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Current Status of Transfer RNA-derived Small RNAs in Cancers

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Abstract: Transfer RNA-derived small RNAs (tsRNAs) are a new type of non-coding small RNAs produced by the processing and splicing of precursor or mature transfer RNAs by specific endonucleases under unfavorable conditions, such as starvation, oxidative stress, hypoxia, etc. tsRNAs have been found to be abnormally expressed in multiple types of cancers. With the development of science and technology, their regulatory mechanisms have been gradually discovered. This review summarizes the progress of tsRNAs in cancers of gastrointestinal system, breast system and reproductive system, and lays the foundation for the diagnosis and treatment of the diseases.

Keywords: tsRNA; Cancers; Disease; Biomarker

Background

Non-coding RNAs are RNA molecules transcribed from the genome that do not code for proteins. According to the results of the study, ncRNAs can be divided into small ncRNAs (sncRNAs, 18-200 nt) and long ncRNAs (lncRNAs, >200 nt) by their length; and into housekeeping ncRNAs (e.g., rRNAs and tRNAs) and regulatory ncRNAs (e.g., miRNAs, piRNAs, tsRNAs, lncRNAs) by their function[1]. Currently, the roles of housekeeping ncRNAs (tRNAs and rRNAs) in protein formation are well defined[2]. Similarly, the role of miRNAs and piRNAs among ncRNAs in various cancers has been increasingly investigated[3, 4], but the molecular mechanisms of tsRNA-mediated gene regulation and their involvement in cancers are just beginning to be studied.

Under some unfavorable conditions such as starvation, oxidative stress, and hypoxia, precursor or mature tRNAs are processed and spliced by specific endonucleases to generate a novel type of non-coding small RNAs called transfer RNA-derived small RNA (tsRNA). Based on the cleavage site, tsRNAs can be divided into tRNA fragments (tRFs) and tRNA-derived stress-induced small RNAs (tiRNAs)[5]. tRFs consist of 14-30 fragments at the end of a precursor or mature tRNA and can be categorized as tRF-1, tRF-3, tRF-5, tRF-2, and i-tRF. tiRNAs typically contain 31-41 nucleotides and also known as "tRNA halves". Under stress conditions, ANG cleaves the anticodon loop of mature tRNA into two halves, producing 3′-tiRNA and 5′-tiRNA[6]. Recently, several studies have confirmed that aberrantly expressed tsRNAs have been found in malignant tumors[7-9]. This review will focus on elucidating the roles of tsRNAs in cancers of the gastrointestinal system, breast system, and reproductive system, and laying the groundwork for the diagnosis, treatment, and prognosis of these diseases.

tsRNA in pancreatic cancer

Pancreatic cancer is one of the most malignant tumors of the gastrointestinal system, which has a high incidence and rapid progression, and the number of pancreatic cancer patients diagnosed each year is gradually increasing worldwide[10]. Therefore, exploring novel biomarkers with high sensitivity and specificity is crucial for early diagnosis and prognosis of pancreatic cancer. A research has found that tRF-Pro-AGG-004 and tRF-Leu-CAG-002 are significantly elevated in the serum of pancreatic cancer patients, and at the same time, the ISH scores of these two markers in the tumor tissues of pancreatic cancer patients also have a prognostic value. Therefore, tRF-Pro-AGG-004 and tRF-Leu-CAG-002 are important for the diagnosis and prognosis of pancreatic cancer[8]. In addition, tRF-3-Leu-AAG-1-1, tRF-3-Gln-CTG-1-1, tRF-3-Ala-CGC-1-1, and tiRNA-5-Pro-CGG-1-1 were abnormally expressed in pancreatic cancer tissues, and these four tsRNAs could be used as potential diagnostic and therapeutic biomarkers for pancreatic cancer[11]. These findings provide new research directions for the diagnosis, treatment and prognosis of pancreatic cancer.

tsRNAs in gastric cancer

Gastric cancer is a malignant tumor disease originating from the epithelial cells of the gastric mucosa and is the second most common cause of cancer death worldwide[12]. Often, patients miss the optimal treatment time due to untimely diagnosis. Therefore, it is necessary to

find new biomarkers with higher sensitivity and specificity for the diagnosis, prognosis and treatment of gastric cancer. Some researchers found that the expression of hsa-tsr013526 and tRF-29-R9J8909NF5JPin the serum of gastric cancer patients was higher than that of healthy individuals[13, 14]. High levels of hsa-tsr013526 promoted the proliferation, invasion, and migration of gastric cancer cells, and patients with high serum tRF-29-R9J8909NF5JP expression had a low overall survival rate and poor prognosis. Therefore, serum hsa-tsr013526 and tRF-29-R9J8909NF5JP can be used as effective biomarkers for prognostic monitoring of gastric cancer patients. In addition, overexpression of tRF-33-P4R8YP9LON4VDP inhibited the proliferation and migration of gastric cancer cells and induced apoptosis, suggesting that tsRNAs can also be used as potential therapeutic targets for gastric cancer[15]. In summary, tsRNAs play an important role in the diagnosis, treatment and prognosis of gastric cancer.

tsRNAs in breast cancer

Breast cancer, a malignant tumor that develops from an abnormal proliferation of cells in breast tissue, is the fifth leading cause of cancer deaths worldwide and still lacks an effective treatment[16]. Some researchers have found that the expression levels of tRF-Arg-CCT-017, tRF-Gly-CCC-001 and tiRNA-Phe-GAA-003 are significantly upregulated in the plasma of breast cancer patients, which can be used as novel diagnostic biomarkers. Meanwhile, high levels of tRF-Arg-CCT-017 or tiRNA-Phe-GAA-003 could also serve as prognostic biomarkers for breast cancer[17]. In addition, researchers have found that tsRNA-26576 inhibits apoptosis while promoting cell growth; therefore, tsRNA-26576 may be a potential clinical therapeutic target[18]. In summary, tsRNAs may become novel biomarkers for breast cancer diagnosis, prognosis and treatment.

tsRNAs in ovarian cancer

Ovarian cancer is one of the common malignant tumors of the female reproductive organs, and its incidence rate ranks third only after cervical cancer and endometrial cancer. Currently, ovarian cancer is treated by surgical resection or chemotherapy[19]. Nonetheless, some patients still experience tumor recurrence or metastasis after treatment. Therefore, it is necessary to explore new biomarkers for the treatment of ovarian cancer. The researchers found that $tRNA^{Gly}$-derived i-tRFs were differentially expressed in the serum of ovarian cancer patients compared with healthy controls, and that this indictor had high specificity and sensitivity for the prediction of ovarian cancer[20]. Meanwhile, 3'U-tRF^{ValCAC} could promote the growth and migration of ovarian cancer cells, and the elevated level of this indicator correlated with the treatment and prognosis of ovarian cancer patients[21]. Nowadays, increasing studies have identified the role of tsRNAs in ovarian cancer, which also provides a new perspective for the development of diagnosis, treatment and prognosis of ovarian cancer.

Conclusion

This review summarizes the research progress of tsRNAs in pancreatic, gastric, breast, and ovarian cancers. Currently, increasing attention has been paid to the study of tsRNAs, for example, tsRNAs play important roles in the regulation of intergenerational inheritance, gene expression and immune activation[22, 23]. With the continuous development of science and technology, more and more roles of tsRNAs in diseases have been gradually identified, which also promotes the development of human health.

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Authors' contributions

Yuting Luo conducted the writing of the manuscript. Yuting Luo, Hehua Hu and Jiayi Chen developed the initial concept and framework of the manuscript and supervised the drafting of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

Not applicable.

References

[1] Mikhail G D, Cory B G, Kristi A K, Jonathan D W: **Systematic classification of non-coding RNAs by epigenomic similarity**. *BMC Bioinformatics* 2013(0).

[2] A Gregory M, Rebecca M T, Michael P T: **Non-coding RNAs: lessons from the small nuclear and small nucleolar RNAs**. *Nat Rev Mol Cell Biol* 2007, **8**(3).

[3] Phuong T B H, Ian M C, Linh T T L: **MicroRNA-Based Diagnosis and Therapy**. *Int J Mol Sci* 2022, **23**(13).

[4] Xin W, Anne R, Martine S, Mo-Fang L: **Emerging roles and functional mechanisms of PIWI-interacting RNAs**. *Nat Rev Mol Cell Biol*, **24**(2).

[5] Yang J, Wei T, Yedi Z: **Transfer RNA-derived small RNAs: potential applications as novel biomarkers for disease diagnosis and prognosis**. *Ann Transl Med* 2020, **8**(17).

[6] Aleksej D, Vera O, Conor T, Eva J, Dorothea A, Markus H, Steffen K, Stefanie K, Matthias R S: **Production and purification of endogenously modified tRNA-derived small RNAs**. *RNA Biol* 2020, **17**(8).

[7] Lin X, Jie W, Shaoqing J, Ming C, Rongrong J: **Disorders and roles of tsRNA, snoRNA, snRNA and piRNA in cancer**. *J Med Genet* 2022, **59**(7).

[8] Fangfang J, Liuqing Y, Weixiang W, Na Y, Shoubin Z, Ping Y, Xi C, Tonghui M, Yanbo W: **A novel class of tsRNA signatures as biomarkers for diagnosis and prognosis of pancreatic cancer**. *Mol Cancer* 2021, **20**(1).

[9] Ting H, Yuexin Z, Guoqin J, Zhixue Y: **tsRNA: A Promising Biomarker in Breast Cancer**. *J Cancer* 2024, **15**(9).

[10] Alison P K: **Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors**. *Nat Rev Gastroenterol Hepatol* 2021, **18**(7).

[11] Lei J, Chunfu Z, Xihu Q: **Expression profile of tRNA-derived fragments in pancreatic cancer**. *Oncol Lett* 2019, **18**(3).

[12] Parisa K, Farhad I, Sharmila A, Neal D F, Farin K: **Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention**. *Cancer Epidemiol Biomarkers Prev* 2014, **23**(5).

[13] Jing X, Yue W, Xian L, Ming Z, Yang L, Weiwei Z: **Clinical value assessment for serum hsa_tsr013526 in the diagnosis of gastric carcinoma**. *Environ Toxicol* 2024, **39**(5).

[14] Xun L, Yu Z, Yang L, Xinliang G, Shaoqing J: **A comprehensive evaluation of serum tRF-29-R9J8909NF5JP as a novel diagnostic and prognostic biomarker for gastric cancer**. *Mol Carcinog* 2023, **62**(10).

[15] Yijing S, Xiuchong Y, Yao R, Zhe L, Yaoyao X, Zhilong Y, Junming G: **Global profile of tRNA-derived small RNAs in gastric cancer patient plasma and identification of tRF-33-P4R8YP9LON4VDP as a new tumor suppressor**. *Int J Med Sci* 2021, **18**(7).

[16] Muhammad A, Mehwish I, Muhammad D, Asmat Ullah K: **Awareness and current knowledge of breast cancer**. *Biol Res* 2017, **50**(1).

[17] Jingyi W, Ge M, Han G, Xu H, Xinrui M, Xinyang W, Jordee Selvamanee V, Tiansong X, Xiaoan L, Shui W: **Circulating tRNA-derived small RNAs (tsRNAs) signature for the diagnosis and prognosis of breast cancer**. *NPJ Breast Cancer* 2021, **7**(1).

[18] Jun Z, Fang W, Yike W, Jinpei L, Xuan Z: **Small RNA sequencing reveals a novel tsRNA-26576 mediating tumorigenesis of breast cancer**. *Cancer Manag Res* 2019, **11**(0).

[19] Stephanie L, Marsela B, Amit M O: **Epithelial ovarian cancer: Evolution of management in the era of precision medicine**. *CA Cancer J Clin* 2019, **69**(4).

[20] Eric Y P, Yang S, Yuke W, Feier Z, Shuangyan T, Yun D, Yiqi D, Haining C, Lei Z, Heng X: **Presence and diagnostic value of circulating tsncRNA for ovarian tumor**. *Mol Cancer* 2018, **17**(1).

[21] Konstantina P, Paraskevi M, Tobias D, Julia D, Eva O, Sven M, Toon vG, Ioana B, Viktor M, Robert Z *et al*: **tRNA-derived small RNA 3'U-tRF(ValCAC) promotes tumour migration and early progression in ovarian cancer**. *Eur J Cancer* 2023, **180**(0).

[22] Menghong Y, Qiwei Z: **Sperm tsRNAs and acquired metabolic disorders**. *J Endocrinol* 2016, **230**(3).

[23] Qiuyan W, Yao W, Yaoyao X, Xiuchong Y, Shuangshuang Z, Jiaxin G, Zhe L, Guoliang Y, Junming G: **Extracellular vesicles-associated tRNA-derived fragments (tRFs): biogenesis, biological functions, and their role as potential biomarkers in human diseases**. *J Mol Med (Berl)* 2022, **100**(5).

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