Transferrin receptor 1 in cancer: a new sight for cancer therapy

Ying Shen1,2, Xin Li1,2, Dandan Dong1,2, Bin Zhang1,2, Yanru Xue1,2, Peng Shang2,3

1School of Life Science, Northwestern Polytechnical University, Xi’an 710072, Shaanxi, China; 2Research and Development Institute in Shenzhen, Northwestern Polytechnical University, Shenzhen 518057, China; 3Key Laboratory for Space Bioscience and Biotechnology, Institute of Special Environment Biophysics, School of Life Science, Northwestern Polytechnical University, Xi’an 710072, Shaanxi, China

Received May 21, 2018; Accepted May 29, 2018; Epub June 1, 2018; Published June 15, 2018

Abstract: Iron as an important element plays crucial roles in various physiological and pathological processes. Iron metabolism behaves in systemic and cellular two levels that usually are in balance conditions. The disorders of the iron metabolism balances relate with many kinds of diseases including Alzheimer’s disease, osteoporosis and various cancers. In systemic iron metabolism that is regulated by hepcidin-ferroportin axis, plasma iron is bound with transferrin (TF) which has two high-affinity binding sites for ferric iron. The generic cellular iron metabolism consists of iron intake, utilization and efflux. During the iron intake process in generic cells, transferrin receptors (TFRs) act as the most important receptor mediated controls. TFR1 and TFR2 are two subtypes of TFRs those bind with iron-transferrin complex to facilitate iron into cells. TFR1 is ubiquitously expressed on the surfaces of generic cells, whereas TFR2 is specially expressed in liver cells. TFR1 has attracted more attention than TFR2 by having diverse functions in both invertebrates and vertebrates. Recently reports showed that TFR1 involved in many kinds of diseases including anemia, neurodegenerative diseases and cancers. Most importantly, TFR1 has been verified to be abnormally expressed in various cancers. Some experimental and clinical drugs and antibodies targeting TFR1 have showed strong anti-tumor effects, herein TFR1 probably become a potential molecular target for diagnosis and treatment for cancer therapy. This paper reviewed the research progresses of the roles of TFR1 in the tumorigenesis and cancer progression, the regulations of TFR1, and the therapeutic effects of targeting TFR1 on many kinds of cancers.

Keywords: Iron, TFR1, TFRC, cancer, cancer targeting drugs

Introduction

Iron as an important element plays crucial roles in various physiological and pathological processes. In all kinds of mammalian cells, iron is indispensable to cell growth and division [1, 2], and it predominantly controls the formation of heme- and iron-containing proteins participating in oxygen transport [3-5], energy metabolism [6-8], neurotransmitter generation and release [9, 10], synthesis of DNA [11-13], collagen and steroid hormones [14-16], nonspecific resistance, etc. [17]. However, iron concentration must be strictly controlled, as iron is involved in the generation of free radicals in cells [18], a process leading to damage of biomolecules (proteins, lipids, nucleic acids) and in the progression of oxidative stress [19]. Iron metabolism has been reported the close related to cancer progression [20-22]. Disorders of iron metabolism, especially excessive iron acquisition and retention, can induce tumorigenesis and cancer’s growth as well [23, 24]. However, high concentration of intracellular iron can make cells in extremely oxidative stress and may induce tumor death. As a novel form of regulated cell death, ferroptosis is typified by lipid peroxidation and relies on iron and reactive oxygen species (ROS). Ferroptosis is morphologically and biochemically different from other known types of cell death [25, 26]. Thus, whether iron deprivation or induced iron overload in tumor cells can inhibit tumor growth and cause tumor cell death. A variety of strategies for antitumor therapies have been designed to target intracellular iron [27, 28],
including utilization of transferrin receptor 1 (TFR1)-mediated cytotoxic drug conjugates and iron chelators. As a membrane protein regulating iron import [29, 30], TFR1 is a member of the TFR family that shows nanomolar affinity to transferrin (TF) bound to Fe (III) [31]. The complex of TF-TFR1 is internalized through endocytosis mediated by clathrin, and Fe (III) is dissociated from TF when pH decreases to 5.5. At this pH, apotransferrin and TFR1 are still associated and recycled to cell surface with physiological pH, so the former is released [32, 33]. Iron uptake by transferrin receptor is the most important way for cancer cells to absorb iron, thus accumulating evidence has proven that TFR1 participated in tumor onset and progression, and its expression was dysregulated significantly in many cancers [34, 35]. The relationship between TFR1 and cancers has been revealed, rendering TFR1 a valuable pharmaceutical target for intervening with cancers [36-39]. Based on these reported studies, in this review will summarize the regulatory effects of TFR1 on tumorigenesis, and the potential therapeutic effects of targeting TFR1 on cancers.

Biological functions and regulations of transferrin receptors

Transferrin receptors (TFRs) encoded by TFRC is a membrane glycoprotein, which can import iron by binding a plasma glycoprotein, transferrin (TF) [40]. TF was first referred to as serum protein, with two specific sites binding Fe (III), so it is an iron source for synthesizing hemoglobin. Meanwhile, TF-bound iron undergoes cellular uptake requiring interaction between this protein and a specific TFR [33, 41]. The molecular weight of TFR as a homodimer is 180 kDa [42]. Each monomer contains a TF-binding C-terminal domain, a short N-terminal domain and a single transmembrane domain [33]. Transferrin receptors have two subtypes, transferrin receptor 1 (TFR1) and transferrin receptor 2 (TFR2). TFR1 is a homodimeric type II transmembrane glycoprotein that is expressed ubiquitously on the surfaces of most cells while another member of TFRs, TFR2 is mainly expressed in the liver [43, 44].

After TF was discovered as the iron source for immature red blood cells synthesizing hemoglobin, TFR1 was first considered as a cell surface receptor by which TF delivered iron to cells [45]. Mammalian TFR1 comprises 760 residue subunits that can be divided into a globular extracellular region, a hydrophobic intramembranous region and the remaining residues within the cytoplasm [33]. Consisting of two monomers, TFR1 is linked by two disulfide bridges, forming a 190 kDa molecule. It is a gatekeeper which regulates iron uptake [46]. Except for mature red cells, almost all cells have TFRs on their surfaces, being most abundant in the placenta, erythron and liver [38]. Human TFR1 has three N-linked and one O-linked oligosaccharide. Appropriate folding and transport of this protein to cell surface are significantly affected by N-linked glycosylation [33].

TFR1 expressions are delicately regulated at many levels, and several genes are involved in the regulation of TFR1 (Table 1). Intracellular iron concentration regulates the TFR gene post-transcriptional regulation by binding iron-regulatory proteins 1 and 2 (IRP1 and IRP2) to the iron response elements in the 5'-untranslated region of TFR transcript [45, 47]. IRPs are activated by the deprivation of cellular iron, which is inhibited through iron repletion [48]. IRP activities can be regulated by other iron-independent effectors such as inflammation [49], oxidative stress [50], hypoxia and xenobiotics [51], or such stimuli under pathophysiological conditions [38, 52]. Hypoxia induces the transcription of TFR1 gene by binding hypoxia-inducible factors (HIFs) to specific promoter elements [53]. This process can also be activated by an oncogenic transcription factor c-Myc [38]. Thirdly, HFE is implicated in the pathogenesis of disordered toxic and progressive iron over-

| Table 1. Genes involved in the regulation of TFR1 |
|-----------------|-----------------|-----------------|
| **Gene**        | **Regulation**  | **Reference**   |
| CREBBP          | Activation      | [56]            |
| EP300           |                  | [57]            |
| HIF-1A          |                  | [58]            |
| ARNT            |                  | [59]            |
| c-myc           |                  | [38]            |
| c-ETS-1         | DNA binding     | [60]            |
| c-Jun           |                  | [60]            |
| HIF-1α          |                  | [61, 62]        |
| ATF-1           |                  | [63]            |
| CREB1           | Inhibition      | [63]            |
The review of TFR1 in cancer

Transferrin receptor 1 and cancer

The transformation of normal cells into tumorigenic ones and tumor progression involve complicated processes which are still largely unknown. The changes mainly result from accumulated mutations of some key genes or proteins [64, 65], thus damaging the balances of tumor cells growth [66], proliferation [67], death [68], gene transcription [69] and angiogenesis [70]. Tumor cells’ proliferation is enhanced and apoptosis is inhibited by some of the essential signaling pathways varied upon tumorigenesis [71-73], while invasion and metastasis are promoted by others [74, 75]. The key roles of transferrin receptors (TFRs) in controlling the above processes have been well demonstrated over the last decade. TFR1 participating in tumor progression is abundantly expressed in liver, breast, lung and colon cancer cells [76-79]. Immunohistochemical findings of TFRC in various tumor tissues showed most cancers displayed moderate to strong cytoplasmic positivity. Carcinoid, prostate and testicular cancer was negative from The Human Protein Atlas [80]. Although the effects of TFRs on cancer pathophysiology have been studied, the expressions of TFR1 in different cancers are inconsistent and the mechanisms by which TFR1 participates in tumor progression remain elusive.

Given that TFR1 is abnormally expressed in various cancers (Figure 2A, 2B), it definitely affects cancer cells’ proliferation [81], migration [82], invasion [83], apoptosis and metastas...
The review of TFR1 in cancer

sis [76, 84]. Accordingly, several examples showed the regulatory effects of abnormal TFR1 expression on the biological behaviors of cancers (Figure 3).

**Transferrin receptor 1 in brain cancer**

TFR1 participates in regulating the physiology of glioma cells and the progression of brain cancer. Rosager et al. reported that TFR1 was overexpressed in brain cancer [84]. TFR1 mediated ROS formation and iron accumulation, as a crucial downstream effector of corresponding transcription factors facilitating proliferation of glioma and glioma-induced death of neurons [85]. Weston et al. reported that iron was necessary for cell division and cancer pathophysiology was affected by dysregulation of IRPs. Based on the public data from The Cancer Genome Atlas (TCGA), they studied the relationships between the expressions of 61 genes coding iron regulatory proteins (IRPs) in patients with Grade II-III gliomas according to the criteria of World Health Organization and survival. The outcomes were poorer in patients with higher TRF1 expressions, indicating TFR1 played a negative role in the prognosis of glioma [86].

By using the univariate Cox regression model, Yu et al. assessed the prognostic values of genes in two independent datasets of glioblastoma multiforme (GBM). TFR1 was highly expressed at the early stage. Besides being related with clinical outcomes, TFR1 also affected chemoresponse. This reference model potentially allowed identification of new prognostic markers and development of novel therapies [87]. Hence, TFR1 may dominantly mediate the biological behaviors of brain cancer, accurately predict the prognosis of GBM, and help identify new drug targets.

**Transferrin receptor 1 in breast cancer**

Breast cancer is the most devastating type among females of Western countries and also has the highest incidence in women patients of China [74]. The growth of breast cancer cells requires increasing iron uptake that can be realized by TFR1 over expression [76]. TFR1 has been reported to be overexpressed in

---

**Figure 2.** Location of TFR1 in three cancer cell lines. Immunofluorescence analysis of TFR1 in A431, U2OS and U251 MG was obtained from The Human Protein Atlas database. TFR1 (Green fluorescence) expressed in vesicles (A), endosomes and lysosomes (B).
The review of TFR1 in cancer

human breast cancer [88, 89], also as a suitable biomarker for diagnosing and treating cancer patients at the early stage [89]. Based on public microarray datasets consisting of 674 cases of breast cancer, Miller et al. detected the expression of TFR1 gene linked to breast cancer prognosis, and high expression of TFR1 indicated poor prognosis [90]. Singh et al. found that TFR1 expressions in benign and normal lesions were significantly lower than those in invasive carcinoma and premalignant lesions. In the meantime, more TFR1 was expressed in high-grade breast cancer than in other grades [83]. Jiang et al. explored whether breast cancer cells altered the expression of TFRC. The growth of breast cancer was suppressed by regulating the expression of iron transporter genes. Reverse transcription-polymerase chain reaction showed that more TFRC was expressed in MCF-7 cells than in human mammary epithelial MCF-12A cells. Moreover, TFRC antisense oligonucleotides decreased intracellular total iron and TFRC mRNA levels, as well as suppressed 4T1 cell proliferation in culture medium and tumor growth and pulmonary metastasis in a 4T1 mouse model of mammary adenocarcinoma [91]. Wang et al. found that upon breast cancer, IRP2 dominated in iron accumulation. IRP2 overexpression was related with increase of TFR1 and reduction of ferritin heavy chain. Knock-down of IRP2 in human triple-negative breast cancer cells MDA-MB-231 elevated the expression of ferritin heavy chain and reduced that of TFR1, thereby decreasing the labile iron pool and inhibiting the growth of MDA-MB-231 cells in the mammary fat pad of mice [92]. Estrogen receptor (ER)/progesterone receptor (PR) invasive ductal breast cancer accounts for approximately 45% of invasive cases in the United States of America. Figure 3. TFR1 expression in various normal tissues and tumor tissues. Immunohistochemistry analysis of TFR1 in various normal tissues and tumor tissues was obtained from The Human Protein Atlas database. TFR1 is overexpression in multiple tumor tissues compared to normal tissues.
The review of TFR1 in cancer

As a prevalent disease, colon cancer has the eighth highest mortality rate among all cancers of adult males at present [95]. The TFR1 levels on cell surface, which modulate the uptake of TF binding iron, are associated with cell proliferation rate [96]. Since cancer cells have higher TFR1 expression than normal cells, it is a potential target for treating cancers. Overexpressed in many types of cancers, TFR1 still exerts unclear effects on colon cancer, needing further studies. Okazaki et al. found that the circadian organization of molecular clock affected TFR1 expression in colon cancer cells of mice and the 24 h rhythm of TFR1 expression may participate in cancer therapies targeting TFR1 [59, 96]. The progression of colorectal cancer has been related to high intake of dietary iron and chronic intestinal inflammation. Chua, et al. found high expression of TFR1 activated the IL-6/IL-11-Stat3 signaling pathway in the colon, enhanced DSS-induced proliferation and apoptosis of colon epithelial cells, and aggravated mucosal damage and tumorigenesis [97]. Okazaki et al. observed a 24 h rhythm of IRP2 expression in colon-26 tumor-bearing mice, and IRP2 post-transcriptionally modulated the 24 h rhythm of TFR1 mRNA expression through binding iron-response elements, i.e. RNA stem-loop structures. Moreover, the expression of CLOCK (Delta19) attenuated the proliferation rate of wild-type colon-26 cancer and the time-dependent changes of iron levels in cells. Accordingly, circadian organization regulated iron metabolism to facilitate tumor cell proliferation [59]. Referring to TCGA database, the expressions of IRP2 and TFR1 were evaluated and compared to common mutations in cancers. Compared with the normal colon mucosa, IRP2 had overexpression in colorectal cancer, also being positively correlated with the expression of TFR1 [77]. These results provide a therapeutic target for intervening with colorectal tumorigenesis.

Transferrin receptor 1 in liver cancer

The liver is the most important organ related to iron storage [32]. Thus, liver cancer is closely linked to iron metabolism and expression of TFR1. Iron metabolism is altered upon hepatocellular carcinoma (HCC), which is typified by iron-deficient phenotype and essential to tumor growth. Iron has been suggested as a risk factor mainly in HCC patients with cirrhosis and hereditary haemochromatosis (HH). Beckman et al. found HFE (wild-type HH) protein complexes of TFR. Cys282Tyr and His63Asp, two HFE mutations, augmented the affinity of TFR to TF, thus promoting cellular iron uptake and HCC progression [98]. Holmström et al. detected significantly higher mRNA levels of genes participating in uptake of iron, especially TFR1, in HCC. Variations in the expressions of TFR1 in HCCs inferred that bioavailable iron was in-
The review of TFR1 in cancer

increasingly required and the iron turnover was high in neoplastic cells [99]. Miwa et al. found that TFRC expression was elevated with increasing cancer stage, and its selective expression in lesions undergoing proliferation indicated that variations in iron homeostasis were involved in the promotion or progression of tumor [100]. By using immunohistochemical assay, Sakurai et al. detected the expressions of TFR1 and TFR2 in tumor and paracancerous normal liver tissues collected from 41 patients with HCC. They also analyzed iron uptake by HCC cells and hepatocytes with iron staining. HCC samples had significantly higher TFR1 expressions than those of normal samples, and such expression was significantly related with the concentrations of serum des-gamma carboxy prothrombin and alpha-fetoprotein [101]. The above results revealed that TFR was expressed responding to iron deficiency in the midst of liver carcinogenesis. Moreover, according to TCGA database, Iryna et al. found that TFRC was overexpressed but microRNA-152 (miR-152) level plummeted in human HCC tissue compared to those in normal liver tissue, suggesting that raised TFRC levels in human HCC cells and tissues may partly be ascribed to the post-transcriptional mechanism that was mediated through miR-152 down-regulation. In short, targeting of TFRC specific to miR-152 may be a selective HCC therapy [78].

Transferrin receptor 1 in lung cancer

TFR1 predominantly mediates the proliferation of lung cancer by regulating the uptake of iron binding TF. Wang et al. demonstrated that TFR1 promoters contained sequences that mediated the transcriptional inhibition depending on cell density. TFR1 expression was affected by lung cancer cell density [105]. Zhu et al. reported that human lung cells SPC-A1 in which more TFR1 was expressed were more sensitive at identical GA concentrations, and TFR1 expression level in tumor tissue, which was quantified by histopathological assay, may predict the sensitivity of lung cancer to treatment with GA [106].

Kukulj et al. reported that TFR1 expression in lung tumor tissue significantly surpassed that in normal lung tissue. The expression in tumor tissue was positively correlated with alphaglobulin level [107]. In addition, epidermal growth factor receptor (EGFR), which drives oncogenesis, binds and modulates subcellular TFR1 distribution through tyrosine kinase activity, thereby being demanded for the import of cellular iron. Accordingly, EGFR can modulate iron homeostasis in cells by redistributing TFR1, so it is necessary for the onset and progression of lung cancer [79].

Transferrin receptor 1 in ovarian cancer

Ovarian cancer is the fifth most fatal malignancy among females in the USA, and also the most deadly gynecologic type. It is well-documented that TFR1 played key roles in ovarian cancer. Basuli et al. demonstrated that iron metabolism underwent targetable alterations during ovarian cancer. As an iron importer, TFR1 expressions increased in tumor tissues collected from patients with high-grade serous ovarian cancer. Moreover, the expression of TFR1 increased in a TIC model of ovarian cancer [102]. The findings can be exploited therapeutically.

Transferrin receptor 1 in prostate cancer

As a devastating health problem, prostate cancer accounts for 25% of all newly diagnosed cancer cases and approximately 9% of all cancer-related deaths of adult men in the USA annually [74]. However, effects of TFR1 expression and body-iron stores on prostate cancer are still controversial. By using enzymatic immunoassay, Kuvibidila et al. detected serum ferritin and serum transferrin receptor (sTFR) levels in 72 controls and 27 males with newly diagnosed, untreated prostate cancer. The levels of sTFR in males with prostate cancer significantly exceeded those without. However, these changes of sTFR did not correlate with tissue inflammation, tumor stage, or acute-phase proteins [103]. While Johnson et al. detected TFR1 expressions in prostate cancer and normal cells, and reported that the former cells had significantly increased mRNA and protein expressions of TFR1 [104]. Taken together, altered TFR1 expression whether can be a novel biomarker for accurate diagnosis of prostate cancer and prognosis need further study.

Transferrin receptor 1 in leukemia

Human leukemias are liquid malignancies characterized by diffuse infiltration of the bone marrow by transformed hematopoietic progenitors
Iron concentration changes significantly in cancer cells. TFR1 binds mutated HFE to promote iron intake. Iron concentration influences TFRC post-transcription by regulating the binding of IRP1 and IRP2. Meanwhile, iron concentration affects the activities of c-Jun, cyclin D and C-myc. Some miRNAs also influence TFRC transcription. These bioprocesses contribute to cell progression and tumor growth.

Iron as the most important hematopoietic element plays a key role in leukemia. TFR1 was initially found as an important iron uptake receptor inducing the growth of leukemia cell lines, HL-60 and KG-1 [109]. Many studies have found that TFR1 was upregulated in leukemia [110]. Liu et al. investigated the TFR1 could be a potential marker in the diagnosis of acute leukemia (AL) [111]. Ploszyńska A et al. evaluated TFR1 expression on acute lymphoblastic leukemia (ALL) cells. TFR1 expression was statistically higher on T-lineage leukemias while in the B lineage ALL, a significant difference in TFR1 expression existed between precursor B ALL and mature B-ALL, which showed higher TFR1 expression. TFR1 expression positively correlated with Hgb concentration at diagnosis [112]. In summary, TFR1 could be a good target for leukemia therapy.

Mechanisms by which transferrin receptor 1 affects cancers

Given that TFR1 is widely overexpressed in cancers, the regulatory mechanisms of TFR1 for carcinogenesis are complicated and often interrelated. (Figures 4 and 5) The high expression of TFR1 in tumor cells is mainly to meet the iron requirement of tumor cell proliferation [93, 102]. It was reported that TFR1 is a signaling molecule and tyrosine phosphorylation at position 20 by Src enhances anti-apoptosis and potentiates breast cancer cell survival [94]. TFR1 was also reported as a mitochondrial regulator contributed to cancer cell growth via activating JNK signaling pathway [36]. Jeong et al. reported that TFR1 induced the growth of human pancreatic ductal adenocarcinoma (PDAC) by supporting ROS production and mitochondrial respiration in tumor cells. Up-regulation of TFR1 expression generated ROS in PDAC cells by inducing oxidative phosphorylation. Moreover, PDAC growth required ROS derived from mitochondria. Furthermore, the sensitivity of PDAC cells to oxidative stress was determined by TFR1 expression. By triggering ROS production and mitochondrial respiration, TFR1 significantly participated in pancreatic cancer growth and survival [34]. Wang et
al. found that IRP2 increased TFR1, playing a key role in breast cancer progression. As an early nodal point for iron metabolism changes upon breast cancer, dysregulation of IRP2 may result in unsatisfactory outcomes of some patients [92]. Pham et al. found that sphingo-sine kinase 1, a lipid kinase catalyzing the production of sphingosine 1-phosphate, could modulate cell proliferation, survival as well as neoplastic transformation by promoting TFR1 expression [113]. Bayeva et al. reported that iron homeostasis was modulated by mammalian target of rapamycin (mTOR) through variations of cellular iron flux and regulation of TFR1 stability. They identified an anti-inflammatory protein, tristetraprolin, as the downstream target of mTOR which bound TFR1 mRNA and facilitated its degradation. Therefore, TFR1 induced carcinogenesis by regulating metabolism, inflammation and iron [114]. Chirasani et al. demonstrated that TFR1-induced accumulation of oxidants altered cellular signaling through inactivation of pRB protein tyrosine phosphatase and p21/cdk-n1a, and activation of Akt and mitogen-activated protein kinase. When the cell cycle regulators were inactivated, cells were prone to entry into the S phase. TFR not only affected proliferation, but also facilitated release of glutamate, causing decrease in neuron mass through the mediation by N-methyl-D-aspartate-receptor [85]. O’Donnell et al. proved that TFR1 was a key down-stream target for c-Myc, and the expressions of TFR1 in both in vitro and in vivo models of B-cell lymphoma were activated by c-Myc which bound the conserved region of TFR1 directly. Also, inhibiting TFR1 attenuated cell proliferation and induced arrest in the G1 phase without influencing the size of cells. Consistently, expression profiling showed that depletion of TFR1 changed the expressions of cell cycle-regulatory genes. Additionally, increasing TFR1 expression was beneficial to cell growth and significantly boosted in vivo tumor formation mediated by c-Myc. The results mentioned above provide molecular bases for elevated expressions of TFR1 in human tumors, confirming the effects of TFR1 on the network of c-Myc target genes. Targeting TFR1 may be useful for cancer therapy [115].

Therapeutic potential of targeting TFR1 in cancers

As TFR1 is expressed in many kinds of cancers and significantly involved in tumorigenesis and progression of cancers, it may be feasible to intervene with the progression of cancers by targeting TFR1. As evidenced by currently available studies targeting TFR1, curcumin was among the most successful chemopreventive compounds. Jiao et al. evaluated the influence of curcumin on iron regulatory proteins and TFR1. Both TFR1 and IRP increased responding to curcumin [116]. Yang et al. also found curcumin induced the autophagy and apoptosis...
The review of TFR1 in cancer

of different tumor cells by inhibiting TFR1 expression, inferring that curcumin was a potential TFR1 inhibitor for cancer therapy [117]. Anti-transferrin receptor monoclonal antibody A24 significantly blocks the proliferation of T-cell leukemia cell, induces apoptosis of tumor T lymphocytes from acute T-cell leukemia patients [118, 119]. Also, miRNA drug targeting TFR1 has been reported to be a good drug in clinical treatment of leukemia [120]. Moreover, nanomedicine and antibodies targeting TFR1 have been developed for tumor-specific targeted therapy, providing a valuable opportunity for developing eligible TFR1 inhibitors in the field of precision oncology [121, 122]. TFR1 is highly expressed in adult T-cell leukemia/lymphoma. Shimosaki et al. developed a novel molecular-targeted therapy against TFR1 to modulate HTLV-1-associated adult T-cell leukemia/lymphoma iron metabolism to inhibit the adult T-cell leukemia/lymphoma. JST-TFR09, an antibody to human TFR1, has great affinity to TFR1 on adult T-cell leukemia/lymphoma cells. It could interfere with binding between TFR1 and TF, inhibited the iron intake of adult T-cell leukemia/lymphoma, which may become a promising therapy for the treatment of adult T-cell leukemia/lymphoma [123].

Conclusions and future directions

We herein reviewed the roles of TFR1 in the onset and progression of cancers, its regulatory effects on tumorigenesis, together with the potential of TFR1-targeted cancer therapies. Regardless of considerable studies concerning TFR1 since it was discovered, several key issues still exist. (Figure 6) Firstly, whether TFR1 interacts with additional signaling pathways or proteins on the cellular level remains elusive, which may be essential to the development of therapies based on TFR1. Being different from the traditional apoptosis and necrosis, the recently discovered ferroptosis is caused by iron-dependent accumulation of lipid peroxides. Cells which are subjected to ferrop-
totic death suffer from shrinkage of volumes and raised density of the mitochondrial membrane. Iron metabolism plays a curial role in ferroptosis [124]. Ferroptosis induced by erastin or Cys2 deprivation is prevented by silencing TFRC gene, which encodes TFR1 required for the uptake of TF-iron complexes into cells. However, TFR1, an important iron intake receptor in cancer cells, still has unclear functions and mechanisms in ferroptosis. Furthermore, TFR1 expressions are up-regulated in some drug-resistant human cancer cells [45], requiring more in-depth studies though. Last but not least, since drug therapies may suppress TFR1 expression, developing a TFR1-specific reversible antagonist is the only single most effective strategy for both basic research and clinical practice. Notably, tumor progression can be inhibited through magnetic fields that augment the concentrations of TFR1-targeted superparamagnetic iron oxides in tumor tissues, inspiring future cancer therapy [125-127].

Acknowledgements

We gratefully acknowledge the funding from the Science and Technology Planning Project of Shenzhen of China (JCYJ2017041214090-4406), and the National Basic Research Program of China (51777171).

Disclosure of conflict of interest

None.

Address correspondence to: Peng Shang, Research & Development Institute in Shenzhen, Northwestern Polytechnical University, Shenzhen 518057, China; Key Laboratory for Space Bioscience and Biotechnology, Institute of Special Environment Biophysics, School of Life Science, Northwestern Polytechnical University, Xi’an 710072, Shaanxi, China. E-mail: shangpeng@nwpu.edu.cn

References

The review of TFR1 in cancer


[37] Moreno-Navarrete JM, Novelle MG, Catalán V, Ortega F, Moreno M, Gomez-Ambrosi J, Xifra G,
The review of TFR1 in cancer


[62] Biswas S, Tapryal N, Mukherjee R, Kumar R, Mukhopadhyay CK. Insulin promotes iron up-
take in human hepatic cell by regulating transferrin receptor-1 transcription mediated by hypoxia inducible factor-1. Biochim Biophys Acta 2013; 1832: 293-301.


[75] Singh M, Mugler K, Hailoo DW, Burke S, Nemesure B, Torkko K, Shroyer KR. Differential
The review of TFR1 in cancer


[105] Wang J, Chen G, Pantopoulos K. Inhibition of transferrin receptor 1 transcription by a cell
The review of TFR1 in cancer


