Огляди Reviews

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A Role of MicroRNAs in Pathogenesis of Renal Cell Carcinoma

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Renal cell carcinoma (RCC) is an oncologic pathology that is found in 3 % of all cases of malignant tumors in adults and approximately in 90 % of malignant kidney lesions [9]. In last decade many scientists actively have investigated part of the MicroRNAs (miRNA, miR) in development of RCC. MiRNAs are small non-coding RNAs that regulate the expression of a broad spectrum of genes by the means of impact on the 3'-untranslated regions (3'-UTR) of complementary mRNAs. MicroRNAs plays the key part in such essential RCC development processes as regulation of cell growth and cell cycle, apoptosis, replicative potential, angiogenesis, tissue invasion and metastasizing [1-8, 10-19].

The purpose of this literature review is to analyze up-to data about a role of microRNAs in pathogenesis of renal cell carcinoma.

Materials and methods. The systematic review of the available scientific literature using on-line scientific database PubMed online and such keywords as "renal cell carcinoma", "pathogenesis", "microRNA", "miRNA" and "miR" has been performed.

Results and discussion. In a result of the database analysis using specific keywords 485 scientific articles have been found. The most relevant results have been selected for the literature review. The mechanism of RCC pathogenesis is complex and continues to be unclear. Multiple signaling pathways as VHL/HIF, PI3K/Akt, Src-STAT3-VEGF, Ras/Raf/ERK1/2 and others are involved in RCC development [1, 13, 14]. At the moment large amount of miRNA investigations in patients with RCC has been performed and the expression levels in tissues, blood and urine have been measured and compared with those in healthy controls. A number of explorations have shown that both overexpression and underexpression of miRNAs are characteristics of RCC. In 2010 Neal et al observed upregulated levels of miR-210, miR-155 and miR-21 expression in the RCC tumor tissues, miR-210 expression levels correlated with a HIF-regulated mRNA, CAIX, as well as with VHL mutation/promoter methylation [14]. Majid and co-authors detected that phospho-Src-regulated ERK1/2 pathway was involved in RCC proliferation suppression by miR-205. MiR-205 inhibited focal adhesion kinase (FAK, cell motility factor) and signal transducer and activator of transcription 3 (STAT3). Up-regulation of miR-205 in A498 cells promoted G0/G1 cell-cycle arrest induction, cell death and simultaneously with downregulated c-Myc and cyclin D1, suppressed cell proliferation, coloniality, invasion and migration of RCC cells [13].

Another study's data have shown that miR-138s direct target is HIF-1 α , downregulation HIF-1 α with miR-138 increasing apoptosis and reducing the migration of 786-O cells [16]. In 2011 Ueno reported that miR-584 up-regulation reduced ccRCCs cell motility. The Rho-associated coiled-coil containing protein kinase 1 (ROCK-1) was direct target of miR-584 [17]. Zhang observed that miR-21 downregulation suppressed cell proliferation and increased cell apoptosis by activation of caspase pathway in RCC cells. Targeting the binding site of the 3'UTR by downregulated miR-21 resulted in Fas and TIMP3 inhibition. Introduction of TIMP3 complementary DNA without 3'UTR revoked was induced by miR-21 cell survival [19]. In 2012 Cui reported that miR-99a expression was noticeably decreased in RCC, and miR-99a up-regulation promoted suppression of the RCC cells growth, migration, invasion clonability and G1-phase cell cycle arrest *in vitro*. In addition, the aim of rapamycin (mTOR) in RCC of the mammalian was identified as a target of microRNA-99a [5]. Dey and his coworkers investigated in their study that downregulation of PTEN in RCC was a result of interaction between miR-21 and its direct target - PTEN mRNA 3'UTR, as the part of Akt phosphorylation. Decrease in PTEN expression and upregulation of CA Akt kinase hindered microRNA-21 Sponge-induced inhibition of proliferation and migration of the renal cancer cells. Transcriptional activation of miRNA-21 post-transcriptionally regulated PTEN and, consequently, concussed Akt/TORC1 pathway to induce proliferation and invasion of RCC [6].

According to Li microRNA-155 was overexpressed in tissues and cell lines of conventional renal cancer. Downregulation of miRNA-155 suppressed RCC cell proliferation, migration and induced apoptosis. The suppressor of cytokine signaling (SOCS1) and transcription regulator protein BACH1 were identified as MiR-155 target genes [11]. In 2012 Lichner and coworkers published results of their study in which they investigated pleiotropic action of dysregulated miRs that involve signaling pathways related to hypoxia in RCC pathogenesis. In RCC tissues there was inverse correlation between microRNA-17-5p expression and its targets - VEGF-A and EGLN3, as well as between microRNA-224 expression and its targets SMAD4 and SMAD5 [12]. In another work Zhai et al reported that in RCC specimens the expression of miRNA-508-3p/miRNA-509-3p was considerably decreased, simultaneously there was a significant difference in plasma levels of miRNA-508-3p but not in miRNA-509-3p of patients with renal cancer vs healthy controls. RCC proliferation was suppressed by overexpressed miRNA-508-3p and miRNA-509-3p while apoptosis and cell migration were inhibited *in vitro* [18]. In 2013 Bera and co-authors evidenced that cyclin D1 and CDK4 mediated RCC proliferation regulated by microRNA-21. The results of this study itemized the sequence of renal cancer proliferation involving NF κ B-dependent cyclin D1 as well as PTEN/Akt/IKK β pathways and upregulated microRNA-21 [3]. Few years later Bera and co-authors published a paper where they explored PDCD4 dissociation from rictor that was induced by miR-21 and the part of Akt-IKK β -mTORC1 path in regulation of RCC cell invasion. It was found that microRNA-21 suppresses programmed cell death protein PDCD4 leading to increased invasion and migration of 786-O RCC and ACHN in result of phosphorylation and of activation Akt/IKK β with consequent NF κ B dependent transcription. Constitutively active (CA) IKK β or CA-Akt hinders PDCD4 mediated inhibition and renovates renal cancer cell invasion and migration, mTORC1 activity was inhibited by PDCD4 and was overturned by CA-IKK β [2].

In 2014 Huang evidenced that HGF/c-Met signaling axis was targeted by microRNA-199a-3p and had a decisive impact on renal cancer development [10]. In 2017 Hao and co-authors found that microRNA-99a suppressed proliferation, invasion and migration and simultaneously induced G1-phase cell cycle arrest through targeting of IGF-1R signaling a pathway in OS-RC-2 and RCC 786-0 cells. Proliferation, invasion, migration and induced G1-phase cell cycle arrest in renal cancer cells inhibited *in vitro* overexpression of microRNA-99a and downregulation of IGF-1R, suggesting tumor suppressive role of microRNA-99a

resolved by means of IGF-1R regulation [7]. Sufficient attempts to integrate existing knowledge on miRNA function in RCC by the means of network analysis were performed by Redova et al. and He et al. elucidating important mechanisms of the disease pathogenesis [8, 15].

In conclusion there is a strong evidence of the important role of miRs in pathogenesis of RCC, however, further investigations are required in order to achieve more profound understanding of genetic mechanisms of development of this pathology.

REFERENCES

1. Banumathy Gowrishankar, Paul Cairns. Signaling Pathways in Renal Cell Carcinoma. *Cancer Biology & Therapy* 10, N 7 (October 1, 2010): 658-664. doi:10.4161/cbt.10.7.13247.
2. Bera Amit, Falguni Das, Nandini Ghosh-Choudhury, Balakuntalam S. Kasinath, Hanna E. Abboud and Goutam Ghosh Choudhury. microRNA-21-Induced Dissociation of PDCD4 from Rictor Contributes to Akt-IKK β -mTORC1 Axis to Regulate Renal Cancer Cell Invasion. *Experimental Cell Research* 328, no. 1 (October 15, 2014): 99-117. doi:10.1016/j.yexcr.2014.06.022.
3. Bera Amit, Nandini Ghosh-Choudhury, Nirmalya Dey, Falguni Das, Balakuntalam S. Kasinath, Hanna E. Abboud and Goutam Ghosh Choudhury. NF κ B-Mediated Cyclin D1 Expression by microRNA-21 Influences Renal Cancer Cell Proliferation. *Cellular Signalling* 25, no. 12 (December 2013): 2575-86. doi:10.1016/j.cellsig.2013.08.005.
4. Croce CM. Causes and consequences of microRNA dysregulation in cancer. *Nat Rev Genet.* 10:704-714. 2009.
5. Cui Li, Hua Zhou, Hu Zhao, Yaojun Zhou, Renfang Xu, Xianlin Xu, Lu Zheng et al. MicroRNA-99a Induces G1-Phase Cell Cycle Arrest and Suppresses Tumorigenicity in Renal Cell Carcinoma. *BMC Cancer* 12 (November 23, 2012): 546. doi:10.1186/1471-2407-12-546.
6. Dey Nirmalya, Falguni Das, Nandini Ghosh-Choudhury, Chandi Charan Mandal, Dipen J. Parekh, Karen Block, Balakuntalam S. Kasinath, Hanna E. Abboud and Goutam Ghosh Choudhury. microRNA-21 Governs TORC1 Activation in Renal Cancer Cell Proliferation and Invasion. *PloS One* 7, no. 6 (2012): e37366. doi:10.1371/journal.pone.0037366.
7. Hao Bo, Li Cui, Yi Gu, Bo Zhang, Min Wang, Hua Zhou, Renfang Xu, Xiaozhou He. MiR-99a Suppresses Proliferation, Migration, Invasion and Induces G1-Phase Cell Cycle Arrest via Targeting IGF-1R Pathway in Renal Cell Carcinoma 786-O and OS-RC-2 Cells. *Urology* 0, no. 0 (January 13, 2017). doi:10.1016/j.urology.2017.01.003.
8. He Jimin, Xiaoxin Guo, Linlin Sun, Kuhao Wang, Haiying Yao. Networks Analysis of Genes and microRNAs in Human Wilms' Tumors. *Oncology Letters* 12, no. 5 (November 2016): 3579-3585. doi:10.3892/ol.2016.5102.
9. Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review 1975-2016 / National Cancer Institute. Bethesda, MD., 2016.
10. Huang Jiwei, BaiJun Dong, Jin Zhang, Wen Kong, Yonghui Chen, Wei Xue, Dongming Liu, Yiran Huang. miR-199a-3p Inhibits Hepatocyte Growth Factor/C-Met Signaling in Renal Cancer Carcinoma. *Tumor Biology* 35, no. 6 (June 1, 2014): 5833-43. doi:10.1007/s13277-014-1774-7.
11. Li Songchao, Tieding Chen, Zhaozhong, Yi Wang, Yangle Li, Xiaokun Zhao. microRNA-155 Silencing Inhibits Proliferation and Migration and Induces Apoptosis by Upregulating BACH1 in Renal Cancer Cells. *Molecular Medicine Reports* 5, no. 4 (April 2012): 949-954. doi:10.3892/mmr.2012.779.
12. Lichner Zsuzsanna, Salvador Mejia-Guerrero, Monika Ignacak, Adriana Krizova, Tian Tian Bao, Andrew HF Girgis, Yousef M. Youssef, George M. Yousef. Pleiotropic Action of Renal Cell Carcinoma-Dysregulated miRNAs on Hypoxia-Related Signaling Pathways. *The American Journal of Pathology* 180, no. 4 (April 2012): 1675-1687. doi:10.1016/j.ajpath.2011.12.030.
13. Majid Shahana, Sharanjot Saini, Altaf A. Dar, Hiroshi Hirata, Varahram Shahryari, Yuichiro Tanaka, Soichiro Yamamura et al. MicroRNA-205 Inhibits Src-Mediated Oncogenic Pathways in Renal Cancer. *Cancer Research* 71, no. 7 (April 1, 2011): 2611-2621. doi:10.1158/0008-5472.CAN-10-3666.
14. Neal Calida S, Michael Z. Michael, Lesley H. Rawlings, Mark B. Van der Hoek, Jonathan M. Gleadle. The VHL-Dependent Regulation of microRNAs in Renal Cancer. *BMC Medicine* 8 (October 21, 2010): 64. doi:10.1186/1741-7015-8-64.
15. Redova Martina, Marek Svoboda, Ondrej Slaby. MicroRNAs and Their Target Gene Networks in Renal Cell Carcinoma. *Biochemical and Biophysical Research Communications* 405, no. 2 (February 11, 2011): 153-156. doi:10.1016/j.bbrc.2011.01.019.
16. Song Tao, Xu Zhang, Chunyang Wang, Yiguang Wu, Wei Cai, Jiangping Gao, Baofa Hong. MiR-138 Suppresses Expression of Hypoxia-Inducible Factor 1 α (HIF-1 α) in Clear Cell Renal Cell Carcinoma 786-O Cells. *Asian Pacific Journal of Cancer Prevention: APJCP* 12, no. 5 (2011): 1307-1311.
17. Ueno K, Hirata H, Shahryari V, Chen Y, Zaman MS, Singh K, Tabatabai ZL, Hinoda Y, Dahiya R. Tumour Suppressor microRNA-584 Directly Targets Oncogene Rock-1 and Decreases Invasion Ability in Human Clear Cell Renal Cell Carcinoma. *British Journal of Cancer* 104, no. 2 (January 18, 2011): 308-315. doi:10.1038/sj.bjc.6606028.
18. Zhai Qingna, Liang Zhou, Chunjuan Zhao, Jun Wan, Zhendong Yu, Xin Guo, Jie Qin, Jing Chen, Ruijing Lu. Identification of miR-508-3p and miR-509-3p That Are Associated with Cell Invasion and Migration and Involved in the Apoptosis of Renal Cell Carcinoma. *Biochemical and Biophysical Research Communications* 419, no. 4 (March 23, 2012): 621-626. doi:10.1016/j.bbrc.2012.02.060.
19. Zhang Aimin, Yi Liu, Yizhen Shen, Youhe Xu, Xiangtie Li. miR-21 Modulates Cell Apoptosis by Targeting Multiple Genes in Renal Cell Carcinoma. *Urology* 78, no. 2 (August 2011): 474. e13-474.e19. doi:10.1016/j.urology.2011.03.030.

REVIEWS

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Renal cell carcinoma (RCC) is an oncologic pathology that is found in 3 % of all cases of malignant tumors in adults and approximately in 90 % of malignant kidney lesions. Part of the MicroRNAs (miRNA, miR) in development of RCC is actively investigated. MiRNAs are small non-coding RNAs that regulate the expression of a broad gene spectrum by the means of impact on the 3'-untranslated regions (3'-UTR) of complementary mRNAs. MicroRNAs play the key part in such essential RCC development processes as cell growth and cell cycle regulation, apoptosis, replicative potential, angiogenesis, tissue invasion and metastasizing.

The purpose of this literature review is to analyze up-to-date data on role of microRNAs in pathogenesis of RCC.

Materials and methods. The systematic review of the available scientific literature using on-line scientific database PubMed and such keywords as "renal cell carcinoma", "pathogenesis", "microRNA", "miRNA" and "miR" has been performed.

Results and discussion. As a result of the database search using specified keywords 485 scientific papers have been found. The most relevant results have been selected for the literature review. The mechanism of RCC pathogenesis is complicated and continues to be unclear. Large amount of investigations of miRNA in patients with RCC has been performed where the expression levels in tissues, blood, and urine have been measured and compared with those in healthy controls. A great number of explorations has showed that both overexpression and underexpression of miRNAs are characteristic for RCC. The mRNAs that seemed to play most important role in RCC pathogenesis are miR-1, miR-20b-5p, miR-22, miR-23b, miR-30c, miR-30d, miR-34a, miR-99a, miR-133a, miR-133b, miR-135a, miR-138, miR-143, miR-145, miR-182-5p, miR-199a-3p, miR-200c, miR-490-5p, miR-509-5p, miR-708, miR-1826 and have an impact on such mechanisms as cell cycle, migration, proliferation, invasion, modulation of the differentiation of mesenchymal stem cells.

Conclusion: there is a strong evidence of the important role of miRs in pathogenesis of RCC, however, further investigations are required in order to achieve more profound understanding of genetic mechanisms of development of this pathology.

Key words: renal cell carcinoma, pathogenesis, microRNA, miRNA, miR.