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FBXW7 Pathway Functions as a Promising Therapeutic Target of Cholangiocarcinoma

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Introduction

Cholangiocarcinomas (CCAs) are a heterogeneous group of rare malignancies originating from the epithelial cells of the biliary tract, which can be classified anatomically as intrahepatic (IHCC), perihilar (PHCC), and distal (DCC) CCA. Although rare, the incidence of CCAs has increased worldwide over the past 3 decades, which may be caused by the following reasons: firstly, diagnosis of CCAs is usually in the 70's of age, its incidence is inevitably increased with the prosperity of aging society; secondly, more CCAs are detected in recent years because of the development of imagology, especially in developing countries. However, the risk factors of CCAs remain to be confirmed at present. In addition, the 5-year overall survival rate after diagnosis remains low at 10% [1,2].

Surgery is the only curative treatment for CCA patients; however, less than one-third of patients are resectable at diagnosis as metastasis already occurred [3]. Moreover, majority of patients with CCAs develop an early recurrence after resection. The relatively low resection rate and high relapse rate provide the rational of adjuvant strategies to improve prognosis of CCA patients. Unfortunately, the highly desmoplastic nature, extensive support by a rich tumor microenvironment, and profound genetic heterogeneity of CCAs all contribute to its therapeutic resistance [4]. Therefore, further investigation on the molecular mechanisms of CCA metastasis is eagerly needed to find new diagnostic biomarkers and therapeutic targets.

Discussion

CCAs are featured by prominent heterogeneous nature and highly desmoplastic and hypovascularized stroma [5]. The initiation and development of CCAs involve genetic and epigenetic alterations, chromosome aberrations and profound changes in oncogene and inflammatory signaling pathways [6]. Furthermore, IHCC, PHCC and DCC exhibited completely different phenotypes in tumor etiopathogenesis, diagnosis and treatment strategies and prognosis, which makes CCAs a group of rather complicated malignances.

Metastasis in early stage is another characteristic of CCAs. IHCC usually disseminated intrahepatically through venous system, while lymphatic system is the most common route for PHCC and DCC metastasis. EGFR has been identified as an independent risk factor for IHCC prognosis and is associated with clinical factors involved in PHCC and DCC progression and invasion. VEGF expression is correlated with IHCC intrahepatic metastasis [7]. Several molecules, including NGF, NCAM, MMP, Ach and TGF have been reported to have prognostic significance, and offer clues to the mechanism of CCA neural invasion [8].

Although many advances have been made in the diagnosis and management of CCA, no standard adjuvant strategy for CCAs has been made at present as current evidences for adjuvant therapy in CCAs is poor. The vast majority of published literatures are statistically underpowered, nonrandomized, restricted to short-term follow-up, or demonstrated poor response rates [9]. Currently existing large-scale randomized clinical trials also have their own inherent limitations. The well-known large-scale randomized phase III trial of systemic therapy performed by Valle J et al. showed that gemcitabine plus cisplatin was associated with a significant survival advantage without the addition of substantial toxicity, as compared with gemcitabine alone (11.7 months *vs* 8.1 months) [10]. However, IHCC, PHCC and DCC were grouped together in this study despite their obvious differences in anatomic location, etiopathogenesis, diagnosis, treatment and prognosis [6,11]. Furthermore, adjuvant therapy agents, doses and scheduling varied greatly among different literatures [12-14]. In addition, the clinical data of CCAs are usually collected over many years with a limited number of patients for the rarity of this disease, which inevitably lead to bias for the variability of diagnosis and treatment strategy. All these factors contribute to the difficulty of making comparisons between series and preclude clinical practice guidelines in establishing a "standard of care" for patients with advanced CCAs [15]. More confirmed evidences and treatment strategies are eagerly awaited for CCA patients.

In the era of precision medicine, targeted therapy based on gene sequence and expression provides a potentially effective way for CCA patients. Breakthroughs of immunologic therapies with antibodies targeting cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and the programmed cell death protein 1 pathway (PD-1/PD-L1) have been made in a variety of malignancies [16-21]. Recent clinical trials of CCAs have focused on the agents targeted to specific genes such as EGFR and VEGFR, but promising clinical activity was not observed to date [22-24]. Further elucidation on tumor biology and molecular markers of CCAs is essential for future evaluation of targeted therapies.

In an article published in Oncotarget, Yang et al. [25] reported that FBXW7, a substrate recognition component of the SCF (complex of SKP1, CUL1 and F-box protein) complex, could suppress epithelial-mesenchymal transition, stemness and metastatic potential of CCA

cells. The expression of FBXW7 was deficient in CCA cell lines and tumor tissues compared with human intrahepatic biliary epithelial cell line and tumor adjacent tissues. Besides, FBXW7 expression was negatively correlates with tumor metastasis, TNM stage and histological grade of IHCC and PHCC. The role of FBXW7 in suppressing CCA metastasis, epithelial-mesenchymal transition and stemness was confirmed both *in vitro* and *in vivo*. Mechanistically, mTOR/ZEB1 signaling pathway was investigated to mediate the function of FBXW7 in suppressing CCA metastasis. These results defined a critical function of FBXW7 in regulating CCA metastasis. Furthermore, mTOR could be a potential therapeutic target of CCAs, especially for patients with FBXW7 deficiency.

The ubiquitin ligase component FBXW7 is regarded as the most commonly deregulated ubiquitin-proteasome system protein in human cancers [26]. It mediates the ubiquitin-dependent proteolysis of numerous well-known oncoproteins, including Cyclin E, Notch, c-Jun, c-Myc and mTOR [27]. Most of these substrates are transcriptional regulators that control complex gene-expression programs and this extends FBXW7 impact far beyond its direct substrates [26]. It has been demonstrated to play an essential role in cell cycle progression, cell proliferation, differentiation, DNA damage response, maintenance of genomic stability, and neural cell stemness. Lessons learned from FBXW7-associated murine cancer models also convincingly demonstrated that it is a bona fide tumor suppressor gene with extensive functions [26]. Recent genetic profiles of human cancers based on high-throughput sequencing revealed that FBXW7 is among the most frequently mutated cancer genes [28-33]. Thus, FBXW7 has been illuminated to be a central mediator in tumorigenesis [34]. Interestingly, a recent report showed that FBXW7 could inhibit cancer metastasis in a non-cell-autonomous manner by modulating the recruitment of both monocytic myeloid-derived suppressor cells and macrophages through FBXW7/NOTCH/CCL2 axis [35], implicating FBXW7 may also be a critical regulator in tumor microenvironment. With the roles and mechanisms of FBXW7 in suppressing tumorigenesis being further illuminated gradually, novel therapeutic strategies targeting FBXW7 pathway in cancer have been designed [26]. Furthermore, FBXW7 has been demonstrated to be a prognostic marker in colorectal cancer, gastric cancer, IHCC, hepatocellular carcinoma and T cell acute lymphoblastic leukemia [36-40], indicating FBXW7 may be measured perioperatively for making adjuvant therapeutic regimen and evaluating prognosis. Yang et al. [25] demonstrated FBXW7 plays a pivotal role in suppressing CCA metastasis, which may serve as an essential clue for targeting FBXW7 pathway in CCA patients.

mTOR is a well-known ubiquitination target of FBXW7 [41]. Several mTOR inhibitors (sirolimus, everolimus and temsirolimus) have been approved by FDA with indications for cancer treatment [42]. Due to the fundamental role that mTOR plays in major cell processes, mTOR inhibitors are usually used in combination with other adjuvant therapy agents. Recently, several preclinical experiments have obtained positive results in enhancing the anti-tumor effects by combining mTOR inhibitors with gemcitabine in treating advanced pancreatic cancer [43,44]. Moreover, phase I clinical trial has demonstrated the favorable toxicity profile of the combination in pancreatic cancer patients [45]. As known, CCAs share many similarities with pancreatic adenocarcinoma in tumor phenotypes, including extremely stroma-rich and resistant to chemotherapy. As mentioned above, gemcitabine is one fundamental agent in CCA chemotherapy. Moreover, mTOR inhibitor, combined with other antitumor agents or not, could inhibit CCA development, and mTOR has been considered to be a potential therapeutic target of CCAs in recent reports [46-48]. Especially, it has been validated that inhibition of mTOR signaling pathway could protect FBXW7-deficient mice from radiation-induced tumor development [49]. Similar result was observed in a clinical case harboring an FBXW7 mutation both clinically and radiographicly benefited from treatment with the mTOR inhibitor temsirolimus [50]. Thus, it is promising to combine mTOR inhibitors with gemcitabine in CCA adjuvant therapeutic regimen, especially for patients with FBXW7 deficiency.

Conclusion

In conclusion, in spite of the significant progress in cancer research and management, the treatment strategy and prognosis of CCA patients are still poor now. More accurate and optimal evidence are needed for discovering novel therapeutic targets and making standard treatment strategy. Considering the metastatic feature of CCAs and the mechanistic and therapeutic roles of FBXW7 and mTOR in CCAs revealed by Yang et al. and others, FBXW7-mTOR pathway may provide a potential therapeutic target of CCAs, which deserves further investigation.

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