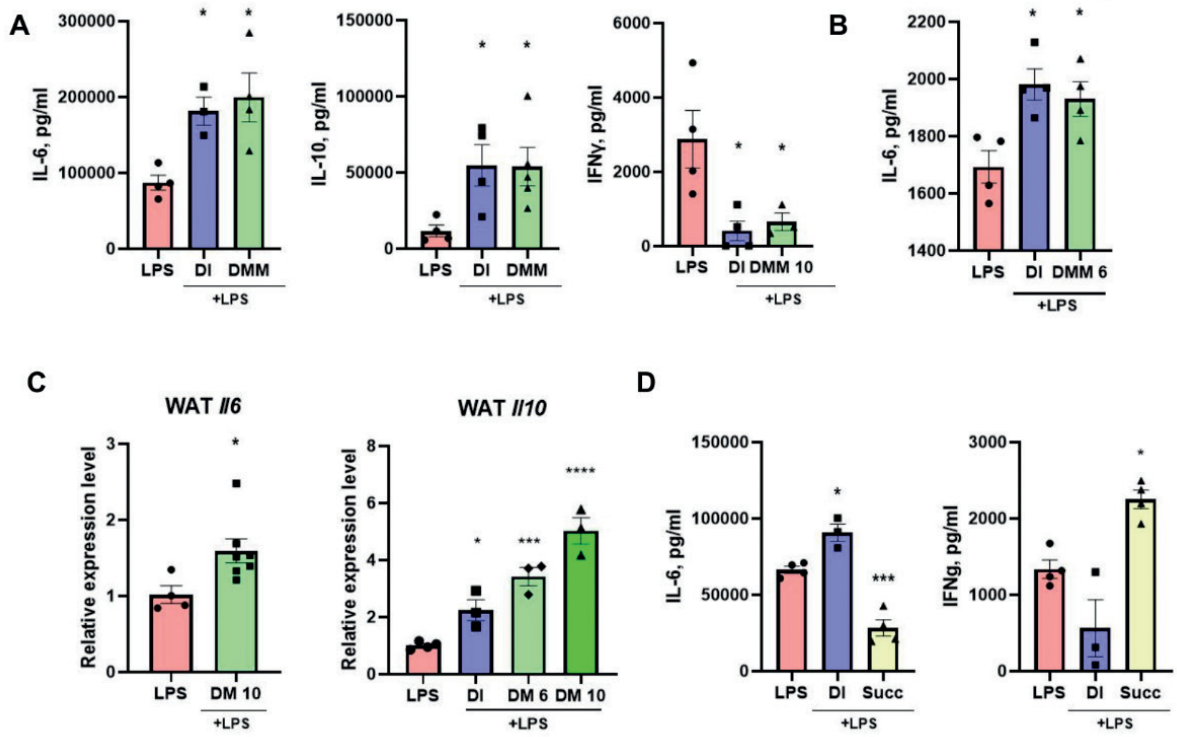

Figure 2. Itaconate regulates cytokine production via SDH inhibition

Note. (A) Blood IL-6, IL-10 and IFNγ levels were measured by ELISA. DI, dimethyl itaconate; DMM, dimethyl malonate. (B) IL-6 concentration in peritoneal lavage. (C) *Il6* and *Il10* relative expression in white adipose tissue (WAT). (D) Blood IL-6 and IFNγ levels. Succ, succinate. * $p < 0.05$, *** $p < 0.001$, **** $p < 0.0001$.

with Zhao et al., which demonstrated that itaconate suppressed IFNγ in $CD8^{+}$T cells [13].

Itaconate is known as an inhibitor of SDH. Itaconate rediscovery as an exogenous SDH suppressor by Lampropoulou et al. shed light on its role in the regulation of the immune response of macrophages [3]. However, the effects of itaconate on macrophage cytokine production *in vitro* are related to the regulation of transcriptional regulators such as IκBζ [1] or TNFAIP3 [14].

Conclusion

We suppose that itaconate effects on cytokine production *in vivo* are related to its ability to suppress SDH activity. This seems to be dispensable in the context of regulation of IL-6 in macrophages *in vitro* [1], however, during inflammatory reaction *in vivo*, the itaconate-SDH axis appears to be a significant contributor to the course of inflammation.

References

1. Bambouskova M., Gorvel L., Lampropoulou V., Sergushichev A., Loginicheva E., Johnson K., Korenfeld D., Mathyer M.E., Kim H., Huang L.H., Duncan D., Bregman H., Keskin A., Santeford A., Apte R.S., Sehgal R., Johnson B., Amarasinghe G.K., Soares M.P., Satoh T., Akira S., Hai T., de Guzman Strong C., Auclair K., Roddy T.P., Biller S.A., Jovanovic M., Klechevsky E., Stewart K.M., Randolph G.J., Artyomov M.N. Electrophilic properties of itaconate and derivatives regulate the IκBζ-ATF3 inflammatory axis. *Nature, 2018, Vol. 556, no. 7702, pp. 501-504.*

2. Hooftman A., Angiari S., Hester S., Corcoran S.E., Runtsch M.C., Ling C., Ruzek M.C., Slivka P.F., McGettrick A.F., Banahan K., Hughes M.M., Irvine A.D., Fischer R., O'Neill L.A.J. The Immunomodulatory Metabolite Itaconate Modifies NLRP3 and Inhibits Inflammasome Activation. *Cell Metab., 2020, Vol. 32, no. 3, pp. 468-478.*

3. Lampropoulou V., Sergushichev A., Bambouskova M., Nair S., Vincent E.E., Loginicheva E., Cervantes-Barragan L., Ma X., Huang S.C., Griss T., Weinheimer C.J., Khader S., Randolph G.J., Pearce E.J., Jones R.G., Diwan A., Diamond M.S., Artyomov M.N. Itaconate links inhibition of succinate dehydrogenase with macrophage metabolic remodeling and regulation of inflammation. *Cell Metab., 2016, Vol. 24, no. 1, pp. 158-166.*

4. Li W., Li Y., Kang J., Jiang H., Gong W., Chen L., Wu C., Liu M., Wu X., Zhao Y., Ren J. 4-octyl itaconate as a metabolite derivative inhibits inflammation via alkylation of STING. *Cell Rep. 2023. Vol. 42, no. 3, 112145.* doi: 10.1016/j.celrep.2023.112145.

5. Mills E.L., Ryan D.G., Prag H.A., Dikovskaya D., Menon D., Zaslona Z., Jedrychowski M.P., Costa A.S.H., Higgins M., Hams E., Szpyt J., Runtsch M.C., King M.S., McGouran J.F., Fischer R., Kessler B.M., McGettrick A.F., Hughes M.M., Carroll R.G., Booty L.M., Knatko E.V., Meakin P.J., Ashford M.L.J., Modis L.K., Brunori G., Sévin D.C., Fallon P.G., Caldwell S.T., Kunji E.R.S., Chouchani E.T., Frezza C., Dinkova-Kostova A.T., Hartley R.C., Murphy M.P., O'Neill L.A. Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1. *Nature, 2018, Vol. 556, no. 7699, pp. 113-117.*
6. Ogger P.P., Albers G.J., Hewitt R.J., O'Sullivan B.J., Powell J.E., Calamita E., Ghai P., Walker S.A., McErlean P., Saunders P., Kingston S., Molyneaux P.L., Halket J.M., Gray R., Chambers D.C., Maher T.M., Lloyd C.M., Byrne A.J. Itaconate controls the severity of pulmonary fibrosis. *Sci. Immunol., 2020, Vol. 5, no. 52, eabc1884*. doi: 10.1126/scitranslmed.ade3782.
7. Qin W., Qin K., Zhang Y., Jia W., Chen Y., Cheng B., Peng L., Chen N., Liu Y., Zhou W., Wang Y.L., Chen X., Wang C. S-glycosylation-based cysteine profiling reveals regulation of glycolysis by itaconate. *Nat. Chem. Biol., 2019, Vol. 15, no. 10, pp. 983-991.*
8. Swain A., Bambouskova M., Kim H., Andhey P.S., Duncan D., Auclair K., Chubukov V., Simons D.M., Roddy T.P., Stewart K.M., Artyomov M.N. Comparative evaluation of itaconate and its derivatives reveals divergent inflammasome and type I interferon regulation in macrophages. *Nat. Metab., 2020, Vol. 2, no. 7, pp. 594-602.*
9. Tomlinson KL, Riquelme SA, Baskota SU, Drikic M, Monk IR, Stinear TP, Lewis IA, Prince AS. Staphylococcus aureus stimulates neutrophil itaconate production that suppresses the oxidative burst. *Cell Rep., 2023, Vol. 42, no. 2, 112064.* doi: 10.1016/j.celrep.2023.112064.
10. Wu R., Liu J., Wang N., Zeng L., Yu C., Chen F., Wang H., Billiar T.R., Jiang J., Tang D., Kang R. Aconitate decarboxylase 1 is a mediator of polymicrobial sepsis. *Sci. Transl. Med., 2022, Vol. 14, no. 659, eabo2028*. doi: 10.1126/scitranslmed.abo2028.
11. Yi Z., Deng M., Scott M.J., Fu G., Loughran P.A., Lei Z., Li S., Sun P., Yang C., Li W., Xu H., Huang F., Billiar T.R. Immune-responsive gene 1/itaconate activates nuclear factor erythroid 2-related factor 2 in hepatocytes to protect against liver ischemia-reperfusion injury. *Hepatology, 2020, Vol. 72, no. 4, pp. 1394-1411.*
12. Zasłona Z., O'Neill L.A.J. Cytokine-like roles for metabolites in immunity. *Mol. Cell., 2020, Vol. 78, no. 5, pp. 814-823.*
13. Zhao H., Teng D., Yang L., Xu X., Chen J., Jiang T., Feng A.Y., Zhang Y., Frederick D.T., Gu L., Cai L., Asara J.M., Pasca di Magliano M., Boland G.M., Flaherty K.T., Swanson K.D., Liu D., Rabinowitz J.D., Zheng B. Myeloid-derived itaconate suppresses cytotoxic $CD8^+$ T cells and promotes tumour growth. *Nat. Metab., 2022, Vol. 4, no. 12, pp. 1660-1673.*
14. Zhu X., Guo Y., Liu Z., Yang J., Tang H., Wang Y. Itaconic acid exerts anti-inflammatory and antibacterial effects via promoting pentose phosphate pathway to produce ROS. *Sci Rep., 2021, Vol. 11, no. 1, 18173.* doi: 10.1038/s41598-021-97352-x.

Авторы:

Анисов Д.Э. *– лаборант-исследователь ФГБУН «Институт молекулярной биологии имени В.А. Энгельгардта» Российской академии наук; студент магистратуры, кафедра иммунологии, биологический факультет ФГБОУ ВО «Московский государственный университет имени М.В. Ломоносова, Москва, Россия*

Друцкая М.С. *– д.б.н., ведущий научный сотрудник лаборатории молекулярных механизмов иммунитета ФГБУН «Институт молекулярной биологии имени В.А. Энгельгардта» Российской академии наук, Москва, Россия*

Носенко М.А. *– к.б.н., научный сотрудник, Тринити-колледж, Дублин, Ирландия*

Недоспасов С.А. *– д.б.н., профессор, академик РАН, главный научный сотрудник, заведующий лабораторией молекулярных механизмов иммунитета ФГБУН «Институт молекулярной биологии имени В.А. Энгельгардта» Российской академии наук; заведующий отделом молекулярной иммунологии Института физико-химической биологии имени А.Н. Белозерского ФГБОУ ВО «Московский государственный университет имени М.В. Ломоносова, Москва; руководитель направления «Иммунобиология и медицина» Научно-технологический университет «Сириус», Федеральная территория Сириус, Россия*

Authors:

Anisov D.E., *Laboratory Assistant, Engelhardt Institute of Molecular Biology, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences; Master Student, Department of Immunology, Faculty of Biology, Lomonosov Moscow State University, Moscow, Russian Federation*

Drutskaya M.S., *PhD, MD (Biology), Leading Research Associate, Laboratory of Molecular Mechanisms of Immunity, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russian Federation*

Nosenko M.A., *PhD (Biology), Research Associate, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland*

Nedospasov S.A., *PhD, MD (Biology), Professor, Full Member, Russian Academy of Sciences, Chief Research Associate, Head, Laboratory of Molecular Mechanisms of Immunity, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences; Head, Department of Molecular Immunology at the Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Moscow; Head, Division of Immunobiology and Biomedicine, Center of Genetic and Life Sciences, Sirius University of Science and Technology, Federal Territory Sirius, Russian Federation*

Поступила 15.04.2023
Отправлена на доработку 24.04.2023
Принята к печати 26.04.2023

Received 15.04.2023
Revision received 24.04.2023
Accepted 26.04.2023