

шью тиазовивина. Он представляет собой малую селективную молекулу, которая непосредственно воздействует на ROCK и увеличивает экспрессию факторов плюрипотентности. Процесс получения ИПСК с использованием тиазовивина может быть проще, быстрее и дешевле, чем без него (Hwang et al., 2008; Mohseni et al., 2015).

ЗАКЛЮЧЕНИЕ

Представленные в обзоре данные демонстрируют разнообразие функций малых ГТФаз семейства Rho в различных клеточных процессах. В целом изучение малых ГТФаз остается активной областью исследований и в будущем может привести к созданию новых методов диагностики и лечения различных заболеваний, включая рак, нейродегенеративные, аутоиммунные и сердечно-сосудистые.

Поскольку малые ГТФазы семейства Rho регулируют клеточную подвижность, они являются потенциальными мишенями для разработки новых методов эффективного подавления способности опухолевых клеток к инвазии и метастазированию; методов, основанных на применении ингибиторов как самих малых ГТФаз семейства Rho, так и ассоциированных с ними киназ.

Кроме того, такие ингибиторы могут оказывать дополнительный эффект путем блокирования ангиогенеза, сокращая поставку питательных веществ и кислорода в опухоль и тем самым замедляя ее рост.

Однако в настоящее время ингибиторы малых ГТФаз имеют ограниченную эффективность и могут вызывать нежелательные побочные эффекты, поэтому для разработки новых лекарственных препаратов необходимо более глубокое исследование механизмов регуляции малых ГТФаз семейства Rho в различных условиях и клетках разных типов.

ФИНАНСИРОВАНИЕ РАБОТЫ

Работа выполнена в рамках Госзадания (№ АААА-А19-119020-190093-9) Института цитологии РАН и поддержана Министерством науки и высшего образования РФ по проекту 15.БРК.21.0011 (соглашение № 075-15-2021-1063).

СОБЛЮДЕНИЕ ЭТИЧЕСКИХ СТАНДАРТОВ

Экспериментов с участием животных или людей авторы не проводили.

КОНФЛИКТ ИНТЕРЕСОВ

Авторы заявляют об отсутствии конфликтов интересов.

СПИСОК ЛИТЕРАТУРЫ

- Полянская Г.Г.* 2018. Сравнительный анализ характеристик линий мезенхимных стволовых клеток человека, полученных в коллекции культур клеток позвоночных (обзор). Клеточные культуры, вып. 34. С. 3. (*Poljanskaya G.G.* 2018. Comparative analysis of the lines of human mesenchymal stem cells derived in the collection of cell cultures of vertebrates (review). Collection "Cell cultures". No. 34. P. 3).
- Прайс К.М.* 1997. Синтез теломерной С-цепи. Биохимия. Т. 62. № 11. С. 1423. (*Price C.M.* 1997. Synthesis of telomeric C-strand. Biochemistry (Moscow). V. 62. P. 1423).
- Хейфлик Л.* 1997. Смертность и бессмертие на клеточном уровне. Биохимия. Т. 62. № 11. С. 1380. (*Hayflick L.* 1997. Mortality and immortality at the cellular level. Biochemistry (Moscow). V. 62. P. 1380).
- Abbi V., Piplani P.* 2020. Rho-kinase (ROCK) inhibitors—a neuroprotective therapeutic paradigm with a focus on ocular utility. Curr. Med. Chem. V. 27. P. 2222. <https://doi.org/10.2174/0929867325666181031102829>
- Aguilar B. J., Zhao Y., Zhou H., Huo S., Chen Y.H., Lu Q.* 2019. Inhibition of Cdc42—intersectin interaction by small molecule ZCL367 impedes cancer cell cycle progression, proliferation, migration, and tumor growth. Cancer Biol. Ther. V. 20 P. 740. <https://doi.org/10.1080/15384047.2018.1564559>
- Al-Azab M., Safi M., Idiattullina E., Al-Shaebi F., Zaky M.* 2022. Aging of mesenchymal stem cell: machinery, markers, and strategies of fighting. Cell. Mol. Biol. Lett. V. 27. P. 69. <https://doi.org/10.1186/s11658-022-00366-0>
- Al-Koussa H., Atat O.E., Jaafar L., Tashjian H., El-Sibai M.* 2020. The role of Rho GTPases in motility and invasion of glioblastoma cells. Anal. Cell. Pathol. V. 2020. P. 9274016. <https://doi.org/10.1155/2020/9274016>
- Amano M., Nakayama M., Kaibuchi K.* 2010. Rho-kinase/ROCK: a key regulator of the cytoskeleton and cell polarity. Cytoskeleton, V. 67 P. 545. <https://doi.org/10.1002/cm.20472>
- Aslam M., Troidl C., Tanislav C., Rohrbach S., Gündüz D., Hamm, C.W.* 2019. Inhibition of protein prenylation of GTPases alters endothelial barrier function. Int. J. Mol. Sci. V. 21. P. 2. <https://doi.org/10.3390/ijms21010002>
- Barbalata C.I., Tefas L.R., Achim M., Tomuta I., Porfire, A.S.* 2020. Statins in risk-reduction and treatment of cancer. J. Clin. Oncol. V. 11. P. 573. <https://doi.org/10.5306/wjco.v11.i8.573>
- Barth H., Fischer S., Möglich A., Förtsch, C.* 2015. Clostridial C3 toxins target monocytes/macrophages and modulate their functions. Front. Immunol. V. 6. P. 339. <https://doi.org/10.3389/fimmu.2015.00339>
- Berthold J., Schenková K., Ramos S., Miura Y., Furukawa M., Aspenström P., Rivero F.* 2008. Characterization of

- RhoBTP-dependent Cul3 ubiquitin ligase complexes — evidence for an autoregulatory mechanism. *Exp. Cell Res.* V. 314. P. 3453. <https://doi.org/10.1016/j.yexcr.2008.09.005>
- Bobkov D., Polyanskaya A., Musorina A., Poljanskaya G.* 2022. The RhoA nuclear localization changes in replicative senescence: new evidence from in vitro human mesenchymal stem cells studies. *Biocell.* V. 46. P. 2053. <https://doi.org/10.32604/biocell.2022.019469>
- Bobkov D., Polyanskaya A., Musorina A., Lomert E., Shabelnikov S.* 2020. Replicative senescence in MSCWJ-1 human umbilical cord mesenchymal stem cells is marked by characteristic changes in motility, cytoskeletal organization, and RhoA localization. *Mol. Biol. Rep.* V. 47. P. 3867. <https://doi.org/10.1007/s11033-020-05476-6>
- Bodnar A.G., Ouellette M., Frolkis M., Holt S.E., Chiu C.P., Morin G.B., Harley C.B., Shay J.W., Lichtsteiner S., Wright W.E.* 1998. Extension of life-span by introduction of telomerase into normal human cells. *Science.* V. 279. P. 349. <https://doi.org/10.1126/science.279.5349.349>
- Bolick S. C.E., Landowski T.H., Boulware D., Oshiro M.M., Ohkanda J., Hamilton A.D., Sebt S.M., Dalton W.S.* 2003. The farnesyl transferase inhibitor, FTI-277, inhibits growth and induces apoptosis in drug-resistant myeloma tumor cells. *Leukemia.* V. 17. P. 451.
- Bos J.L., Rehmann H., Wittinghofer A.* 2007. GEFs and GAPs: critical elements in the control of small G proteins. *Cell.* V. 129. P. 865. <https://doi.org/10.1016/j.cell.2007.05.018>
- Cabrera M., Echeverria E., Lenicov F.R., Cardama G., Gonzalez N., Davio C., Fernández N., Menna P.L.* 2017. Pharmacological Rac1 inhibitors with selective apoptotic activity in human acute leukemic cell lines. *Oncotarget.* V. 8: 98509. <https://doi.org/10.18632/oncotarget.21533>
- Cai R., Wang Y., Huang Z., Zou Q., Pu Y., Yu C., Cai Z.* 2021. Role of RhoA/ROCK signaling in Alzheimer's disease. *Behav. Brain Res.* V. 414: 113481. <https://doi.org/10.1016/j.bbr.2021.113481>
- Cardama G.A., Gonzalez N., Ciarlantini M., Gandolfi Donadio, L., Comin M.J., Alonso D. F., Menna P. L., Gomez D. E.* 2014. Proapoptotic and antiinvasive activity of Rac1 small molecule inhibitors on malignant glioma cells. *Onco Targets Ther.* V. 2021-2033. <https://doi.org/10.2147/OTT.S67998>
- Chen Y., Wang X., Wu Z., Jia S., Wan M.* 2023. Epigenetic regulation of dental-derived stem cells and their application in pulp and periodontal regeneration. *Peer J.* V. 11: 14550. <https://doi.org/10.7717/peerj14550>
- Chircop M.* 2014. Rho GTPases as regulators of mitosis and cytokinesis in mammalian cells. *Small GTPases.* V. 5: e29770. <https://doi.org/10.4161/sgtp.29770>
- Comunale F., Causeret M., Favard C., Cau J., Taulet N., Charrasse S., Gauthier-Rouvière C.* 2007. Rac1 and RhoA GTPases have antagonistic functions during N-cadherin-dependent cell-cell contact formation in C2C12 myoblasts. *Biol. Cell.* V. 99. P. 503. <https://doi.org/10.1042/BC20070011>
- Cordova E., Wei, J., Patel C., Shan N. L., Gionco J., Sargsyan D., Wu R., Cai L., Kong A., Jacinto E., Minden A.* 2019. KPT-9274, an inhibitor of PAK4 and NAMPT, leads to downregulation of mTORC2 in triple negative breast cancer cells. *Chem. Res. Toxicol.* V. 33. P. 482.
- Crosas-Molist E., Samain R., Kohlhammer L., Orgaz J. L., George S. L., Maiques O., Barcelo J., Sanz-Moreno V.* 2022. Rho GTPase signaling in cancer progression and dissemination. *Physiol. Rev.* V. 102. P. 455.
- De Curtis I., Meldolesi J.* 2012. Cell surface dynamics-how Rho GTPases orchestrate the interplay between the plasma membrane and the cortical cytoskeleton. *J. Cell. Sci.* V. 125. P. 4435. <https://doi.org/10.1242/jcs.108266>
- Debidda M., Williams D. A., Zheng Y.* 2006. Rac1 GTPase regulates cell genomic stability and senescence. *J. Biol. Chem.* V. 281. P. 38519.
- Dharmawardhane S., Hernandez E., Vlaar C.* 2013. Development of EHop-016: a small molecule inhibitor of Rac. *The Enzymes.* V. 33. P.117.
- Diep D. T. V., Hong K., Khun T., Zheng M., Ul-Haq A., Jun H. S., Kim Y. B., Chun K. H.* 2018. Anti-adipogenic effects of KD025 (SLx-2119), a ROCK2-specific inhibitor, in 3T3-L1 cells. *Sci. Rep.* V. 8. P. 2477. <https://doi.org/10.1038/s41598-018-20821-3>
- Dill J., Patel, A. R., Yang X. L., Bachoo R., Powell C. M., Li S.* 2010. A molecular mechanism for ibuprofen-mediated RhoA inhibition in neurons. *J. Neurosci.* V. 30. P. 963.
- Dominici M., Le Blanc K., Mueller I., Slaper-Cortenbach I., Marini F., Krause D., Deans R., Keating A., Prockop D.J., Horwitz E.* 2006. Minimal criteria for defining multipotent mesenchymal stromal cells. *Int. Soc. Cell. Ther. Position Statement.* *Cytother.* V. 8. P. 315.
- Dubash A. D., Guilluy C., Srougi M. C., Boulter E., Burrige K., Garcia-Mata R.* 2011. The small GTPase RhoA localizes to the nucleus and is activated by Net1 and DNA damage signals. *PloS One.* V. 6: 7380. <https://doi.org/10.1371/journal.pone.0017380>
- East M. P., Asquith C. R.* 2021. CDC42BPA/MRCK [alpha]: a kinase target for brain, ovarian and skin cancers. *Nat. Rev. Drug Discov.* V. 20. P. 167. <https://doi.org/10.1038/d41573-021-00023-9>
- Ellenbroek S. I., Collard J. G.* 2007. Rho GTPases: functions and association with cancer. *Clin. Exp. Metastasis.* V. 24. P. 657.
- Florian M. C., Dörr K., Niebel A., Daria D., Schrezenmeier H., Rojewski M., Filippi M.D., Hasenberg A., Gunzer M., Scharffetter-Kochanek K., Zheng Y., Geiger H.* 2012. Cdc42 activity regulates hematopoietic stem cell aging and rejuvenation. *Cell Stem Cell.* V. 10. P. 520. <https://doi.org/10.1016/j.stem.2012.04.007>
- Florian M. C., Klenk J., Marka G., Soller K., Kiryakos H., Peter R., Herbolsheimer F., Rothenbacher D., Denking M., Geiger H.* 2017. Expression and activity of the small RhoGTPase Cdc42 in blood cells of older adults are associated with age and cardiovascular disease. *J. Gerontol. A. Biol. Sci. Med. Sci.* V. 72. P. 1196. <https://doi.org/10.1093/gerona/glx091>
- Gilkes D. M., Xiang L., Lee S. J., Chaturvedi P., Hubbi M. E., Wirtz D., Semenza G. L.* 2014. Hypoxia-inducible factors mediate coordinated RhoA-ROCK1 expression and signaling in breast cancer cells. *Proc. Natl. Acad. Sci. USA.* V. 111. P. 384.

- Goh L.L., Manser E. 2012. The GTPase-deficient Rnd proteins are stabilized by their effectors. *J. Biol. Chem.* V. 287. P. 31311.
- Goodman K.B., Cui H., Dowdell S.E., Gaitanopoulos D.E., Ivy R.L., Sehon C.A., Stavenger R.A., Wang G.Z., Viet A.Q., Xu W., Ye G., Semus S.F., Evans C., Fries H.E., Jolivet L.J., et al. 2007. Development of dihydropyridone indazole amides as selective Rho-kinase inhibitors. *J. Med. Chem.* V. 50. P. 6.
- Gray J.L., von Delft F., Brennan P.E. 2020. Targeting the small GTPase superfamily through their regulatory proteins. *Angew. Chem. Int. Ed.* V. 59. P. 6342. <https://doi.org/10.1002/anie.201900585>
- Guiler W., Koehler A., Boykin C., Lu Q. 2021. Pharmacological modulators of small GTPases of rho family in neurodegenerative diseases. *Front. Cell. Neurosci.* V. 15. P. 661612. <https://doi.org/10.3389/fncel.2021.661612>
- Guo Y., Kenney S.R., Muller C.Y., Adams S., Rutledge T., Romero E., Murray-Krezan C., Prekeris R., Sklar L.A., Hudson L.G., Wandinger-Ness A. 2015. R-Ketorolac targets Cdc42 and Rac1 and alters ovarian cancer cell behaviors critical for invasion and metastasis. *Mol. Cancer Ther.* 2015. V. 14. P. 2215. <https://doi.org/10.1158/1535-7163.MCT-15-0419>
- Haga R. B., Ridley A. J. 2016. Rho GTPases: regulation and roles in cancer cell biology. *Small GTPases.* V. 7. P. 207. <https://doi.org/10.1080/21541248.2016.1232583>
- Hanna S., El-Sibai M. 2013. Signaling networks of Rho GTPases in cell motility. *Cell. Signal.* V. 25. P. 1955. <https://doi.org/10.1016/j.cellsig.2013.04.009>
- Hervé J.C., Bourmeyster N. 2015. Rho GTPases at the crossroad of signaling networks in mammals. *Small GTPases.* V. 6. P. 43. <https://doi.org/10.1080/21541248.2015.1044811>
- Hezan K., Mo R., Wang C., Yue L., Zongjin L. 2022. Anti-inflammatory effects of mesenchymal stem cells and their secretomes in Pneumonia. *Curr. Pharm. Biotechnol.* V. 23. P. 1153. <https://doi.org/10.2174/1389201022666210907115126>
- Hinde E., Yokomori K., Gaus K., Hahn K.M., Gratton E., 2014. Fluctuation-based imaging of nuclear Rac1 activation by protein oligomerisation. *Sci. Rep.* 2014. V. 4. P. 4219. <https://doi.org/10.1038/srep04219>
- Ho A.L., Brana I., Haddad R., Bauman J., Bible K., Oosting S., Wong D.J., Ahn M., Boni V., Even C., Fayette J., MD, Flor M.J., Harrington K., Hong D.S., Kim S.B., et al. 2021. Tipifarnib in head and neck squamous cell carcinoma with HRAS mutations. *J. Clin. Oncol.* V. 39. P. 1856. <https://doi.org/10.1200/JCO.20.02903>
- Hodge R.G., Ridley A.J. 2016. Regulating Rho GTPases and their regulators. *Nat. Rev. Mol. Cell Biol.* 2016. V. 17. P. 496. <https://doi.org/10.1038/nrm.2016.67>
- Hong L., Kenney S.R., Phillips G.K., Simpson G., Schroeder C.E., Nöth J., Romero E., Swanson S., Waller A., Strouse J.J., Carter M., Chigaev A., Ursu O., Oprea T., Hjelle B. 2013. Characterization of a Cdc42 protein inhibitor and its use as a molecular probe. *J. Biol. Chem.* V. 288. P. 8531.
- Humphries-Bickley T., Castillo-Pichardo L., Hernandez-O'Farrill E., Borrero-Garcia L.D., Forestier-Roman I., Gerena Y., Blanco M., Rivera-Robles M., Rodriguez-Medina J.R., Cubano L.A., Vlaar C.P., Dharmawardhane S. 2017. Characterization of a Dual Rac/Cdc42 Inhibitor MBQ-167 in Metastatic Cancer MBQ-167, a Rac/Cdc42 inhibitor in breast cancer cells. *Mol. Cancer Ther.* V. 16. P. 805. <https://doi.org/10.1158/1535-7163.MCT-16-0442>
- Humphries B., Wang Z., Yang C. 2020. Rho GTPases: big players in breast cancer initiation, metastasis and therapeutic responses. *Cells.* V. 9. P. 2167. <https://doi.org/10.3390/cells9102167>
- Hwang K.C., Kim J.Y., Chang W., Kim D.S., Lim S., Kang S.M., Kim D.W. 2008. Chemicals that modulate stem cell differentiation. *Proc. Natl. Acad. Sci. USA.* V. 105. P. 7467.
- Jaffe A.B., Hall A. 2005. Rho GTPases: biochemistry and biology. *Annu. Rev. Cell Dev. Biol.* 2005. V. 21. P. 247.
- Jayasinghe M., Prathiraja O., Prashan B., Jena R., Silva M., Weerawarna P., Singhal M., Kayani A., Karnakoti S., Jain S. 2022. The role of mesenchymal stem cells in the treatment of type 1 diabetes. *Cureus.* V. 14. P. e27337. <https://doi.org/10.7759/cureus.27337>
- Jim Leu S.J., Sung J.S., Huang M.L., Chen M.Y., Tsai T.W. 2013. A novel anti-CCN1 monoclonal antibody suppresses Rac-dependent cytoskeletal reorganization and migratory activities in breast cancer cells. *Biochem. Biophys. Res. Commun.* 2013. V. 434. P. 885.
- Yung Y.C., Stoddard N.C., Chun J. 2014. LPA receptor signaling: pharmacology, physiology, and pathophysiology. *J. Lipid Res.* V. 55. P. 1192.
- Kale V.P., Hengst J.A., Desai D.H., Dick T.E., Choe K.N., Colledge A.L., Takahashi Y., Sung S.S., Amin S.G., Yun G.K. 2014. A novel selective multikinase inhibitor of ROCK and MRCK effectively blocks cancer cell migration and invasion. *Cancer Letters.* V. 354. P. 299.
- Kaneko Y., Ohta M., Inoue T., Mizuno K., Isobe T., Tanabe S., Tanihara H. 2016. Effects of K-115 (Ripasudil), a novel ROCK inhibitor, on trabecular meshwork and Schlemm's canal endothelial cells. *Sci. Rep.* V. 6. P. 1. <https://doi.org/10.1038/srep19640>
- Kast R., Schirok H., Figueroa-Pérez S., Mittendorf J., Gnoth M.J., Apeler H., Lenz J., Franz J. K., Knorr A., Hütter J., Lobell M., Zimmermann K., Münter K., Augstein H., Ehmke H., Staschet J.P. 2007. Cardiovascular effects of a novel potent and highly selective azaindole-based inhibitor of Rho-kinase. *Br. J. Pharmacol.* V. 152. P. 1070.
- Kent D.G., Copley M.R., Benz C., Wöhrer S., Dykstra B.J., Ma E., Eaves C.J. 2009. Prospective isolation and molecular characterization of hematopoietic stem cells with durable self-renewal potential. *Blood.* V. 113. P. 6342.
- Kerber R.A., O'Brien E., Cawthon R.M. 2009. Gene expression profiles associated with aging and mortality in humans. *Aging Cell.* 2009. V. 8. P. 239. <https://doi.org/10.1111/j.1474-9726.2009.00467.x>
- Kim J., Islam R., Cho J.Y., Jeong H., Cap K.C., Park Y., Hossain A.J., Park J.B. 2018. Regulation of RhoA GTPase and various transcription factors in the RhoA pathway. *J. Cell. Physiol.* V. 233 P. 6381.
- Kristó I., Bajusz I., Bajusz C., Borkúti P., Vilmos P. 2016. Actin, actin-binding proteins, and actin-related proteins in the nucleus. *Histochem. Cell Biol.* V. 145. P. 373.

- Lanning C.C., Daddona J.L., Ruiz-Velasco R., Shafer S.H., Williams C.L. 2004. The Rac1 C-terminal polybasic region regulates the nuclear localization and protein degradation of Rac1. *J. Biol. Chem.* V. 279. P. 44197.
- Lawson C.D., Ridley A.J. 2018. Rho GTPase signaling complexes in cell migration and invasion. *J. Cell Biol.* V. 217. P. 447.
- Lee K.H., Koh M., Moon A. 2016. Farnesyl transferase inhibitor FTI-277 inhibits breast cell invasion and migration by blocking H-Ras activation. *Oncol. Lett.* V. 12. P. 2222. <https://doi.org/10.3892/ol.2016.4837>
- Leins H., Mulaw M., Eiwien K., Sakk V., Liang Y., Denkin-ger M., Geiger H., Schirmbeck R. 2018. Aged murine hematopoietic stem cells drive aging-associated immune remodeling. *Blood.* V. 132. P. 565.
- Li C., Zhen G., Chai Y., Xie L., Crane J. L., Farber E., Wan M. 2016. RhoA determines lineage fate of mesenchymal stem cells by modulating CTGF-VEGF complex in extracellular matrix. *Nat. Commun.* V. 7. P. 11455. <https://doi.org/10.1038/ncomms11455>
- Liao J. K., Seto M., Noma K. 2007. Rho kinase (ROCK) inhibitors. *J. Cardiovasc. Pharmacol.* V. 50. P. 17.
- Lin B. J., Tsao S. H., Chen A., Hu S. K., Chao L., Chao P. H. G. 2017. Lipid rafts sense and direct electric field-induced migration. *Proc. Natl. Acad. Sci. USA.* V. 114. P. 8568.
- Lin T., Ambasadhan R., Yuan X., Li W., Hilcove S., Abuja-rour R., Ding S. 2009. A chemical platform for improved induction of human iPSCs. *Nat. Methods.* V. 6. P. 805. <https://doi.org/10.1038/nmeth.1393>
- Linseman D. A., Lu Q. 2023. Rho family GTPases and their effectors in neuronal survival and neurodegeneration. *Front. Cell. Neurosci.* V. 17. P. 67.
- Liu Y., Schwam J., Chen Q. 2022. Senescence-associated cell transition and internation (SACTAI): a proposed mechanism for tissue aging, repair and degeneration. *Cells.* V. 11. P. 1089. <https://doi.org/10.3390/cells11071089>
- Liu H. W., Halayko A. J., Fernandes D. J., Harmon G. S., McCauley J. A., Kocieniewski P., Solway J. 2003. The RhoA/Rho kinase pathway regulates nuclear localization of serum response factor. *Am. J. Physiol. Lung Cell Mol. Physiol.* V. 29. P. 39.
- Löhn M., Plettenburg O., Ivashchenko Y., Kannt A., Hofmeis-ter A., Kadereit D., Ruetten H. 2009. Pharmacological characterization of SAR407899, a novel rho-kinase inhibitor. *Hypertension.* V. 54. P. 676. <https://doi.org/10.1161/HYPERTENSIONAHA.109.134353>
- Loirand G., Guérin P., Pacaud P. 2006. Rho kinases in car-diovascular physiology and pathophysiology. *Circ. Res.* V. 98. P. 322.
- Ma N., Xu E., Luo Q., Song G. 2023. Rac1: A regulator of cell migration and a potential target for cancer therapy. *Molecules.* V. 28. P. 2976. <https://doi.org/10.3390/mol-ecules28072976>
- Magalhaes Y. T., Farias J. O., Silva L. E., Forti F. L. 2021. GTPases, genome, actin: a hidden story in DNA damage response and repair mechanisms. *DNA repair.* V. 100: 103070. <https://doi.org/10.1016/j.dnarep.2021.103070>
- Maldonado M. D. M., Dharmawardhane S. 2018. Targeting rac and Cdc42 GTPases in cancer. *Cancer Res.* V. 78. P. 3101.
- Maldonado M. D. M., Medina J. I., Velazquez L., Dharmawardhane S. 2020. Targeting Rac and Cdc42 GEFs in metastatic cancer. *Front. Cell Dev. Biol.* V. 8. P. 201. <https://doi.org/10.3389/fcell.2020.00201>
- Malhi M., Norris M. J., Duan W., Moraes T. J., Maynes J. T. 2021. Statin-mediated disruption of Rho GTPase prenylation and activity inhibits respiratory syncytial virus infection. *Commun. Biol.* V. 4. P. 1239. <https://doi.org/10.1038/s42003-021-02754-2>
- Matsumura T., Zerrudo Z., Hayflick L. 1979. Senescent human diploid cells in culture: survival, DNA synthesis and morphology. *J. Gerontol.* V. 34. P. 328.
- McLeod R., Kumar R., Papadatos-Pastos D., Mateo J., Brown J. S., Garces A. H. I., Banerji U. 2020. First-in-human study of AT13148, a dual ROCK-AKT inhibitor in patients with solid tumors. *Clin. Cancer Res.* V. 26. P. 4777. <https://doi.org/10.1158/1078-0432.CCR-20-0700>
- Mizukawa B., Wei J., Shrestha M., Wunderlich M., Chou F. S., Griesinger A., Mulloy J. C. 2011. Inhibition of Rac GTPase signaling and downstream prosurvival Bcl-2 proteins as combination targeted therapy in MLL-AF9 leukemia. *Blood.* V. 118. P. 5235.
- Mohseni R., Shoaee-Hassani A., Verdi J. 2015. Reprogramming of endometrial adult stromal cells in the presence of a ROCK inhibitor, thiazovivin, could obtain more efficient iPSCs. *Int. J. Cell Biol.* V. 39. P. 515. <https://doi.org/10.1002/cbin.10411>
- Moissoglu K., Schwartz M.A. 2014. Spatial and temporal control of Rho GTPase functions. *Cell. Logist.* V. 4: e943618. <https://doi.org/10.4161/21592780.2014.943618>
- Mosaddeghzadeh N., Ahmadian M.R. 2021 The Rho family GTPases: mechanisms of regulation and signaling. *Cells.* 2021. V. 10. P. 1831. <https://doi.org/10.3390/cells10071831>
- Mou C., Wang X., Li W., Li Z., Liu N., Xu Y. 2023. Efficacy of mesenchymal stromal cells intraspinal transplantation for patients with different degrees of spinal cord injury: a systematic review and meta-analysis. *Cytotherapy.* V. 25. P. 530. <https://doi.org/10.1016/j.jcyt.2023.01.012>
- Narumiya S., Ishizaki T., Ufhata M. 2000. Use and properties of ROCK-specific inhibitor Y-27632. *Meth. Enzymol.* V. 325. P. 273.
- Narumiya S., Thumkeo D. 2018. Rho signaling research: history, current status and future directions. *FEBS Lett.* V. 592. P. 1763.
- Navarro L., Chen X., Viviecas L.T., Ardila-Roa A., Luna-Gonzalez M., Sossa C., Arango-Rodriguez M. 2022. Mesenchymal stem cells for critical limb ischemia: their function, mechanism, and therapeutic potential. *Stem Cell Res. Ther.* V. 13. P. 345. <https://doi.org/10.1186/s13287-022-03043-3>
- Navarro-Lérida I., Sánchez-Álvarez M., del Pozo M.Á., 2021. Post-translational modification and subcellular compartmentalization: emerging concepts on the regulation and physiopathological relevance of RhoGTPases. *Cells.* 2021. V. 10. P. 1990. <https://doi.org/10.3390/cells10081990>

- Nguyen L. K., Kholodenko B. N., Von Kriegsheim A. 2018. Rac1 and RhoA: networks, loops and bistability. *Small GTPases*. V. 9. P. 316. <https://doi.org/10.1080/21541248.2016.1224399>
- Okura H., Golbourn B. J., Shahzad U., Agnihotri S., Sabha N., Krieger J. R., Rutka J. T. 2016. A role for activated Cdc42 in glioblastoma multiforme invasion. *Oncotarget*. V. 7. P. 56958. <https://doi.org/10.18632/oncotarget.10925>
- Onesto C., Shutes A., Picard V., Schweighoffer F., Der C. J. 2008. Characterization of EHT 1864, a novel small molecule inhibitor of Rac family small GTPases. *Meth. Enzymol*. V. 439. P. 111.
- Özcan S., Alessio N., Acar M.B., Mert E., Omerli F., Peluso G., Galderisi U. 2016. Unbiased analysis of senescence associated secretory phenotype (SASP) to identify common components following different genotoxic stresses. *Aging (Albany NY)*. V. 8. P. 1316. <https://doi.org/10.18632/aging.100971>
- Park S., Kim D., Jung Y. G., Roh S. 2015. Thiazovivin, a Rho kinase inhibitor, improves stemness maintenance of embryo-derived stem-like cells under chemically defined culture conditions in cattle. *Anim. Reprod. Sci*. V. 161. P. 47. <https://doi.org/10.1016/j.anireprosci.2015.08.003>
- Patel R. A., Forinash K. D., Pireddu R., Sun Y., Sun N., Martin M. P., Sebt S. M. 2012. RKI-1447 is a potent inhibitor of the Rho-associated ROCK kinases with anti-invasive and antitumor activities in breast cancer RKI-1447, a potent ROCK inhibitor with antitumor activity. *Cancer Res*. V. 72. P. 5025. <https://doi.org/10.1158/0008-5472.CAN-12-0954>
- Pawelec G. P. 2018. CASIN the joint: immune aging at the stem cell level. *Blood. The J. Am. Soc. Hematol*. V. 132. P. 553.
- Payapilly A., Malliri A. 2018. Compartmentalisation of RAC1 signalling. *Curr. Opin. Cell Biol*. 2018. V. 54. P. 50. <https://doi.org/10.1016/j.ccb.2018.04.009>
- Pelish H. E., Peterson J. R., Salvarezza S. B., Rodriguez-Boulan E., Chen J. L., Stamnes M., Kirchhausen T. 2006. Secramine inhibits Cdc42-dependent functions in cells and Cdc42 activation *in vitro*. *Nat. Chem. Biol*. V. 2. P. 39. <https://doi.org/10.1038/nchembio751>
- Pischiutta F., Caruso E., Cavaleiro H., Salgado A., Loane D., Zanier E. 2022. Mesenchymal stromal cell secretome for traumatic brain injury: Focus on immunomodulatory action. *Exp. Neurol*. V. 357: 114199. <https://doi.org/10.1016/j.expneurol.2022.114199>
- Poljanskaya G.G., Bobkov D.E., Koltsova A.M., Musorina A.S., Mikhailova N.A. 2022. Creation, working principles, development of applied and scientific activities of the Collection of cell cultures of vertebrate. (review). *Bio. Comm*. V. 67. P. 312. <https://doi.org/10.21638/spbu03.2022.406>
- Porter A. P., Papaioannou A., Malliri A. 2016. Deregulation of Rho GTPases in cancer. *Small GTPases*. V. 7. P. 123. <https://doi.org/10.1080/21541248.2016.1173767>
- Prieto-Dominguez N., Parnell C., Teng Y. 2019. Drugging the small GTPase pathways in cancer treatment: promises and challenges. *Cells*. V. 8. P. 255. <https://doi.org/10.3390/cells8030255>
- Qadir M. I., Parveen A., Ali M. 2015. Cdc42: role in cancer management. *Chem. Biol. Drug Des*. V. 86. P. 432.
- Rajakylä E.K., Vartiainen M.K. 2011. Rho, nuclear actin, and actin-binding proteins in the regulation of transcription and gene expression. *Small GTPases*. 2014. V. 5. P. e27539. <https://doi.org/10.4161/sgtp.27539>
- Ramachandran C., Patil R.V., Combrink K., Sharif N.A., Srinivas S.P. 2011. Rho-Rho kinase pathway in the actomyosin contraction and cell-matrix adhesion in immortalized human trabecular meshwork cells. *Mol. Vision*. V. 17. P. 1877. <https://doi.org/PMC3144732>
- Rane C.K., Minden A. 2014. P21 activated kinases. *Small GTPases*. 2014. V. 5. P. e28003. <https://doi.org/10.4161/sgtp.28003>
- Ratushnyy A., Ezdakova M., Buravkova L. 2020. Secretome of senescent adipose-derived mesenchymal stem cells negatively regulates angiogenesis. *Int. J. Mol. Sci*. V. 21. <https://doi.org/10.3390/ijms21051802>
- Ren R., Humphrey A. A., Koczynski C., Gong H. 2023. Rho kinase inhibitor AR-12286 reverses steroid-induced changes in intraocular pressure, effective filtration areas, and morphology in mouse eyes. *Investig. Ophthalmol. Vis. Sci*. V. 64. P. 7. <https://doi.org/10.1167/iovs.64.2.7>
- Ridley A.J. 2015. Rho GTPase signalling in cell migration. *Curr. Opin. Cell Biol*. 2015. V. 36. P. 103. <https://doi.org/10.1016/j.ccb.2015.08.005>
- Rotblat B., Ehrlich M., Haklai R., Kloog, Y. 2008. The Ras inhibitor farnesylthiosalicylic acid (Salirasib) disrupts the spatiotemporal localization of active Ras: a potential treatment for cancer. *Meth. Enzymol*. V. 439. P. 467–489. [https://doi.org/10.1016/S0076-6879\(07\)00432-6](https://doi.org/10.1016/S0076-6879(07)00432-6)
- Sadok A., Marshall C.J. 2014. Rho GTPases: Masters of cell migration. *Small GTPases*. V. 5. P. e983878. <https://doi.org/10.4161/sgtp.29710>
- Sahai E., Olson M.F. 2006. Purification of TAT-C3 exoenzyme. *Meth. Enzymol*. V. 406. P. 128.
- Samsonraj R., Law S., Chandra A., Pignolo R. 2023. An unbiased proteomics approach to identify the senescence-associated secretory phenotype of human bone marrow-derived mesenchymal stem cells. *Bone Rep. V*. 18. P. 101674. <https://doi.org/10.1016/j.bonr.2023.101674>
- Sandrock K., Bielek H., Schradi K., Schmidt G., Klugbauer N. 2010. The nuclear import of the small GTPase Rac1 is mediated by the direct interaction with karyopherin $\alpha 2$. *Traffic*. V. 11. P. 198. <https://doi.org/10.1111/j.1600-0854.2009.01015.x>
- Santos G. L., Hartmann S., Zimmermann W. H., Ridley A., Lutz S. 2019. Inhibition of Rho-associated kinases suppresses cardiac myofibroblast function in engineered connective and heart muscle tissues. *J. Mol. Cell. Cardiol*. V. 134. P. 13. <https://doi.org/10.1016/j.yjmcc.2019.06.015>
- Santos J. C., Profitós-Pelejà N., Sánchez-Vinces S., Roué G. 2023. RHOA therapeutic targeting in hematological cancers. *Cells*. V. 12. P. 433. <https://doi.org/10.3390/cells12030433>
- Sarrabayrouse G., Pich C., Teiti I., Tilkin-Mariame A.F. 2017. Regulatory properties of statins and Rho GTPases prenylation inhibitors to stimulate melanoma immunogenicity and promote anti-melanoma immune

- response. *Int. J. Cancer*. V. 140. P. 747. <https://doi.org/10.1002/ijc.30422>
- Schmidt S. I., Blaabjerg M., Freude K., Meyer M. 2022. RhoA signaling in neurodegenerative diseases. *Cells*. V. 11. P. 1520. <https://doi.org/10.3390/cells11091520>
- Semenova E., Grudniak M. P., Machaj E.K., Bocian K., Chroscinska-Krawczyk M., Trochonowicz M., Stepaniec I.M., Murzyn M., Zagorska K.E., Boruczowski D., Kolanowski T.J., Oldak T., Rozwadowska N. 2021. Mesenchymal stromal cells from different parts of umbilical cord: approach to comparison and characteristics. *Stem Cell Rev. Rep.* V. 17. P. 1. <https://doi.org/10.1007/s12015-021-10157-3>
- Shan D., Chen L., Njardarson J.T., Gaul C., Ma X., Danishefsky S.J., Huang X.Y. 2005. Synthetic analogues of migrastatin that inhibit mammary tumor metastasis in mice. *Proc. Natl. Acad. Sci. USA*. 2005. V. 102. P. 3772.
- Shang X., Marchioni F., Evelyn C.R., Sipes N., Zhou X., Seibel W., Wortman M., Zheng Y., 2013. Small-molecule inhibitors targeting G-protein-coupled Rho guanine nucleotide exchange factors. *Proc. Natl. Acad. Sci. USA*. 2013. V. 110. P. 3155.
- Shang X., Marchioni F., Sipes N., Evelyn C. R., Jerabek-Willemsen M., Duhr S., Seibel W., Wortman M., Zheng Y. 2012. Rational design of small molecule inhibitors targeting RhoA subfamily Rho GTPases. *Chem. Biol.* V. 19. P. 699. <https://doi.org/10.1016/j.chembiol.2012.05.009>
- Shi J., Wei L. 2013. Rho kinases in cardiovascular physiology and pathophysiology: the effect of fasudil. *J. Cardiovasc. Pharmacol.* V. 62. <https://doi.org/10.1097/FJC.0b013e3182a3718f>
- Shimizu A., Nakayama H., Wang P., König C., Akino T., Sandlund J., Klagsbrun M. 2013. Netrin-1 promotes glioblastoma cell invasiveness and angiogenesis by multiple pathways including activation of RhoA, cathepsin B, and cAMP-response element-binding protein. *J. Biol. Chem.* V. 288. P. 2210.
- Shin S., Lee J., Kwon Y., Park K-S., Jeong J-H., Choi S-J., Bang S., Chang J., Lee C. 2021. Comparative proteomic analysis of the mesenchymal stem cells secretome from adipose, bone marrow, placenta and Wharton's jelly. *Int. J. Mol. Sci.* V. 22. P. 845. <https://doi.org/10.3390/ijms22020845>
- Sousa A. Coelho P., Leite F., Teixeira C., Rocha A., Santos I., Baylina P., Fernandes R., Soares R., Costa R, Gomes A. 2023. Impact of umbilical cord mesenchymal stromal/stem cell secretome and cord blood serum in prostate cancer progression. *Hum. Cell*. V. 36. P. 1160.
- Spiering D., Hodgson L. 2011. Dynamics of the Rho-family small GTPases in actin regulation and motility. *Cell Adh. Migr.* V. 5. P. 170. <https://doi.org/10.4161/cam.5.2.14403>
- Surviladze Z., Waller A., Wu Y., Romero E., Edwards B.S., Wandinger-Ness A., Sklar L.A. 2010. Identification of a small GTPase inhibitor using a high-throughput flow cytometry bead-based multiplex assay. *J. Biomol. Screen.* V. 15. P. 10. <https://doi.org/10.1177/1087057109352240>
- Szczepanowska J. 2009. Involvement of Rac/Cdc42/PAK pathway in cytoskeletal rearrangements. *Acta Biochimica Polonica*. V. 56. P. 225.
- Taniuchi K., Yokotani K., Saibara T. 2012. BART inhibits pancreatic cancer cell invasion by Rac1 inactivation through direct binding to active Rac1. *Neoplasia*. V. 14. P. 440. <https://doi.org/10.1593/neo.12352>
- Tong J., Li L., Ballermann B., Wang Z. 2016. Phosphorylation and activation of RhoA by ERK in response to epidermal growth factor stimulation. *PLoS One*. V. 11. P. e0147103. <https://doi.org/10.1371/journal.pone.0147103>
- Turano E., Scambi I., Virla F., Bonetti B., Mariotti R. 2023. Extracellular vesicles from mesenchymal stem cells: towards novel therapeutic strategies for neurodegenerative diseases. *Int. J. Mol. Sci.* V. 24. P. 2917. <https://doi.org/10.3390/ijms24032917>
- Turinetto V., Vitale E., Giachino C. 2016. Senescence in human mesenchymal stem cells: Functional changes and implications in stem cell-based therapy. *Int. J. Mol. Sci.* V. 17. P. 1164. <https://doi.org/10.3390/ijms17071164>
- Ueyama T., Geiszt M., Leto T.L. 2006. Involvement of Rac1 in activation of multicomponent Nox1- and Nox3-based NADPH oxidases. *Mol. Cell. Biol.* V. 26. P. 2160. <https://doi.org/10.1128/MCB.26.6.2160-2174.2006>
- Umbayev B., Yermekova A., Nessipbekova A., Syzdykova A., Askarova S. 2023. Role of a small GTPase Cdc42 in aging and age-related diseases. *Biogerontology*. P. 1. <https://doi.org/10.1007/s10522-022-10008-9>
- Unbekandt M., Croft D. R., Crighton D., Mezna M., McArthur D., McConnell P., Olson M. F. 2014. A novel small-molecule MRCK inhibitor blocks cancer cell invasion. *Cell Commun. Signal.* V. 12. P. 1. <https://doi.org/10.1186/s12964-014-0054-x>
- Unsal-Kacmaz K., Ragunathan S., Rosfjord E., Dann S., Upeklacis E., Grillo M., Hernandez R., Mack F., Klippel A. 2012. The interaction of PKN3 with RhoC promotes malignant growth. *Mol. Oncol.* V. 6. P. 284. <https://doi.org/10.1016/j.molonc.2011.12.001>
- Van Aelst L., D'Souza-Schorey C. 1997. Rho GTPases and signaling networks. *Genes Dev.* V. 18. P. 2295. <https://doi.org/10.1101/gad.11.18.2295>
- Van Buul J. D., Geerts D., Huvenceers S. 2014. Rho GAPs and GEFs: controlling switches in endothelial cell adhesion. *Cell Adh. Migr.* V. 8. P. 108. <https://doi.org/10.4161/cam.27599>
- Vidal C., Geny B., Melle J., Jandrot-Perrus M., Fontenay-Roupie M. 2002. Cdc42/Rac1-dependent activation of the p21-activated kinase (PAK) regulates human platelet lamellipodia spreading: implication of the cortical-actin binding protein cortactin. *Blood*. V. 100. P. 4462.
- Wang L., Yang L., Tian L., Mai P., Jia S., Yang L., Li L. 2017. Cannabinoid receptor 1 mediates homing of bone marrow-derived mesenchymal stem cells triggered by chronic liver injury. *J. Cell. Physiol.* V. 232. P. 110.
- Williams C.L. 2003. The polybasic region of Ras and Rho family small GTPases: a regulator of protein interactions and membrane association and a site of nuclear localization signal sequences. *Cell. Signal.* V. 15. P. 1071. [https://doi.org/10.1016/s0898-6568\(03\)00098-6](https://doi.org/10.1016/s0898-6568(03)00098-6)
- Xin Y.L., Yu J.Z., Yang X.W., Liu C.Y., Li Y.H., Feng L., Chai Z., Wan-Fang Yang W.F., Qing Wang Q., Jiang W.J., Zhang G.X., Xiao B.G., Ma C.G. 2015. FSD-C10: A more promising novel ROCK inhibitor than Fasudil for

- treatment of CNS autoimmunity. *Bioscience Rep.* V. 35. <https://doi.org/10.1042/BSR20150032>
- Xu J., Li Y., Yang X., Chen Y., Chen M. 2013. Nuclear translocation of small G protein RhoA via active transportation in gastric cancer cells. *Oncol. Rep.* V. 30. P. 1878. <https://doi.org/10.3892/or.2013.2638>
- Yang B., Radel C., Hughes D., Kelemen S., Rizzo V. 2011. p190 RhoGTPase-activating protein links the β 1 integrin/caveolin-1 mechanosignaling complex to RhoA and actin remodeling. *Arterioscler. Thromb. Vasc. Biol.* V. 31. P. 376. <https://doi.org/10.1161/ATVBAHA.110.217794>
- Yang Y., Zhang W., Wang X., Yang J., Cui Y., Song H., Li W., Li W., Wu L., Du Y., He Z., Shi J., Zhang J. 2023. A passage-dependent network for estimating the in vitro senescence of mesenchymal stromal/stem cells using microarray, bulk and single cell RNA sequencing. *Front. Cell Dev. Biol.* V. 11: 998666. <https://doi.org/10.3389/fcell.2023.998666>
- Zhang Q. G., Wang R., Han D., Dong Y., Brann D. W. 2009. Role of Rac1 GTPase in JNK signaling and delayed neuronal cell death following global cerebral ischemia. *Brain Res.* V. 1265. P. 138.
- Zhang Z., Liu M., Zheng Y. 2021. Role of Rho GTPases in stem cell regulation. *Biochem. Soc. Trans.* V. 49. P. 2941. <https://doi.org/10.1042/BST20211071>
- Zins K., Lucas T., Reichl P., Abraham D., Aharinejad S. 2013. A Rac1/Cdc42 GTPase-specific small molecule inhibitor suppresses growth of primary human prostate cancer xenografts and prolongs survival in mice. *PloS one.* V. 8. P. 74924. <https://doi.org/10.1371/journal.pone.0074924>

THE ROLE OF THE Rho FAMILY SMALL GTPases IN REGULATION OF NORMAL AND PATHOLOGICAL PROCESSES

D. E. Bobkov^{a, b, c, *}, A. V. Lukacheva^a, A. I. Gorb^d, G. G. Poljanskaya^a

^a Institute of Cytology RAS, St. Petersburg, 194064, Russia

^b Almazov National Medical Research Centre, St. Petersburg, 197341, Russia

^c Smorodintsev Research Institute of Influenza, St. Petersburg, 197376, Russia

^d Peter the Great St. Petersburg Polytechnic University, St. Petersburg, 194064, Russia

*E-mail: bobkov@incras.ru

Small GTPases are small (about 21 kDa) proteins that regulate many biological processes, such as vesicle transport, cell division cycle, cell migration, invasion, adhesion, proliferation and DNA repair, they are involved in carcinogenesis and neurodegenerative diseases. Some of these proteins, like those in the Rho family, are important regulators of the actin cytoskeleton, which has an impact on cell adhesion and motility. The review considers normal and pathological processes in human cells, which are regulated by the Rho family small GTPases. Particular attention is paid to inhibitors of small GTPases and their use in the treatment of various diseases.

Keywords: cytoskeleton, small GTPases, Rho, ROCK, mesenchymal stem cells, replicative senescence, carcinogenesis, invasion