аутофагии и шаперонов позволит увеличить генетическую нестабильность опухолей, увеличить апоптоз, привести к сбою процессов синтеза и деградации белков. Таким образом, ингибирование систем протеостаза позволит модулировать клеточные процессы на клеточном и белковом уровне, а также на уровне ДНК.

ЗАКЛЮЧЕНИЕ

В результате интегрированного ответа опухолевой клетки на стресс, который часто активирует проводимая терапия, клетка движется по определенным "рельсам", приобретая все большую автономность и злокачественность. Это дает ей возможность прогрессировать гораздо быстрее, чем это позволили бы ей сделать случайные мутации. В числе прочих реакций на стресс активируются аутофагия и шапероны. Это позволяет клетке обрести все большую независимость от микроокружения, приобрести стволовые свойства и лекарственную устойчивость, избежать апоптоза, восстановить стабильность ДНК и в дальнейшем активно пролиферировать, приводя к рецидивам онкозаболеваний. По всей видимости, ответ на стресс сопровождается активацией адаптивных генов, способствующих выживанию, и приводит к определенному эволюционному упрощению, позволяющему клетке активно делиться. Понимание этих механизмов делает возможным разработку новых терапевтических подходов, основанных на нивелировании клеточного ответа на стресс.

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СПИСОК ЛИТЕРАТУРЫ

Aggarwal S., Tsuruo T., Gupta S.J. 1997. Altered expression and function of P-glycoprotein (170 kDa), encoded by the MDR 1 gene, in T cell subsets from aging humans. Clin. Immunol. V. 17. P. 448. https://doi.org/10.1023/a:1027363525408

Albakova Z., Armeev G.A., Kanevski L.M., Kovalenko E.I., Sapozhnikov A.M. 2020. HSP70 multi-functionality in cancer. Cells. V. 9. P. 587. https://doi.org/10.3390/cells9030587

Anand S.K., Sharma A., Singh N., Kakkar P. 2020. Entrenching role of cell cycle checkpoints and autophagy for maintenance of genomic integrity. DNA Repair (Amst). V. 86. P. 102748. https://doi.org/10.1016/j.dnarep.2019.102748

Apel A., Herr I., Schwarz H., Rodemann P., Mayer A. 2008. Blocked autophagy sensitizes resistant carcinoma cells to radiation therapy. Cancer Res. V. 68. P. 1485. https://doi.org/10.1158/0008-5472.CAN-07-0562

Benassi B., Fanciulli M., Fiorentino F., Porrello A., Chiorino G., Loda M., Zupi G., Biroccio A. 2006. c-Myc phosphorylation is required for cellular response to oxidative stress. Mol. Cell. V. 21. P. 509. https://doi.org/10.1016/j.molcel.2006.01.009

Bradley E., Bieberich E., Mivechi N.F., Tangpisuthipongsa D., Wang G. 2012. Regulation of embryonic stem cell pluripotency by heat shock protein 90. Stem Cells. V. 30. P. 1624. https://doi.org/10.1002/stem.1143

Büchler P., Reber H.A., Lavey R.S., Tomlinson J., Büchler M.W., Friess H., Hines O.J. 2004. Tumor hypoxia correlates with metastatic tumor growth of pancreatic cancer in an orthotopic murine model. J. Surg. Res. V. 120. P. 295. https://doi.org/10.1016/j.jss.2004.02.014

Chakraborty C., Agoramoorthy G. 2012. Stem cells in the light of evolution. Indian J. Med. Res. V. 135. P. 813.

Chao T., Shih H.T., Hsu S.C., Chen P.J., Fan Y.S., Jeng Y.M., Shen Z.Q., Tsai T.F., Chang Z.F. 2021. Autophagy restricts mitochondrial DNA damage-induced release of ENDOG (endonuclease G) to regulate genome stability. Autophagy. V. 17. P. 3444. https://doi.org/10.1080/15548627.2021.1874209

Chen N., Karantza-Wadsworth V. 2009. Role and regulation of autophagy in cancer. Biochim. Biophys. Acta. V. 1793. P. 1516. https://doi.org/10.1016/j.bbamcr.2008.12.013

Condon K.J., Sabatini D.M. 2019. Nutrient regulation of mTORC1 at a glance. J. Cell Sci. V. 132. P. jcs222570. https://doi.org/10.1242/jcs.222570

Das C.K., Mandal M., Kögel D. 2018a. Pro-survival autophagy and cancer cell resistance to therapy. Cancer Metastasis Rev. V. 37. P. 749. https://doi.org/10.1007/s10555-018-9727-z

Das C.K., Linder B., Bonn F., Rothweiler F., Dikic I., Michaelis M., Cinatl J., Mandal M., Kögel D. 2018b. BAG3 overexpression and cytoprotective autophagy mediate apoptosis resistance in chemoresistant breast cancer cells. Neoplasia. V. 20. P. 263. https://doi.org/10.1016/j.neo.2018.01.001

Dinić J., Podolski-Renić A., Jovanović M., Musso L., Tsakovska I., Pajeva I., Dallavalle S., Pešić M. 2019. Novel heat shock protein 90 inhibitors suppress P-Glycoprotein activity and overcome multidrug resistance in cancer cells. Int. J. Mol. Sci. V. 20. P. 4575. https://doi.org/10.3390/ijms20184575

Dubrez L., Causse S., Bonan N.B., Dumétier B., Garrido C. 2020. Heat-shock proteins: chaperoning DNA repair. Oncogene. V. 39. P. 516. https://doi.org/10.1038/s41388-019-1016-y

Erenpreisa J., Salmina K., Anatskaya O., Cragg M.S. 2022. Paradoxes of cancer: survival at the brink. Semin. Cancer Biol. V. 81. P. 119. https://doi.org/10.1016/j.semcancer.2020.12.009

Feng Y., Klionsky D.J. 2017. Autophagy regulates DNA repair through SQSTM1/p62. Autophagy. V. 13. P. 995. https://doi.org/10.1080/15548627.2017.1317427

Galati S., Boni C., Gerra M.C., Lazzaretti M., Buschini A. 2019. Autophagy: a player in response to oxidative stress and DNA damage. Oxid. Med. Cell Longev. V. 2019. P. 5692958. https://doi.org/10.1155/2019/5692958

Gomes L.R., Menck C.F.M., Leandro G.S. 2017. Autophagy roles in the modulation of DNA repair pathways. Int. J. Mol. Sci. V. 18. P. 2351 https://doi.org/10.3390/ijms18112351

Gremke N., Polo P., Dort A., Schneikert J., Elmshäuser S., Brehm C., Klingmüller U., Schmitt A., Reinhardt H.C., Timofeev O., Wanzel M., Stiewe T. 2020. mTOR-mediated cancer drug resistance suppresses autophagy and generates a druggable metabolic vulnerability. Nat. Commun. V. 11. P. 4684. https://doi.org/10.1038/s41467-020-18504-7

Hewitt G., Korolchuk V.I. 2017. Repair, reuse, recycle: The expanding role of autophagy in genome maintenance. Trends Cell Biol. V. 27. P. 340. https://doi.org/10.1016/j.tcb.2016.11.011

Ikwegbue P.C., Masamba P., Mbatha L.S., Oyinloye B.E., Kappo A.P. 2019. Interplay between heat shock proteins, inflammation and cancer: a potential cancer therapeutic target. Am. J. Cancer Res. V. 9. P. 242.

Jewer M., Lee L., Leibovitch M., Zhang G., Liu J., Findlay S.D., Vincent K.M., Tandoc K., Dieters-Castator D., Quail D.F., Dutta I., Coatham M., Xu Z., Puri A., Guan B.J. et al. 2020. Translational control of breast cancer plasticity. Nat. Commun. V. 11. P. 2498. https://doi.org/10.1038/s41467-020-16352-z

Juretschke T., Beli P. 2021. Causes and consequences of DNA damage-induced autophagy. Matrix Biol. V. 100–101. P. 39. https://doi.org/10.1016/j.matbio.2021.02.004

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. https://doi.org/10.1074/jbc.273.35.22284

Karabicici M., Alptekin S., Fırtına Karagonlar Z., Erdal E. 2021. Doxorubicin-induced senescence promotes stemness and tumorigenicity in EpCAM-/CD133- nonstem cell population in hepatocellular carcinoma cell line, HuH-7. Mol. Oncol. V. 15. P. 2185. https://doi.org/10.1002/1878-0261.12916

Kim H.B., Lee S.H., Um J.H., Oh W.K., Kim D.W., Kang C.D., Kim S.H. 2015a. Sensitization of multidrug-resistant human cancer cells to Hsp90 inhibitors by down-regulation of SIRT1. Oncotarget. V. 6. P. 36202. https://doi.org/10.18632/oncotarget.5343

Kim B.M., Hong Y., Lee S., Liu P., Lim J.H., Lee Y.H., Lee T.H., Chang K.T., Hong Y. 20156. Therapeutic implications for overcoming radiation resistance in cancer therapy. Int. J. Mol. Sci. V. 16. P. 26880. https://doi.org/10.3390/ijms161125991

Kögel D., Linder B., Brunschweiger A., Chines S., Behl C. 2020. At the crossroads of apoptosis and autophagy: multiple roles of the co-chaperone BAG3 in stress and therapy resistance of cancer. Cells. V. 9. P. 574. https://doi.org/10.3390/cells9030574

Kumar S., Stokes J. 3rd, Singh U.P., Scissum Gunn K., Acharya A., Manne U., Mishra M. 2016. Targeting Hsp70: A possible therapy for cancer. Cancer Lett. V. 374. P. 156. https://doi.org/10.1016/j.canlet.2016.01.056

Li Y.J., Lei Y.H., Yao N., Wang C.R., Hu N., Ye W.C., Zhang D.M., Chen Z.S., Chin J. 2017. Autophagy and multidrug resistance in cancer. Cancer. V. 36. P. 52. https://doi.org/10.1186/s40880-017-0219-2

Liang B., Liu X., Liu Y., Kong D., Liu X., Zhong R., Ma S. 2016. Inhibition of autophagy sensitizes MDR-phenotype ovarian cancer SKVCR cells to chemotherapy. Biomed. Pharmacother. V. 82. P. 98. https://doi.org/10.1016/j.biopha.2016.04.054

Lin F., Gao L., Su Z., Cao X., Zhan Y., Li Y., Zhang B. 2018. Knockdown of KPNA2 inhibits autophagy in oral squamous cell carcinoma cell lines by blocking p53 nuclear translocation. Oncol. Rep. V. 40. P. 179. https://doi.org/10.3892/or.2018.6451

Liu J., Chang B., Li Q., Xu L., Liu X., Wang G., Wang Z., Wang L. 2019. Redox-responsive dual drug delivery nanosystem suppresses cancer repopulation by abrogating doxorubicin-promoted cancer stemness, metastasis, and drug resistance. Adv. Sci. (Weinh). V. 6. P. 1801987. https://doi.org/10.1002/advs.201801987

Margulis B., Tsimokha A., Zubova S., Guzhova I. 2020. Molecular chaperones and proteolytic machineries regulate protein homeostasis in aging cells. Cells. V. 9. P. 1308. https://doi.org/10.3390/cells9051308

Mehta A.P., Supekova L., Chen J.H., Petonjamasp K., Webster P., Ko Y., Henderson S.C., McDermott G., Supek F., Schullz P.G. 2018. Engineering yeast endosymbionts as a step toward the evolution of mitochondria. Proc. Natl. Acad. Sci. USA. V. 115. P. 11796–11801. https://doi.org/10.1073/pnas.1813143115

Mendez F., Sandigursky M., Franklin W.A., Kenny M.K., Kureekattil R., Bases R. 2000. Heat-shock proteins associated with base excision repair enzymes in HeLa cells. Radiat Res. 153:186–195. https://doi.org/10.1667/0033-7587(2000)153[0186:hspawb]-2.0.co;2

Menendez J.A., Vellon L., Oliveras-Ferraros C., Cufí S., Vazquez-Martin A. 2011. mTOR-regulated senescence and autophagy during reprogramming of somatic cells to pluripotency: a roadmap from energy metabolism to stem cell renewal and aging. Cell Cycle. V. 10. P. 3658. https://doi.org/10.4161/cc.10.21.18128

Mizushima N. 2007. Autophagy: process and function. Genes Dev. V. 21. P. 2861. https://doi.org/10.1101/gad.1599207

Ozates N.P., Soğutlu F., Lerminoglu F., Demir B., Gunduz C., Shademan B. 2021. Effects of rapamycin and AZD3463 combination on apoptosis, autophagy, and cell cycle for resistance control in breast cancer. Life Sci. V. 264. P. 118643. https://doi.org/10.1016/j.lfs.2020.118643

Pan Y., Gao Y., Chen L, Gao G., Dong H., Yang Y., Dong B., Chen X. 2011. Targeting autophagy augments in vitro and in vivo antimyeloma activity of DNA-damaging chemotherapy. Clin. Cancer Res. V. 17. P. 3248. https://doi.org/10.1158/1078-0432.CCR-10-0890

Pandita T.K., Higashikubo R., Hunt C.R. 2004. HSP70 and genomic stability. Cell Cycle. V. 3. P. 591. https://doi.org/10.4161/cc.3.5.863

Pani G., Galeotti T., Chiarugi P. 2010. Metastasis: cancer cell's escape from oxidative stress. Cancer Metastasis Rev. V. 29. P. 351. https://doi.org/10.1007/s10555-010-9225-4

Pennisi R., Ascenzi P., di Masi A. 2015. Hsp90: a new player in DNA repair? Biomolecules. V. 5. P. 2589. https://doi.org/10.3390/biom5042589

Quanz M., Herbette A., Sayarath M., Koning L., Dubois T., Sun J.S., Dutreix M. 2012. Heat shock protein 90α (Hsp90α) is phosphorylated in response to DNA damage and accumulates in repair foci. J. Biol. Chem. V. 287. P. 8803. https://doi.org/10.1074/jbc.M111.320887

Roshani-Asl E., Mansori B., Mohammadi A., Najafi S., Danesh-Pouya F., Rasmi Y. 2020. Interaction between DNA damage response and autophagy in colorectal cancer. Gene. V. 730. P. 144323. https://doi.org/10.1016/j.gene.2019.144323

Roufayel R., Kadry S. 2019. Molecular chaperone HSP70 and key regulators of apoptosis – A review. Curr. Mol. Med. V. 19. P. 315. https://doi.org/10.2174/1566524019666190326114720

Sannino S., Yates M.E., Schurdak M.E., Oesterreich S., Lee A.V., Wipf P., Brodsky J.L. 2021. Unique integrated stress response sensors regulate cancer cell susceptibility when Hsp70 activity is compromised. Elife. V. 10. P. e64977. https://doi.org/10.7554/eLife.64977

Smith A.G., Macleod K.F. 2019. Autophagy, cancer stem cells and drug resistance. J. Pathol. V. 7. P. 708. https://doi.org/10.1002/path.5222

Song X., Lee D.H., Dilly A.K., Lee Y.S., Choudry H.A., Kwon Y.T., Bartlett D.L., Lee Y.J. 2018. Crosstalk between apoptosis and autophagy is regulated by the arginylated BiP/Beclin-1/p62 complex. Mol. Cancer Res. V. 16. P. 1077. https://doi.org/10.1158/1541-7786.MCR-17-0685

Sottile M.L., Nadin S.B. 2018. Heat shock proteins and DNA repair mechanisms: an updated overview. Cell Stress Chaperones. V. 23. P. 303. https://doi.org/10.1007/s12192-017-0843-4

Stagni V., Ferri A., Cirotti C., Barilà D. 2021. ATM kinase-dependent regulation of autophagy: a key player in senescence? Front. Cell Dev. Biol. V. 8. P. 599048. https://doi.org/10.3389/fcell.2020.599048

Sun W.L., Lan D., Gan T.Q., Cai Z.W. 2015. Autophagy facilitates multidrug resistance development through inhibition of apoptosis in breast cancer cells. Neoplasma. V. 62. P. 199. https://doi.org/10.4149/neo_2015_025

Tabata M., Tsubaki M., Takeda T., Tateishi K., Maekawa S., Tsurushima K., Imano M., Satou T., Ishizaka T., Nishida S. 2020. Inhibition of HSP90 overcomes melphalan resistance through downregulation of Src in multiple myeloma cells. Clin. Exp. Med. V. 20. P. 63. https://doi.org/10.1007/s10238-019-00587-2

Tian X., Zhang S., Zhou L., Seyhan A.A., Hernandez Borrero L., Zhang Y., El-Deiry W.S. 2021. Targeting the integrated stress response in cancer therapy. Front. Pharmacol. V. 12. P. 747837. https://doi.org/10.3389/fphar.2021.747837

Tian Z.C., Wang J.Q., Ge H.J. 2019. Apatinib ameliorates doxorubicin-induced migration and cancer stemness of osteosarcoma cells by inhibiting Sox2 via STAT3 signalling. Orthop. Translat. V. 22. P. 132. https://doi.org/10.1016/j.jot.2019.07.003

Trigos A.S, Pearson R.B, Papenfuss A.T, Goode D.L. 2017. Altered interactions between unicellular and multicellular genes drive hallmarks of transformation in a diverse range of solid tumors. Proc. Natl. Acad. Sci. USA. V. 114. P. 6406.

Vilaboa N.E., Galán A., Troyano A., de Blas E., Aller P. 2000. Regulation of multidrug resistance 1 (MDR1)/P-glycoprotein gene expression and activity by heat-shock transcription factor 1 (HSF1). J. Biol. Chem. V. 275. P. 24970. https://doi.org/10.1074/jbc.M909136199

Vilas-Boas V., Silva R., Gaio A.R., Martins A.M., Lima S.C., Cordeiro-da-Silva A., Bastos M.L., Remião F. 2011. P-glycoprotein activity in human Caucasian male lymphocytes does not follow its increased expression during aging. Cytometry A. V. 79. P. 912. https://doi.org/10.1002/cyto.a.21135

Wang R., Shao F., Liu Z., Zhang J., Wang S., Liu J., Liu H., Chen H., Liu K., Xia M., Wang Y. 2013. The Hsp90 inhibitor SNX-2112, induces apoptosis in multidrug resistant K562/ADR cells through suppression of Akt/NF-κB and disruption of mitochondria-dependent pathways. Chem. Biol. Interact. V. 205. P. 1. https://doi.org/10.1016/j.cbi.2013.06.007

Wang Y., Zhang N., Zhang L., Li R., Fu W., Ma K., Li X., Wang L., Wang J., Zhang H., Gu W., Zhu W.G., Zhao Y. 2016. Autophagy regulates chromatin ubiquitination in DNA damage response through elimination of SQSTM1/p62. Mol. Cell. V. 63. P. 34. https://doi.org/10.1016/j.molcel.2016.05.027

Wang F., Xia X., Yang C., Shen J., Mai J., Kim H.C., Kirui D., Kang Y., Fleming J.B., Koay E.J., Mitra S., Ferrari M., Shen H. 2018. *SMAD4* Gene mutation renders pancreatic cancer resistance to radiotherapy through promotion of autophagy. Clin. Cancer Res. V. 24. P. 3176. https://doi.org/10.1158/1078-0432.CCR-17-3435

Wawrzynow B., Zylicz A., Zylicz M. 2018. Chaperoning the guardian of the genome. The two-faced role of molecular chaperones in p53 tumor suppressor action. Biochim. Biophys. Acta Rev. Cancer. V. 1869. P. 161. https://doi.org/10.1016/j.bbcan.2017.12.004

Yang S., Wang X., Contino G., Liesa M, Sahin E., Ying H., Bause A., Li Y., Stommel J.M., Dell'antonio G., Mautner J., Tonon G., Haigis M., Shirihai O.S., Doglioni C. et al. 2011. Pancreatic cancers require autophagy for tumor growth. Genes Dev. V. 25. P. 717. https://doi.org/10.1101/gad.2016111

Zhang D., Tang B., Xie X., Xiao Y.F., Yang S.M., Zhang J.W. 2015. The interplay between DNA repair and autophagy in cancer therapy. Cancer Biol. Ther. V. 16. P. 1005. https://doi.org/10.1080/15384047.2015.1046022

Zhang H., Chen J., Zeng Z., Que W., Zhou L. 2013. Knockdown of DEPTOR induces apoptosis, increases chemosensitivity to doxorubicin and suppresses autophagy in RPMI-8226 human multiple myeloma cells *in vitro*. Int. J. Mol. Med. V. 31. P. 1127. https://doi.org/10.3892/ijmm.2013.1299

The Role of the Integrated Response of Tumor Cells to Stress, Autophagy, and Chaperones in the Origin of Recurrent Resistant Tumors

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Chemotherapy and radiotherapy are a colossal stress factor for tumor cells. In response to therapy, the entire evolutionarily fixed response of cells to stress is activated. This happens at all levels of cell organization, namely at the protein level and the DNA level. This response involves the cell proteostasis system, DNA repair systems, tumor suppressor genes, and many other cell systems. We will consider the role of the main systems of proteostasis in these processes, namely, macroautophagy and chaperones, which are part of the integrated response of the cell to stress. As a result of the cell's response to stress, the tumor cell becomes even less differentiated, activating the genes and intracellular systems necessary for survival. Cells that have responded to stress in this way have a more aggressive phenotype that is significantly more resistant to therapy. Under the influence of stress, the cell evolutionarily simplifies, which gives it additional chances for survival. On the one hand, autophagy contributes to a decrease in tumor cell differentiation and its plasticity, and on the other hand, it maintains a certain stability, being responsible for the integrity of the genome and freeing the cell from damaged organelles and defective proteins. Both autophagy and chaperones contribute to the acquisition of multidrug resistance by the tumor, which further complicates therapy. Understanding these processes makes it possible to develop new therapeutic approaches, taking into account the multistage nature of carcinogenesis.

Keywords: autophagy, chaperones, DNA stability, MDR phenotype, aging, apoptosis, stemness