ISSN: 2664-9640

Research progress of iron-associated protein Lipocalin-2 in tumor

Jiahui Zhang, Yan Wang*

Department of Otolaryngology, First Affiliated Hospital of China Medical University (110001), China.

* Corresponding Author

Abstract

Early diagnosis and treatment is an effective method to improve the 5-year survival rate of tumor patients. Iron-associated protein Lipocalin-2 (LCN2) is considered to be a key molecule in different tumor types. It was initially identified as an iron transporter by binding to iron carriers and played an up-or down-regulated role in many tumors. This review summarizes the latest research progress related to LCN2 in recent years and the possibility of judging its mechanism and therapeutic potential.

Keywords

Tumor, Iron metabolism, Lipocalin-2(LCN2), Epithelial-mesenchymal transformation.

1. Introduction

The balance of iron metabolism is maintained by complex and strict regulation in mammals. When iron storage capacity is overloaded, free iron participates in the Fenton reaction (Fenton) and Haber-Weiss reaction [1], which leads to the production of oxygen free radicals, attack the cell membrane and destroy the synthesis of DNA. A large number of epidemiological evidence shows that iron is involved in the occurrence and development of tumors, whether in the disorder of redox balance or in cell replication [2]. A large number of literatures have reported that the genes involved in iron regulation are deregulated and maintain high cell turnover and DNA synthesis of tumors. In the "old" iron age, cells maintained basic iron levels through the balance regulation of transferrin (TF)-TF receptors and iron transporters [3]. In the "new" iron era, LCN2 is considered to be another pathway of iron uptake, and there is a relationship between iron internalization and apoptosis regulation. Therefore, it is meaningful to explore whether LCN2 plays a related role in tumors.

2. The dual effects of lipocalin2 (LCN2) on Iron Metabolism

2.1. structure and function of LCN2

In the past two decades, iron-associated apolipoprotein Lipocalin (LCN) has received great clinical attention as a biomarker of kidney injury, cardiovascular injury and cancer. LCN is a molecular weight 24kDa glycoprotein [4]. Secreted by adipocyte [5], tumor cells and immune cells (neutrophils and macrophages) [6], with a variety of biological functions [7]. Play a role in signaling pathways and genetic regulation related to cell growth and inflammation [8]. Upregulation of LCN2 is observed in a variety of cancers, such as lung, breast, prostate, pancreatic and esophageal cancer [9,10]. On the contrary, in nasopharyngeal carcinoma and oropharyngeal carcinoma, the level of LCN2 decreased and the invasiveness of the tumor was down-regulated [11]. Tumor microenvironment (TME) often involves complex interactions with the immune system, which is closely related to tumor progression and plays a key role.

ISSN: 2664-9640

Understanding the dynamic regulation mechanism of matrix and immune components in TME remains an elusive challenge [12].

2.2. LCN2 and iron metabolism

LCN2 as new roles in regulating iron homeostasis, it is an important way to meet the high iron demand of tumor cells, under pathophysiological conditions. So far, the role of iron in regulating tumors is not fully understood. It can be believed that cancer cells have evolved special mechanisms for iron uptake, transport, storage and release. Mammalian cells transport iron by binding to a small hydrophobic iron carrier such as DHBA (2-dihydroxybenzoic acid) or catechol. The iron carrier shuttle to TAM in tumor cells will allow reverse transport of LCN2 iron-loaded and iron-loaded LCN2 [13]. Studies have shown that Bcl-2 induced by holo-LCN2 is beneficial to cell survival, promoting glycolysis and cell division leading to cancer cell survival and metastasis. The increase of intracellular iron ions in tumor cells leads to the transition of iron transporter-ferritin regulatory axis. The mechanism is unknown. Apo-LCN2 induces apoptosis by inducing the expression of Bim through iron efflux, which is similar to that of cytotoxic iron chelator. The regulation of apoptosis or survival by LCN2 may depend on the status of iron carrier loading [14]. At present, it is not clear whether holo- and apo-LCN2 compete for LCN2R combination. In the study of iron death, it was found that transcriptional regulatory factor (NUPR1) could transactivate the upstream of LCN2 expression gene [15], reduce intracellular iron accumulation and induce iron sag resistance. It is suggested that LCN2 is involved in the efflux of Fe^{2+} in unstable iron pool [16]. The relationship between LCN2 and iron metabolism has been controversial, but the relationship between LCN2 and iron metabolism and tumor indicates that LCN2 can interfere with iron metabolism in tumor cells and may be a potential target for tumor therapy.

3. Lipocalin 2 (LCN2) as a biomarker

The abnormal expression of LCN2 in human malignant tumors indicates its potential as a clinical biomarker. Based on TCGA data, a number of studies have explored the beneficial and harmful functions of LCN2 in various cancer models [17]. LCN2 can bind to the inactive zymogen form of proMMP-9 to form disulfide-linked complexes, and its high expression is related to the poor prognosis of patients with gastric cancer, breast cancer, liver cancer, pancreatic cancer and colorectal cancer. However, LCN2 has also been down-regulated in colorectal cancer, indicating that the role of LCN2 in tumor progression is not fully determined. Because of the involvement of LCN2 in iron metabolism, we must consider the binding of LCN2 to its hydrophobic ligand and whether the iron load state plays a decisive role in the function of LCN2.

LCN2 can also change the subcellular localization of E-cadherin and Rac1 (one of the small GTPases of Bauer) through the iron-dependent mechanism, thus increasing the motility and invasiveness of colon cancer cells [18]. Bauer et al observed a significant correlation between high LCN2 levels and negative estrogen receptor, HER-2 overexpression and high Ki-67 proliferation index in breast cancer tissues, thus reducing the sensitivity of MCF7 cells to hormone therapy [19]. Some studies have shown that LNC2 has a tumor inhibitory effect. In hepatocellular carcinoma, LNC2 inhibits the proliferation and invasion of hepatocellular carcinoma cells by blocking JNK and PI3/Akt signaling pathways. In the model of advanced pancreatic cancer, down-regulation of LCN2 interferes with FAK activation, blocking VEGF production inhibits angiogenesis [20]. In a breast cancer study, the overexpression of LCN2 in 4T1-H-Ras transformed cells (4T1-R) up-regulated E-cadherin, decreased vimentin and inhibited cell invasion, which reversed the mesenchymal phenotype of 4T1-R cells to epithelial phenotype through the inhibition of Ras-MEK signal pathway [21]. LCN2 now seems to be a pluripotent cytokine. Its unique and multiple functions and its widespread expression in

ISSN: 2664-9640

different types of cancer prompt us to think that LCN2 can be regarded as a biomarker of diagnostic and prognostic value.

4. Summary and prospect

To sum up, as a promising biomarker and a variety of important tumor mediators, LCN2 has received hot attention. Its abnormal expression is closely related to the development of tumors, depending on the different tumor microenvironment and different signal pathways. It needs to be further studied and clarified in order to clarify its role in tumor pathogenesis and to further explore its gene and molecular mechanism, which is helpful to provide new theoretical support and basis for early screening and treatment of tumor patients.

Acknowledgements

Liaoning Province Natural Science Foundation+20170541026.

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