МОЛЕКУЛЯРНАЯ БИОЛОГИЯ, 2023, том 57, № 1, с. 106–108

МОЛЕКУЛЯРНАЯ БИОЛОГИЯ КЛЕТКИ

УДК 577.25,577.19:57.042.2

МЕТИЛОФИОПОГОНАНОН А ИНГИБИРУЕТ LPS/ATP-ИНДУЦИРОВАННЫЙ ПИРОПТОЗ МАКРОФАГОВ ЧЕРЕЗ ПУТЬ ROS/NLRP3[1]

© 2023 г. H. B. Zeng[a], L. H. Zhang[a], D. P. Yuan[a], W. Wang[b], X. M. Su[a], W. X. Weng[a], R. Miao[a], J. Y. Xu[a], J. Long[a, *], Y. H. Song[c, **]

[a]*Jiangsu Key Laboratory for Pharmacology and Safety Evaluation of Chinese Materia Medica, School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China*

[b]*Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China*

[c]*Department of Cardiology, Nanjing Hospital of Chinese Medicine Affilicated to Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China*

**e-mail: longjun@njucm.edu.cn*

***e-mail: sfy003@njucm.edu.cn*

Поступила в редакцию 05.05.2022 г.
После доработки 18.07.2022 г.
Принята к публикации 27.07.2022 г.

Как побочный продукт митохондриального дыхания или метаболизма активные формы кислорода (ROS) могут действовать как сигнальные молекулы для активации инфламмасомы NLRP3 (NLR family pyrin domain containing 3), тем самым индуцируя иммунный ответ. NLRP3 инфламмасома действует как сенсор различных опасных сигналов и играет центральную роль в контроле возникновения пироптоза. Пироптоз макрофагов тесно связан с атеросклерозом, артритом, фиброзом легких и другими воспалительными заболеваниями. Метилофиопогонанон А (МО-А) – основной гомоизофлавоноид, входящий в состав китайского лекарственного растения Ophiopogonis Radix и проявляющий антиоксидантную активность. Однако неясно, может ли МО-А ослаблять пироптоз макрофагов путем ингибирования окислительного стресса. Нами показано, что МО-А усиливает активность супероксиддисмутазы и каталазы, ингибирует образование ROS, снижает активацию NLRP3-инфламмасомы и высвобождение лактатдегидрогеназы, а также подавляет пироптоз в макрофагах, индуцированный липополисахаридами (LPS) и аденозинтрифосфатом (ATP). Эти эффекты могут быть отменены активатором ROS – пероксидом водорода (H_2O_2). Таким образом, МО-А может ингибировать пироптоз макрофагов через путь ROS/NLRP3 и, следовательно, рассматриваться в качестве кандидата для разработки противовоспалительного лекарственного средства.

Ключевые слова: инфламмасома NLRP3, пироптоз, макрофаги, активные формы кислорода, метилофиопогонанон А

DOI: 10.31857/S0026898423010196, **EDN:** AWTQTV

СПИСОК ЛИТЕРАТУРЫ

1. Cookson B.T., Brennan M.A. (2001) Pro-inflammatory programmed cell death. *Trends Microbiol.* **9**(3), 113–114.
2. Kovacs S.B., Miao E.A. (2017) Gasdermins: effectors of pyroptosis. *Trends Cell Biol.* **27**(9), 673–684.
3. Shi J.J., Gao W.Q., Shao F. (2017) Pyroptosis: gasdermin-mediated programmed necrotic cell death. *Trends Biochem. Sci.* **42**(4), 245–254.
4. Takeuchi O., Akira S. (2010) Pattern recognition receptors and inflammation. *Cell.* **140**(6), 805–820.
5. Franchi L., Muñoz-Planillo R., Núñez G. (2012) Sensing and reacting to microbes through the inflammasomes. *Nat. Immunol.* **13**(4), 325–332.
6. Liu X., Zhang Z.B., Ruan J.B., Pan Y., Magupalli V.G., Wu H., Lieberman J. (2016) Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. *Nature.* **535**(7610), 153–158.
7. Miao E.A., Leaf I.A., Treuting P.M., Mao D.P., Dors M., Sarkar A., Warren S.E., Wewers M.D., Aderem A.

[1] Статья представлена авторами на английском языке.

(2010) Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria. *Nat. Immunol.* **11**(12), 1136–1142.

8. Lin X.B., Wang H., An X.F., Zhang J., Kuang J., Hou J., Yan M. (2021) Baeckein E suppressed NLRP3 inflammasome activation through inhibiting both the priming and assembly procedure: implications for gout therapy. *Phytomedicine*. **84**, 153521.
9. Zou Y., Luo X., Feng Y., Fang S., Tian J., Yu B., Li J. (2021) Luteolin prevents THP-1 macrophage pyroptosis by suppressing ROS production via Nrf2 activation. *Chem. Biol. Interact*. **345**, 109573.
10. Lin M.B., Sun W., Gong W., Zhou Z., Ding Y., Hou Q. (2015) Methylophiopogonanone A protects against cerebral ischemia/reperfusion injury and attenuates blood-brain barrier disruption *in vitro*. *PLoS One*. **10**(4), e124558.
11. He F., Xu B.L., Chen C., Jia H.J., Wu J.X., Wang X.C., Sheng J.L., Huang L., Cheng J. (2016) Methylophiopogonanone A suppresses ischemia/reperfusion-induced myocardial apoptosis in mice via activating PI3K/Akt/eNOS signaling pathway. *Acta Pharmacol. Sin*. **37**(6), 763–771.
12. Li Z., Wu Y.Y., Yu B.X. (2020) Methylophiopogonanone A, an *Ophiopogon* homoisoflavonoid, alleviates high-fat diet-induced hyperlipidemia: assessment of its potential mechanism. *Braz. J. Med. Biol. Res*. **53**(3), e9201.
13. Qiu Z., He Y.H., Ming H., Lei S., Leng Y., Xia Z.Y. (2019) Lipopolysaccharide (LPS) aggravates high glucose- and hypoxia/reoxygenation-induced injury through activating ROS-dependent NLRP3 inflammasome-mediated pyroptosis in H9C2 cardiomyocytes. *J. Diabetes Res*. **2019**, 8151836.
14. Wree A., Eguchi A., McGeough M.D., Pena C.A., Johnson C.D., Canbay A., Hoffman H.M., Feldstein A.E. (2014) NLRP3 inflammasome activation results in hepatocyte pyroptosis, liver inflammation, and fibrosis in mice. *Hepatology*. **59**(3), 898–910.
15. Zheng M., Kanneganti T.D. (2020) The regulation of the ZBP1-NLRP3 inflammasome and its implications in pyroptosis, apoptosis, and necroptosis (PANoptosis). *Immunol. Rev*. **297**(1), 26–38.
16. Xie Q., Shen W.W., Zhong J., Huang C., Zhang L., Li J. (2014) Lipopolysaccharide/adenosine triphosphate induces IL-1β and IL-18 secretion through the NLRP3 inflammasome in RAW264.7 murine macrophage cells. *Int. J. Mol. Med*. **34**(1), 341–349.
17. Zhang W.B., Tao A., Lan T., Cepinskas G., Kao R., Martin C.M., Rui T. (2017) Carbon monoxide releasing molecule-3 improves myocardial function in mice with sepsis by inhibiting NLRP3 inflammasome activation in cardiac fibroblasts. *Basic Res. Cardiol*. **112**(2), 16.
18. Fernandes-Alnemri T., Wu J., Yu J.W., Datta. P, Miller B., Jankowski W., Rosenberg S., Zhang J., Alnemri E.S. (2007) The pyroptosome: a supramolecular assembly of ASC dimers mediating inflammatory cell death via caspase-1 activation. *Cell Death Differ*. **14**(9), 1590–1604.
19. Liu X., Zhang X., Ding Y., Zhou W., Tao L., Lu P., Wang Y., Hu R. (2017) Nuclear factor E2-related factor-2 negatively regulates NLRP3 inflammasome activity by inhibiting reactive oxygen species-induced NLRP3 priming. *Antioxid. Redox Signal*. **26**(1), 28–43.
20. Lei F.Y., Weckerle C., Heinrich M. (2021) Liriopogons (Genera *Ophiopogon* and *Liriope*, Asparagaceae): a critical review of the phytochemical and pharmacological research. *Front. Pharmacol*. **12**, 769929.
21. Lin Y., Zhu D., Qi J., Qin M., Yu B. (2010) Characterization of homoisoflavonoids in different cultivation regions of *Ophiopogon japonicus* and related antioxidant activity. *J. Pharm. Biomed. Anal*. **52**(5), 757–762.
22. Han X.J., Xu T.S., Fang Q.J., Zhang H., Yue L., Hu G., Sun L. (2021) Quercetin hinders microglial activation to alleviate neurotoxicity via the interplay between NLRP3 inflammasome and mitophagy. *Redox Biol*. **44**, 102010.
23. Burdette B.E., Esparza A.N., Zhu H., Wang S. (2021) Gasdermin D in pyroptosis. *Acta Pharm. Sin. B*. **11**(9), 2768–2782.
24. Orning P., Lien E., Fitzgerald K.A. (2019) Gasdermins and their role in immunity and inflammation. *J. Exp. Med*. **216**(11), 2453–2465.

Methylophiopogonanone A Inhibits LPS/ATP-Induced Macrophage Pyroptosis via ROS/NLRP3 Pathway

H. B. Zeng[1], L. H. Zhang[1], D. P. Yuan[1], W. Wang[2], X. M. Su[1], W. X. Weng[1], R. Miao[1], J. Y. Xu[1], J. Long[1, *], and Y. H. Song[3, **]

[1] *Jiangsu Key Laboratory for Pharmacology and Safety Evaluation of Chinese Materia Medica, School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China*

[2] *Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China*

[3] *Department of Cardiology, Nanjing Hospital of Chinese Medicine Affilicated to Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China*

**e-mail: longjun@njucm.edu.cn*

***e-mail: sfy003@njucm.edu.cn*

As a byproduct of mitochondrial respiration or metabolism, reactive oxygen species (ROS) can act as a signaling molecule to activate NLR family pyrin domain containing 3 (NLRP3) inflammasome, thereby triggering immune response. NLRP3 inflammasome acts as a sensor of various danger signals and is central to

the control of pyroptosis occurrence. Macrophage pyroptosis is closely related to atherosclerosis, arthritis, pulmonary fibrosis and other inflammatory diseases. Methylophiopogonanone A (MO-A) is a main homoisoflavonoid in Chinese herb Ophiopogonis Radix, which has antioxidant effect. However, it is not clear whether MO-A can alleviate macrophage pyroptosis by inhibiting oxidative stress. Here we have shown that MO-A increases the activities of superoxide dismutase (SOD) and catalase (CAT), inhibits the production of ROS, reduces the activation of NLRP3 inflammasome and the release of lactate dehydrogenase (LDH), and inhibits pyroptosis in macrophages induced by lipopolysaccharides (LPS) and adenosine triphosphate (ATP). These effects can be reversed by the ROS promoter hydrogen peroxide (H_2O_2). Therefore, MO-A can inhibit macrophage pyroptosis through the ROS/NLRP3 pathway and may be considered as a candidate drug for the treatment of inflammatory diseases.

Keywords: NLRP3 inflammasome, pyroptosis, macrophages, ROS, methylophiopogonanone A