В вязи с широким спектром эффектов аутофагии следует считать ее одним из важных ключей, регулирующих биологические функции клетки. Вследствие этого аутофагия может стать предпочтительной целью при разработке терапевтических подходов.

На основании новейших литературных данных можно заключить, что подавление аутофагии активирует провоспалительные функции макрофагов и может стать перспективной основой подхода к терапии онкозаболеваний. Напротив, активация аутофагии, переводящая микроглию в фенотип М2, может применяться для терапии нейродегенеративных заболеваний, в частности болезни Альцгеймера, Паркинсона и рассеянного склероза.

Основное ограничение парадигмы М1/М2 заключается в том, что процесс образования подтипов М1 и М2 более вероятен для моноцитарных макрофагов, чем для макрофагов резидентных, которые могут не иметь выраженной склонности к поляризации М1/М2. Несмотря на это, исследование парадигмы, актуальной для макрофагов и микроглии, открывает широкие горизонты для дальнейшего изучения фагоцитирующих клеток, появившихся на ранних этапах эволюции жизненных форм и выполняющих фундаментальные биологические функции у млекопитающих.

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СПИСОК ЛИТЕРАТУРЫ

Agrawal I., Jha S. 2020. Mitochondrial dysfunction and Alzheimer's disease: role of microglia. Front. Aging Neurosci. V. 12. P. 252.

Ahmed B., Sultana R., Greene M.W. 2021. Adipose tissue and insulin resistance in obese. Biomed. Pharmacother. V. 137. P. 111315. https://doi.org /10.1016/j.biopha.2021.111315

Aoki S., Shimizu K., Ito K. 2020. Autophagy-dependent mitochondrial function regulates osteoclast differentiation and maturation. Biochem. Biophys. Res. Commun. V. 527. P. 874.

Azam S., Haque M.E., Kim I.S., Choi D.K. 2021. Microglial turnover in ageing-related neurodegeneration: therapeutic avenue to intervene in disease progression. Cells. V. 10. P. 150.

Blagosklonny M.V. 2011. Progeria, rapamycin and normal aging: recent breakthrough. Aging. V. 3. P. 685.

Blagosklonny M.V. 2018. Does rapamycin slow down time? Oncotarget. V. 9. P. 30210. https://doi.org /10.18632/oncotarget.25788

Cao L., He C. 2013. Polarization of macrophages and microglia in inflammatory demyelination. Neurosci. Bull. V. 29. P. 189.

Carroll B., Dunlop E.A. 2017. The lysosome: a crucial hub for AMPK and mTORC1 signalling. Biochem. J. V. 474. P. 1453.

Chen W., Chen Y., Liu Y., Wang X.J. 2022. Autophagy in muscle regeneration: potential therapies for myopathies. Cachexia Sarcopenia Muscle. V. 13. P. 1673.

Cheng J., Liao Y., Dong Y., Hu H., Yang N., Kong X., Li S., Li X., Guo J., Qin L., Yu J., Ma C., Li J., Li M., Tang B., Yuan Z. 2020. Microglial autophagy defect causes parkinson disease-like symptoms by accelerating inflammasome activation in mice. Autophagy. V. 16. P. 2193–2205. https://doi.org /10.1080/15548627.2020.1719723

Chylikova J., Dvorackova J., Tauber Z., Kamarad V. 2018. M1/M2 macrophage polarization in human obese adipose tissue. Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech. Repub. V. 162. P. 79.

Cui X., Morales R.T., Qian W., Wang H., Gagner J.P., Dolgalev I., Placantonakis D., Zagzag D., Cimmino L., Snuderl M., Lam R.H.W., Chen W. 2018. Hacking macrophage-associated immunosuppression for regulating glioblastoma angiogenesis. Biomaterials. V. 161. P. 164.

Davies L.C., Jenkins S.J., Allen J.E., Taylor P.R. 2013. Tissue-resident macrophages. Nat. Immunol. V. 14. P. 986.

Fenn A.M., Henry C.J., Huang Y., Dugan A., Godbout J.P. 2012 Lipopolysaccharide-induced interleukin (IL)-4 receptor-α expression and corresponding sensitivity to the M2 promoting effects of IL-4 are impaired in microglia of aged mice. Brain Behav. Immunol. V. 26. P. 7667.

Florencio-Silva R., Sasso G.R., Simões M.J., Simões R.S., Baracat M.C., Sasso-Cerri E., Cerri P.S. 2017. Osteoporosis and autophagy: what is the relationship? Rev. Assoc. Med. Bras. V. 63. P. 173.

Fujisaka S., Usui I., Nawaz A., Takikawa A., Kado T., Igarashi Y., Tobe K. 2016. M2 macrophages in metabolism. Diabetol. Int. V. 7. P. 342.

Ghosh A.K., Mau T., O'Brien M., Garg S., Yung R. 2016. Impaired autophagy activity is linked to elevated ER-stress and inflammation in aging adipose tissue. Aging (Albany NY). V. 8. P. 2525.

Glick D., Barth S., Macleod K. 2010. Autophagy: cellular and molecular mechanisms. J. Pathol. V. 221. P. 3.

Green D.R., Llambi F. 2015. Cell death signaling. Cold Spring Harb. Perspect. Biol. V. 7. P. a006080. https://doi.org / 10.1101/cshperspect.a006080

Guo Y., Lin C., Xu P., Wu S., Fu X., Xia W., Yao M. 2016. AGEs induced autophagy impairs cutaneous wound healing via stimulating macrophage polarization to M1 in diabetes. Sci. Rep. V. 6. P. 36416. https://doi.org/ 10.1038/srep36416

Guo Y., Feng Y., Cui X., Wang Q., Pan X. 2019. Autophagy inhibition induces the repolarisation of tumour-associated macrophages and enhances chemosensitivity of laryngeal cancer cells to cisplatin in mice. Cancer Immunol. Immunother. V. 68. P. 1909.

Han X., Sun S., Sun Y., Song Q., Zhu J., Song N., Chen M., Sun T., Xia M., Ding J., Lu M., Yao H., Hu G. 2019. Small molecule-driven NLRP3 inflammation inhibition

via interplay between ubiquitination and autophagy: implications for Parkinson disease. Autophagy. V. 15. P. 1860.

Hesketh M., Sahin K.B., West Z.E, Murray R.Z. 2017. Macrophage phenotypes regulate scar formation and chronic wound healing. Int. J. Mol. Sci. V. 18. P. 1545. https://doi.org /10.3390/ijms18071545

Jha M.K., Lee W.H. 2016. Functional polarization of neuroglia: Implications in neuroinflammation and neurological disorders. Suk. K. Biochem. Pharmacol. V. 103. P. 1.

Jin M.M., Wang F., Qi D., Liu W.W., Gu C, Mao C.J., Yang Y.P., Zhao Z., Hu L.F., Liu C.F. 2018. A critical role of autophagy in regulating microglia polarization in neurodegeneration. Front. Aging Neurosci. V. 10. P. 378.

Kabeya Y., Mizushima N., Ueno T., Yamamoto A., Kirisako T., Noda T., Kominami E., Ohsumi Y., Yoshimori T. 2000. LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing. EMBO J. V. 19. P. 5720.

Kametaka S., Okano T., Ohsumi M., Ohsumi Y. 1998. Apg14p and Apg6/Vps30p form a protein complex essential for autophagy in the yeast, *Saccharomyces cerevisiae*. J. Biol. Chem. V. 273. P. 22284.

Kang Y.H., Cho M.H., Kim J.Y., Kwon M.S., Peak J.J., Kang S.W., Yoon S.Y., Song Y. 2016. Impaired macrophage autophagy induces systemic insulin resistance in obesity. Oncotarget. V. 7. P. 35577.

Kapetanovic R., Bokil N.J., Sweet M.J. 2015. Innate immune perturbations, accumulating DAMPs and inflammasome dysregulation: A ticking time bomb in ageing. Ageing Res. Rev. V. 24. Pt A. P. 40.

Kapoor N., Niu J., Saad Y., Kumar S., Sirakova T., Becerra E., Li X., Kolattukudy P.E. 2015. Transcription factors STAT6 and KLF4 implement macrophage polarization via the dual catalytic powers of MCPIP. J. Immunol. V. 194. P. 6011.

Kawamata T., Kamada Y., Kabeya Y., Sekito T., Ohsumi Y. 2008. Organization of the pre-autophagosomal structure responsible for autophagosome formation. Mol. Biol. Cell. V. 19. P. 2039.

Kawano A., Ariyoshi W., Yoshioka Y., Hikiji H., Nishihara T., Okinaga T. 2019. Docosahexaenoic acid enhances M2 macrophage polarization via the p38 signaling pathway and autophagy. J. Cell Biochem. V. 120. P. 12604–12617.

Klionsky D.J., Abdel-Aziz A.K., Abdelfatah S., Abdellatif M., Abdoli A., Abel S., Abeliovich H., Abildgaard M.H., Abudu Y.P., Acevedo-Arozena A., Adamopoulos I.E., Adeli K., Adolph T.E., Adornetto A., Aflaki E., et al. 2021. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition). Autophagy. V. 17. P. 1.

Kuo W.T., Chang J.M., Chen C.C., Tsao N., Chang C.P. 2022. Autophagy drives plasticity and functional polarization of tumor-associated macrophages. IUBMB Life. V. 74. P. 157.

Lee D.E., Bareja A., Bartlett D.B., White J.P. 2019. Autophagy as a therapeutic target to enhance aged muscle regeneration. Cells. V. 8. P. 183.

Lee J.W., Park S., Takahashi Y., Wang H.G. 2010. The association of AMPK with ULK1 regulates autophagy. PLoS. One. V. 5. P. e15394.

Liu K., Zhao E., Ilyas G., Lalazar G., Lin Y., Haseeb M., Tanaka K.E., Czaja M.J. 2015. Impaired macrophage autophagy increases the immune response in obese mice by promoting proinflammatory macrophage polarization. Autophagy. V. 11. P. 271.

Liu R., Cui J., Sun Y., Xu W., Wang Z., Wu M., Dong H., Yang C., Hong S., Yin S., Wang H. 2021. Autophagy deficiency promotes M1 macrophage polarization to exacerbate acute liver injury via Atg5 repression during aging. Cell Death Discov. V. 7. P. 397.

Lu B., Huang L., Cao J., Li L., Wu W., Chen X., Ding C. 2021. Adipose tissue macrophages in aging-associated adipose tissue function. J. Physiol. Sci. V. 71. P. 38.

Mauthe M., Orhon I., Rocchi C., Zhou X., Luhr M., Hijlkema K.J., Coppes R.P., Engedal N., Mari M., Reggiori F. 2018. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. Autophagy. V. 14. P. 1435.

Mazher M., Moqidem Y.A., Zidan M., Sayed A.A., Abdellatif A. 2023. Autophagic reprogramming of bone marrow-derived macrophages. Immunol. Res. V. 71. P. 229.

Metchnikoff E. 1892. Lecons sur la pathologie comparee de L'inflammation. Masson: Paris.

Miron V.E., Boyd A., Zhao J.W., Yuen T.J., Ruckh J.M., Shadrach J.L., van Wijngaarden P., Wagers A.J., Williams A., Franklin R.J.M., Ffrench-Constant C. 2013. M2 microglia and macrophages drive oligodendrocyte differentiation during CNS remyelination. Nat. Neurosci. V. 16. P. 1211.

Moehle M.S., West A.B. 2015. M1 and M2 immune activation in Parkinson's disease: foe and ally? Neurosci. V. 302. P. 59.

Montaseri A., Giampietri C., Rossi M., Riccioli A., Del Fattore A., Filippini A. 2020. The role of autophagy in osteoclast differentiation and bone resorption function. Biomolecules. V. 10. P. 1398.

Nawaz A., Tobe K. 2019. M2-like macrophages serve as a niche for adipocyte progenitors in adipose tissue. J. Diabetes Investig. V. 10. P. 1394.

Nikodemova M., Small A.L., Kimyon R.S., Watters J.J. 2016. Age-dependent differences in microglial responses to systemic inflammation are evident as early as middle age. Physiol. Genomics. V. 48. P. 336.

Nayak D., Roth T.L., McGavern D.B. 2014. Microglia development and function. Annu. Rev. Immunol. V. 32. P. 367.

Orihuela R., McPherson C.A., Harry G.J. 2016. Microglial M1/M2 polarization and metabolic states. Br. J. Pharmacol. V. 73. P. 649.

Peled M., Fisher E.A. 2014. Dynamic aspects of macrophage polarization during atherosclerosis progression and regression. Front. Immunol. V. 5. P. 579.

Perandini L.A., Chimin P., Lutkemeyer D.D.S, Câmara N.O.S. 2018. Chronic inflammation in skeletal muscle impairs satellite cells function during regeneration: can physical exercise restore the satellite cell niche? FEBS J. V. 285. P. 1973.

Pomilio C., Gorojod R.M., Riudavets M., Vinuesa A., Presa J., Gregosa A., Bentivegna M., Alaimo A., Alcon S.P.,

Sevlever G., Kotler M.L., Beauquis J., Saravia F. 2020. Microglial autophagy is impaired by prolonged exposure to β-amyloid peptides: evidence from experimental models and Alzheimer's disease patients. Geroscience. V. 42. P. 613.

Rojas J., Salazar J., Martínez M.S., Palmar J., Bautista J., Chávez-Castillo M., Gómez A., Bermúdez V. 2015. Macrophage heterogeneity and plasticity: impact of macrophage biomarkers on atherosclerosis. Hindawi Publ. Corporation Scientifica. P. 851252. https://doi.org/10.1155/2015/851252

Schlundt C., Fischer H., Bucher C.H., Rendenbach C., Duda G.N., Schmidt-Bleek K. 2021.The multifaceted roles of macrophages in bone regeneration: A story of polarization, activation and time. Acta Biomat. V. 133. P. 46.

Serý O., Povová J., Míšek I., Pešák L., Janout V. 2013. Molecular mechanisms of neuropathological changes in Alzheimer's disease: a review. Folia Neuropathol. V. 51. P. 1.

Singh L.P., Yumnamcha T., Swornalata Devi T. 2018. Mitophagic flux deregulation, lysosomal destabilization and NLRP3 inflammasome activation in diabetic retinopathy: potentials of gene therapy targeting TXNIP and the redox system. Ophthalmol. Res. Rep. V. 3. P. ORRT-126.

Stone A.E.L., Green R., Wilkins C., Hemann E.A., Gale M. 2019. RIG-I-like receptors direct inflammatory macrophage polarization against West Nile virus infection. Jr. Nat. Commun. V. 10. P. 3649.

Su T.T. 2018. Cellular plasticity, caspases and autophagy; that which does not kill us, well, makes us different. Open Biol. 2018. V. 8. P. 180157. https://doi.org /10.1098/rsob.180157

Suzuki K., Akioka M., Kondo-Kakuta C., Yamamoto H., Ohsumi Y. 2013. Fine mapping of autophagy-related proteins during autophagosome formation in Saccharomyces cerevisiae. J. Cell Sci. V. 126. P. 2534.

Urwanisch L., Luciano M., Horejs-Hoeck J. 2021. The NLRP3 inflammasome and its role in the pathogenicity of leukemia. Int. J. Mol. Sci. V. 22. P. 1271. https://doi.org /10.3390/ijms22031271

Van Eijk M., Aerts J.M.F.G. 2021. The unique phenotype of lipid-laden macrophages. Int. J. Mol. Sci. V. 22: P. 4039. https://doi.org /10.3390/ijms22084039

Xue Y., Nie D., Wang L.J., Qiu H.C., Ma L., Dong M.X., Tu W.J., Zhao J. 2021. Microglial polarization: novel therapeutic strategy against ischemic stroke. Aging Dis. V. 12. P. 466.

Yamate J, Izawa T, Kuwamura M. J 2023. Macrophage pathology in hepatotoxicity. Toxicol. Pathol. V. 36. P. 51. https://doi.org /10.1293/tox.2022-0112

Yang L., Xiao L., Gao W., Huang X., Wei F., Zhang Q., Xiao Y. 2021. Macrophages at low-inflammatory status improved osteogenesis via autophagy regulation. Tiss. Eng. Part. A. P. 021.

Yao K., Zhao Y.F. 2018. Aging modulates microglia phenotypes in neuroinflammation of MPTP-PD mice. Exp. Gerontol. V. 111. P. 86.

Yuan Y., Li L., Zhu L., Liu F., Tang X., Liao G., Liu J., Cheng J., Chen Y., Lu Y. 2020. Mesenchymal stem cells elicit macrophages into M2 phenotype via improving transcription factor EB-mediated autophagy to alleviate diabetic nephropathy. Stem Cells. V. 38. P. 639.

Zhang Q., Sioud M. 2023. Tumor-associated macrophage subsets: shaping polarization and targeting. Int. J. Mol. Sci. V. 24: 7493.
doi: 10.3390/ijms24087493

Zubova S.G., Suvorova I.I., Karpenko M.N. 2022. Macrophage and microglia polarization: focus on autophagy-dependent reprogramming. Front Biosci. (Schol Ed). V. 14: 3. doi: 10.31083/j.fbs1401003

THE ROLE OF AUTOPHAGY AND MACROPHAGE POLARIZATION IN THE PROCESSES OF CHRONIC INFLAMMATION AND REGENERATION

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The cause of many serious illnesses, including diabetes, obesity, osteoporosis and neurodegenerative diseases is chronic inflammation that develops in adipose tissue, bones or the brain. This inflammation occurs due to a shift in the polarization of macrophages/microglia towards the pro-inflammatory phenotype M1. It has now been proven that the polarization of macrophages is determined by the intracellular level of autophagy in the macrophage. By modulating autophagy, it is possible to cause switching of macrophage activities towards M1 or M2. Summarizing the material accumulated in the literature, we believe that the activation of autophagy reprograms the macrophage towards M2, replacing its protein content, receptor apparatus and including a different type of metabolism. The term reprogramming is most suitable for this process, since it is followed by a change in the functional activity of the macrophage, namely, switching from cytotoxic pro-inflammatory activity to anti-inflammatory (regenerative). Modulation of autophagy can be an approach to the treatment of oncological diseases, neurodegenerative disorders, osteoporosis, diabetes and other serious diseases.

Keywords: macrophage, microglia, M1/M2 phenotype, autophagy, reprogramming