НАУКА ЮГА РОССИИ 2025 Т. 21 № 3 С. 75–80
SCIENCE IN THE SOUTH OF RUSSIA 2025 VOL. 21 No. 3 P. 75–80

БИОЛОГИЯ

УДК 616-002.04:577.2
DOI: 10.7868/S25000640250311

(ПРО)РЕНИНОВЫЙ РЕЦЕПТОР – НОВЫЙ ОНКОМАРКЕР

© 2025 г. Е.А. Черногубова[1], А.Н. Машкарина[1]

Аннотация. Несмотря на значительный прогресс в понимании молекулярных механизмов инициации и развития рака, отмечается неуклонный рост заболеваемости злокачественными новообразованиями. В связи с этим приоритетным направлением исследований остается идентификация молекулярных маркеров и молекулярных мишеней онкологических заболеваний человека, новых диагностических маркеров инициации, развития и прогрессии злокачественных опухолей.

Ренин-ангиотензиновый каскад представляет собой физиологический путь, способствующий пролиферации опухолевых клеток, ангиогенезу и воспалительной реакции в опухолевой ткани, инвазии и метастазированию. (Про)ренинoвый рецептор ((P)RR)/MAP-киназа – альтернативный путь регуляции ренин-ангиотензиновой системы (РАС).

Цель обзора – проанализировать роль (про)ренинового рецептора в молекулярных механизмах канцерогенеза, оценить его перспективы стать новым биомаркером и потенциальной терапевтической мишенью для диагностики, лечения и прогнозирования рака.

Рецептор (про)ренина идентифицирован как новый член локальной РАС. Первоначально наши знания о (P)RR в основном ограничивались данными о его роли в физиологических процессах, при сердечно-сосудистых заболеваниях и болезнях почек. За последние годы убедительно доказано, что (P)RR аберрантно экспрессируется и способствует развитию различных видов рака. Проанализирована потенциальная роль (P)RR в молекулярных механизмах инициации и прогрессии различных видов рака. (P)RR играет важную роль в таких онко-ассоциированных сигнальных путях, как Wnt/β-катенин, РАС, MAPK/ERK и PI3K/AKT/mTOR.

Установлена взаимосвязь между уровнем экспрессии (P)RR и его растворимой формы (s(P)RR) с развитием злокачественных новообразований. s(P)RR может быть новым неинвазивным биомаркером для злокачественных новообразований, но необходимы дальнейшие исследования для определения его диагностической ценности.

Таким образом, (про)ренинoвый рецептор, включая его полноразмерную форму в опухолевых тканях и растворимую форму в крови, имеет значительный потенциал в качестве нового биомаркера для диагностики злокачественных новообразований.

Ключевые слова: злокачественные новообразования, ренин-ангиотензиновая система, (про)ренинoвый рецептор, растворимый (про)ренинoвый рецептор, канцерогенез.

(PRO)RENIN RECEPTOR – A NEW CANCER MARKER

E.A. Chernogubova[1], A.N. Mashkarina[1]

Abstract. Despite significant progress in understanding the molecular mechanisms of cancer initiation and development, there has been a steady increase in the incidence of malignant neoplasms. In this regard, the identification of molecular markers and molecular targets of human cancer diseases, new diagnostic markers of the initiation, development and progression of malignant tumors remains a priority area of research.

The renin-angiotensin cascade is a physiological pathway that promotes the proliferation of tumor cells, angiogenesis and inflammatory response in tumor tissue, invasion and metastasis. (Pro)renin receptor ((P)RR)/MAP kinase is an alternative pathway of regulation of the renin-angiotensin system (RAS).

[1] Федеральный исследовательский центр Южный научный центр Российской академии наук (Federal Research Centre the Southern Scientific Centre of the Russian Academy of Sciences, Rostov-on-Don, Russian Federation), Российская Федерация, 344006, г. Ростов-на-Дону, пр. Чехова, 41, e-mail: eachernogubova@mail.ru, aina_mashkarina@mail.ru

The purpose of the review is to analyze the role of the (pro)renin receptor in the molecular mechanisms of carcinogenesis, to assess its prospects for role of a new biomarker and a potential therapeutic target for the diagnosis, treatment and prognosis of cancer.

The (pro)renin receptor has been identified as a new member of the local RAS. However, our knowledge of (P)RR was mainly limited to its role in physiological processes, in cardiovascular diseases and kidney diseases. In recent years, it has been convincingly proven that (P)RR is aberrantly expressed and contributes to the development of various types of cancer. The review analyzes the potential role of (P)RR in the molecular mechanisms of initiation and progression of various types of cancer. It is shown that (P)RR plays an important role in cancer-associated signaling pathways such as Wnt/β-catenin, RAS, MAPK/ERK, and PI3K/AKT/mTOR.

The relationship between the expression level of (P)RR and its soluble form (s(P)RR) with the development of malignant neoplasms has been established. s(P)RR may be a new non-invasive biomarker for malignancies, but further research is needed to determine its diagnostic value.

Thus, the (pro)renin receptor, including its full-size form in tumor tissues and its soluble form in blood, has significant potential as a new biomarker for the diagnosis of malignant neoplasms.

Keywords: malignant neoplasms, renin-angiotensin system, (pro)renin receptor, soluble (pro)renin receptor, carcinogenesis.

1. Kanugula A.K., Kaur J., Batra J., Ankireddypalli A.R., Velagapudi R. 2023. Renin-angiotensin system: updated understanding and role in physiological and pathophysiological states. *Cureus*. 15(6): e40725. doi: 10.7759/cureus.40725

2. Triebel H., Castrop H. 2024. The renin angiotensin aldosterone system. *Pflügers Archiv European Journal of Physiology.* 476(5): 705–713. doi: 10.1007/s00424-024-02908-1

3. George A.J., Thomas W.G., Hannan R.D. 2010. The renin-angiotensin system and cancer: old dog, new tricks. *Nature Reviews Cancer*. 10(11): 745–759. doi: 10.1038/nrc2945

4. Hassani B., Attar Z., Firouzabadi N. 2023. The renin-angiotensin-aldosterone system (RAAS) signaling pathways and cancer: foes versus allies. *Cancer Cell International* . 23(1): 254. doi: 10.1186/s12935-023-03080-9

5. Santos R.A.S., Oudit G.Y., Verano-Braga T., Canta G., Steckelings U.M., Bader M. 2019. The renin-angiotensin system: going beyond the classical paradigms. *American Journal of Physiology-Heart and Circulatory Physiology.* 316(5): H958–H970. doi: 10.1152/ajpheart.00723.2018

6. Nguyen G., Delarue F., Burcklé C., Bouzhir L., Giller T., Sraer J.-D. 2002. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *The Journal of Clinical Investigation.* 109: 1417–1427. doi: 10.1172/JCI14276

7. Wang J., Nishiyama A., Matsuyama M., Wang Z., Yuan Y. 2020. The (pro)renin receptor: a novel biomarker and potential therapeutic target for various cancers. *Cell Communication and Signaling.* 18(1): 39. doi: 10.1186/s12964-020-0531-3

8. Ichihara A., Yatabe M.S. 2019. The (pro)renin receptor in health and disease. *Nature Reviews Nephrology.* 15(11): 693–712. doi: 10.1038/s41581-019-0160-5

9. Ksiazek S.H., Hu L., Andò S., Pirklbauer M., Säemann M.D., Ruotolo C., Zaza G., La Manna G., De Nicola L., Mayer G., Provenzano M. 2024. Renin–angiotensin–aldosterone system: from history to practice of a secular topic. *International Journal of Molecular Sciences.* 25(7): 4035. doi: 10.3390/ijms25074035

10. Burcklé C., Bader M. 2006. Prorenin and its ancient receptor. *Hypertension.* 48(4): 549–551. doi: 10.1161/01.HYP.0000241132.48495.df

11. Cruciat C.M., Ohkawara B., Acebron S.P., Karaulanov E., Reinhard C., Ingelfinger D., Boutros M., Niehrs C. 2010. Requirement of prorenin receptor and vacuolar H^+-ATPase–mediated acidification for Wnt signaling. *Science.* 327(5964): 459–463. doi: 10.1126/science.1179802

12. Oshima Y., Kinouchi K., Ichihara A., Sakoda M., Kurauchi-Mito A., Bokuda K., Narita T., Kurosawa H., Sun-Wada G.H., Wada Y., Yamada T., Takemoto M., Saleem M.A., Quaggin S.E., Itoh H. 2011. Prorenin receptor is essential for normal podocyte structure and function. *Journal of the American Society of Nephrology*. 22(12): 2203–2212. doi: 10.1681/ASN.2011020202

13. Ouyang X., Xu C. 2023. Targeting the (pro)renin receptor in cancers: from signaling to pathophysiological effects. *Journal of Cancer Research and Clinical Oncology*. 149(6): 2595–2605. doi: 10.1007/s00432-022-04373-8

14. Yamamoto H., Kaneko K., Ohba K., Morimoto R., Hirose T., Satoh F., Totsune K., Takahashi K. 2013. Increased expression of (pro)renin receptor in aldosterone-producing adenomas. *Peptides.* 49: 68–73. doi: 10.1016/j.peptides.2013.08.022.

15. Ohba K., Suzuki T., Nishiyama H., Kaneko K., Hirose T., Totsune K., Sasano H., Takahashi K. 2014. Expression of (pro) renin receptor in breast cancers and its effect on cancercell proliferation. *Biomedical Research.* 35(2): 117–126. doi: 10.2220/biomedres.35.117

16. Shibayama Y., Fujimori T., Nguyen G., Hirose T., Totsune K., Ichihara A., Kitada K., Nakano D., Kobori H., Kohno M., Masaki T., Suzuki Y., Yachida S., Nishiyama A. 2015. (Pro)renin receptor is crucial for Wnt/β-catenin-dependent genesis of pancreatic ductal adenocarcinoma. *Scientific Reports.* 5: 8854. doi: 10.1038/srep0885

17. Arundhathi A., Chuang W.-H., Chen J.-K., Wang S.-E, Shyr Y.-M., Chen J.-Y., Liao W.-N., Chen H.-W., Teng Y.-M., Pai C.-C., Wang C.-H. 2016. Prorenin receptor acts as a potential molecular target for pancreatic ductal adenocarcinoma diagnosis. *Oncotarget.* 7(34): 55437–55448. doi: 10.18632/oncotarget.10583

18. Kaneko K., Ohba K., Hirose T., Totsune K., Furuyama K., Takahashi K. 2017. Expression of (pro)renin receptor during rapamycin-induced erythropoiesis in K562 erythroleukemia cells and its possible dual actions on erythropoiesis. *Tohoku Journal of Experimental Medicine.* 241(1): 35–43. doi: 10.1620/tjem.241.35

19. Kouchi M., Shibayama Y., Ogawa D., Miyake K., Nishiyama A., Tamiya T. 2017. (Pro)renin receptor is crucial for glioma development via the Wnt/β-catenin signaling pathway. *Journal of Neurosurgery.* 127(4): 819–828. doi: 10.3171/2016.9.JNS16431

20. Mohammad A.H., Assadian S., Couture F., Lefebvre K.J., El-Assaad W., Barrès V., Ouellet V., Boulay P.-L., Yang J., Latour M., Furic L., Muller W., Sonenberg N., Mes-Masson A.-M., Saad F., Day R., Teodoro J.G. 2019. V-ATPase-associated prorenin receptor is upregulated in prostate cancer after

PTEN loss. *Oncotarget.* 10(48): 4923–4936. doi: 10.18632/oncotarget.27075

21. Wang J., Shibayama Y., Zhang A., Ohsaki H., Asano E., Suzuki Y., Kushida Y., Kobara H., Masaki T., Wang Z., Nishiyama A. 2019. (Pro)renin receptor promotes colorectal cancer through the Wnt/beta-catenin signalling pathway despite constitutive pathway component mutations. *British Journal of Cancer.* 120(2): 229–237. doi: 10.1038/s41416-018-0350-0
22. Beitia M., Solano-Iturri J.D., Errarte P., Calvete-Candenas J., Loizate A., Etxezarraga M.C., Sanz B., Larrinaga G. 2019. (Pro) renin receptor expression increases throughout the colorectal adenoma-adenocarcinoma sequence and it is associated with worse colorectal cancer prognosis. *Cancers.* 11(6): 881. doi: 10.3390/cancers11060881
23. Larrinaga G., Calvete-Candenas J., Solano-Iturri J.D., Martín A.M., Pueyo A., Nunes-Xavier C.E., Pulido R., Dorado J.F., López J.I., Angulo J.C. 2021. (Pro)renin receptor is a novel independent prognostic marker in invasive urothelial carcinoma of the bladder. *Cancers.* 13(22): 5642. doi: 10.3390/cancers13225642
24. Liu J., Xiao Q., Xiao J., Niu C., Li Y., Zhang X., Zhou Z., Shu G., Yin G. 2022. Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities. *Signal Transduction and Targeted Therapy*. 7(1): 3. doi: 10.1038/s41392-021-00762-6
25. Krop M., Lu X., Jan Danser A.H., Meima M.E. 2013. The (pro)renin receptor. A decade of research: what have we learned? *Pflügers Archiv*. 465(1): 87–97. doi: 10.1007/s00424-012-1105-z
26. Huang Y., Wongamorntham S., Kasting J., McQuillan D., Owens R.T., Yu L., Noble N.A., Border W. 2006. Renin increases mesangial cell transforming growth factor-beta1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms. *Kidney International.* 69(1): 105–113. doi: 10.1038/sj.ki.5000011
27. Huang Y., Noble N.A., Zhang J., Xu C., Border W.A. 2007. Renin-stimulated TGF-β1 expression is regulated by a mitogen-activated protein kinase in mesangial cells. *Kidney International.* 72(1): 45–52. doi: 10.1038/sj.ki.5002243
28. Peng H., Li W., Seth D.M., Nair A.R., Francis J., Feng Y. 2013. (Pro)renin receptor mediates both angiotensin II-dependent and -independent oxidative stress in neuronal cells. *PLoS One*. 8(3): e58339. doi: 10.1371/journal.pone.0058339
29. Howe L.R., Brown A.M.C. 2004. Wnt signaling and breast cancer. *Cancer Biology and Therapy.* 3(1): 36–41. doi: 10.4161/cbt.3.1.561
30. Kurayoshi M., Oue N., Yamamoto H., Kishida M., Inoue A., Asahara T., Yasui W., Kikuchi A. 2006. Expression of Wnt-5a is correlated with aggressiveness of gastric cancer by stimulating cell migration and invasion. *Cancer Research.* 66(21): 10439–10448. doi: 10.1158/0008-5472.CAN-06-2359
31. Gupta S., Iljin K., Sara H., Mpindi J.P., Mirtti T., Vainio P., Rantala J., Alanen K., Nees M., Kallioniemi O. 2010. FZD4 as a mediator of ERG oncogene-induced WNT signaling and epithelial-to-mesenchymal transition in human prostate cancer cells. *Cancer Research.* 70(17): 6735–6745. doi: 10.1158/0008-5472.CAN-10-0244
32. De Sousa E. Melo F., Vermeulen L., Richel D., Medema J.P. 2011. Targeting Wnt signaling in colon cancer stem cells. *Clinical Cancer Research.* 17(4): 647–653. doi: 10.1158/1078-0432.CCR-10-1204
33. El Wakil A., Lalli E. 2011. The Wnt/beta-catenin pathway in adrenocortical development and cancer. *Molecular and Cellular Endocrinology*. 332(1–2): 32–37. doi: 10.1016/j.mce.2010.11.014
34. Kashio-Yokota Y., Sato S., Hirose T., Watanabe T., Endo A., Watanabe F., Endo M., Ohba K., Mori T., Takahashi K. 2021. Elevated (pro)renin receptor expression by anti-cancer drugs, carboplatin and paclitaxel, in cultured cancer cells: possible involvement of apoptosis and autophagy. *Tohoku Journal of Experimental Medicine*. 255(2): 91–104. doi: 10.1620/tjem.255.91
35. Delforce S.J., Lumbers E.R. Corbisier de Meaultsart C., Wang Y., Proietto A., Otton G., Scurry J., Verrills N.M., Scott R.J., Pringle K.G. 2017. Expression of renin-angiotensin system (RAS) components in endometrial cancer. *Endocrine Connections*. 6(1): 9–19. doi: 10.1530/EC-16-0082
36. Zavadil J., Böttinger E.P. 2005. TGF-beta and epithelial-to-mesenchymal transitions. *Oncogene.* 24(37): 5764–5774. doi: 10.1038/sj.onc.1208927
37. Khoshghamat N., Jafari N., Toloue-Pouya V., Azami S., Mirnourbakhsh S.H., Khazaei M., Ferns G.A., Rajabian M., Avan A. 2021. The therapeutic potential of renin-angiotensin system inhibitors in the treatment of pancreatic cancer. *Life Sciences.* 270: 119118. doi: 10.1016/j.lfs.2021.119118
38. Cousin C., Bracquart D., Contrepas A., Corvol P., Muller L., Nguyen G. 2009. Soluble form of the (pro)renin receptor generated by intracellular cleavage by furin is secreted in plasma. *Hypertension*. 53(6): 1077–1082. doi: 10.1161/HYPERTENSIONAHA.108.127258
39. Yoshikawa A., Aizaki Y., Kusano K., Kishi F., Susumu T., Iida S., Ishiura S., Nishimura S., Shichiri M., Senbonmatsu T. 2011. The (pro)renin receptor is cleaved by ADAM19 in the Golgi leading to its secretion into extracellular space. *Hypertension Research.* 34: 599–605. doi: 10.1038/hr.2010.284
40. Qin M., Xu C., Yu J. 2021. The soluble (pro)renin receptor in health and diseases: foe or friend? *Journal of Pharmacology and Experimental Therapeutics*. 378(3): 251–261. doi: 10.1124/jpet.121.000576
41. Liu C., Song S., Yi X., Yang H., Xiong J., Wang M., Tan W., Zhu M., Zheng L., Yu J., Xu C. 2024. Soluble (pro)renin receptor as a novel laboratory biomarker of atherosclerosis. *Acta Biochimica et Biophysica Sinica.* 57(3): 501–504. doi: 10.3724/abbs.2024150
42. Endo M., Ohba K., Sato S., Yokota Y., Takahashi K. 2020. Increased soluble (pro)renin receptor protein by autophagy inhibition in cultured cancer cells. *Genes to Cells*. 25(7): 483–497. doi: 10.1111/gtc.12776

Поступила 16.06.2025
Принята 30.06.2025