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Review

Soluble resistance-related calcium-binding protein in cancers

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ABSTRACT

Soluble resistance-related calcium binding protein (Sorcin) is an oncoprotein expressed at high levels in human cancers and confers multidrug resistance (MDR) in several tumors. Sorcin participates in a number of neoplastic processing including metastasis and apoptosis. In this review, we summarize and discuss the relationship of Sorcin with tumors as well as its regulatory mechanisms. Sorcin is increasingly considered as a potential molecular target for therapeutic intervention.

1. Introduction

Cancer is considered a major public health problem worldwide, with an estimated 1,688,780 new cases and 600,920 deaths in 2017 according to the latest global statistics [1].Soluble resistance related calcium binding protein (Sorcin) is oncoprotein expressed at high levels in several human cancers and confers multidrug resistance (MDR) in several tumors. Sorcin located in chromosome 7, in the same amplicon of other proteins involved inmultidrug resistance (MDR) such as ABCB4 and ABCB1 (MDR1, P-glycoprotein, P-gp),and participates in the regulation of calcium homeostasis in cells [2]. Sorcin has two main isoforms: the 22-kDa isoform, quantitatively the major band, is found in the cytosol, whereas 18-kDa isoform is specifically localized in the mitochondrial fraction.

The EF-hand is a common helix-loop-helix structural motif used by proteins to bind calcium, which determines the transition from a “closed” structure to an “open” structure [2–4]. Sorcin belongs to the penta-EF-hand (PEF) protein family, which contains five EF-hand motifs that associate with membranes in a calcium-dependent manner. Sorcin was first identified in a vincristine resistant Chinese hamster lung cell line [5,6], and its upregulation is usually associated with the development of MDR phenotypes in a variety of cancer cell lines. Sorcin is also overexpressed in many tumors and pointed at a possible role as an oncoprotein [7,8], such as colorectal cancer, lung cancer, leukemia, breast cancer, gastric cancer and so on. In this study, we aim to present an overview of the current literature on the role of Sorcin in multiple cancers. Aggregating available evidence might support further research into Sorcin as a potential target for cancer diagnostics, treatment regimens and prognoses, thereby improving global cancer care and patient well-being.

2. Sorcin in cancers

2.1. Colorectal cancer

Colorectal cancer (CRC) is one of the common digestive tract malignancies, being the third most commonly diagnosed cancer and the fourth cause of cancer-related mortality worldwide [9]. A recent study has reported that upregulation of Sorcin is correlated with tumor metastasis and triggering apoptosis and a poor prognosis of CRC.

Overexpression of Sorcin in CRC cells (HCT116) enhanced migration and invasion and led to remarkable downregulation of E-cadherin and upregulation of N-cadherin, vimentin, fibronectin, and a-SMA. Concluding, Sorcin promoted the transition from the epithelial to the mesenchymal (EMT) phenotype, which is considered a pivotal process in cancer metastasis. Moreover, this study demonstrated that Sorcin enhances metastasis of CRC through activating the PI3K/Akt/mTOR pathway [10] (Fig. 1).

The 22-kDa Sorcin isoform is upregulated in human CRCs and in drug resistant human CRC cells (HT-29 and HCT-116). Sorcin enhances the accumulation of Ca^{2+} in the endoplasmic reticulum (ER). As such it prevents ER stress and, in support of this function, the 22-kDa Sorcin was upregulated under conditions of ER stress. In contrast, silencing of Sorcin activated caspase-3, caspase-12 and GRP78/BiP, triggering apoptosis through the mitochondrial pathway [11] (Fig. 1).

The 18-kDa isoform of Sorcin and TNF receptor-associated protein 1

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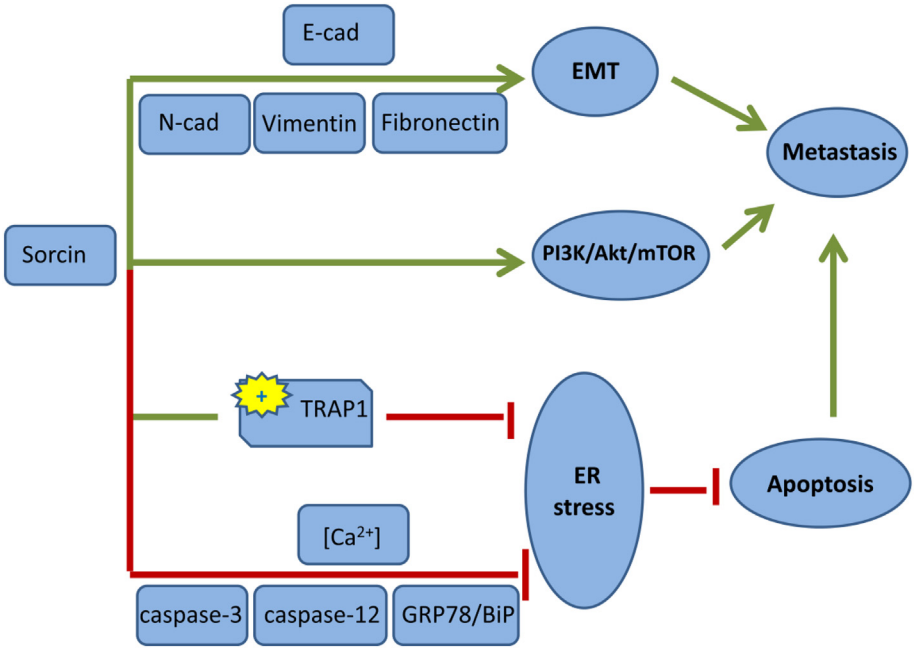

Fig. 1. Sorcin play a role in CRC. Sorcin promote EMT and trigger apoptosis.

(TRAP1) are both coupregulated and implicated in multidrug resistance in human CRC. TRAP1, the only mitochondrial member of the anti-apoptotic heat shock protein 90 protein family, is involved in protection from oxidative stress and apoptosis [12–14]. TRAP1 specifically interacts with Sorcin in a Ca^{2+}-dependent manner and this interaction is required for the antiapoptotic function of TRAP1. TRAP1/Sorcin interaction is prevented in case of Ca^{2+} chelation [12,13] (Fig. 1).

2.2. Lung cancer

Lung cancer is one of the most common malignant tumors. More than 50% of the lung cancer patients are diagnosed in advanced stages with a 5-year survival of less than 20%, despite the rapid development of diagnosis and treatment [15–17].

Sorcin can bind and thereby sequester cytosolic calcium, which may contribute to cisplatin-resistant and taxol-resistant phenotypes of human lung adenocarcinoma cells (A549) [18].In this process, Sorcin may inhibit the PI3K/Akt and MEK/ERK pathways [18].

The Sorcin-depleted phenotype attenuates EMT and suppresses metastases in lung adenocarcinoma cells (A549) and lung fibrosarcoma cells (HT1080) [19].

Gemcitabine-based chemotherapy is one of the more effective chemotherapy regimens against non-small cell lung cancer (NSCLC), Sorcin overexpression was associated with gemcitabine resistance and a poor prognosis in NSCLC patients [20]. Sorcin could be a gemcitabine resistance associated target for further validation.

2.3. Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is an epidemic cancer in Southeast Asian countries, and North Africa. Often, NPC patients are diagnosed at advanced stages with a combination of chemotherapy and radiotherapy as an effective therapy to improve the survival status [21,22], and chemoresistance being an essential aspect of NPC chemotherapy failure.

Sorcin was found to be upregulated in a NPC cisplatin-resistant cell line (CNE2/DDP). Sorcin silencing increased the cisplatin sensitivity of the cells. Mechanisms have been reported that Sorcin may modulate the activity of NF-kB and phosphorylation of AKT [23].

2.4. Breast cancer

Breast cancer is a disease affecting many women worldwide, and the incidence of breast cancer in Asian countries has been increasing over the past decades [24,25].

The role of Sorcin in breast cancer metastasis has mainly been described via its effect on EMT and cancer stem cells (CSCs). Sorcin-depletion reduces the pool of $CD44^{+}/CD24^{-}$ and $ALDH1^{high}$ CSCs as well as mammosphere-forming capacity in MDA-MB-231 breast cancer cells. Downregulation of Sorcin attenuates EMT and CSCs partly through E-cadherin and vascular endothelial growth factor expression with subsequent suppression of the metastasis. In addition, overexpression of Sorcin in MCF7 cells has been shown to increase their migration and invasion in vitro [26].

Sorcin plays a critical role in the maintenance of the MDR phenotype of the human breast cancer cell line. Knockdown of Sorcin expression promotes chemotherapeutic agent induced apoptosis through regulating c-fos/c-jun and Bcl-2/Bax expressions. Nevertheless, knockdown of Sorcin did not alter expression or function of P-gp, which is a typical form of MDR [27] (Fig. 2).

The 18-kDa isoform of Sorcin, together with TRAP1 mitochondrial antiapoptotic protein, protects f breast carcinoma cells rom apoptosis induced by ER stress agents and paclitaxel [28] (Fig. 2).

Sorcin expression was upregulated in the human serum of breast cancer patients who are resistant to neoadjuvant chemotherapy (NAC) when compared with that of NAC sensitive patients [29]. Sorcin expression was also upregulated in paclitaxel resistance of breast and ovarian cancer cells [30]. Furthermore, Sorcin takes part in the process of dihydromyricetin reverses MDR by increasing free Ca^{2+}, as well as inducing apoptosis in MCF-7/ADR and K562/ADR [31] (Fig. 2).

2.5. Diffuse large B cell lymphoma

Diffuse large B cell lymphoma (DLBCL) is a subtype of B cell non-Hodgkin lymphoma with clinically aggressive behavior. DLBCL has high response rate to chemoimmunotherapy and is potentially curable [32].

Development of resistance to the CHOP chemotherapeutic regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) is a major cause of treatment failure and mortality in approximately 40% of