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Review Article

An Embryonic Gene (Cripto-1) in Cancer Stem Cells

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Abstract

Cripto-1 (TDGF-1) is a cell surface glycosylphosphatidylinositol-linked glycoprotein which functions as an obligatory co-receptor for transforming growth factor-β (TGF-β) family members. Cripto-1 is essential for early embryonic development and maintenance of embryonic stem cells. Cripto-1 has been shown to be activated in numerous human tumors. Notably, it is expressed in a population of cancer stem cells (CSCs) and facilitates the epithelial to mesenchymal transition (EMT) program. Furthermore, Cripto-1 can significantly enhance tumor cell migration, invasion and angiogenesis. Collectively, these facts suggest that Cripto-1 may be an attractive target in the diagnosis, prognosis and therapy aiming at cancer cell subpopulations with stem-like properties within aggressive tumors.

ABBREVIATIONS

TDGF-1: Teratocarcinoma-Derived Growth Factor 1; EGF: Epidermal Growth Factor; TGF-β: The Transforming Growth Factor-β; EMT: Epithelial to Mesenchymal Transition; CSCs: Cancers Stem Cells.

INTRODUCTION

The treatment of cancer is undergoing evolutionary changes as new information about the biology of cancer emerges. Nevertheless, one in four deaths are estimated to result from cancer according to data from 2013 [1]. Conventional therapies such as cytotoxic chemotherapy, radiotherapy and surgical resection can temporarily shrink and restrain the primary tumor but generally the tumor tends to relapse. New targeted therapies, which act on specific molecular targets that are associated with cancer such as Trastuzumab (a monoclonal antibody specifically targeting HER2/neu-over expressing breast tumors), Bevacizumab (a monoclonal antibody therapy against VEGF) or Gefitinib (a tyrosine kinase inhibitor targeting the EGFR, used to treat advanced non-small cell lung cancer),increase the effectiveness and precision of treatment, survival and quality of the patient's life. Unfortunately, even targeted therapies do have limitations. Mainly, cancer cells can become resistant to them. Resistance to chemotherapy and molecularly-targeted therapies is one of the major causes which under lies cancer treatment failure [2]. Ginsburg and Willard [3] have reported that chemoresistance and treatment effects depend on the distinct patterns of genes associated with stemness/differentiation pathways. Indeed, tumors are a heterogeneous mixture consisting of epithelial non-stem cells and cancer stem cells (CSCs) with mixed epithelial to mesenchymal phenotypes [4]. Reports have shown a link between stem-like properties and therapy resistance in glioblastoma, colon cancer, breast cancer, acute myelogenous leukemia and numerous other tumors demonstrating that CSCs are more resistant to therapy compared to non-CSCs [5-8]. This minority tumor subpopulation of CSCs, due to features like over expression of ABC transporters, a slow rate of self-renewal, and an active DNA repair capacity, is probably responsible for chemoresistance in cancer and the reason why treatment fails [9]. Interestingly, many current drug treatments result in an enrichment of CSCs in the tumor [10] e.g. oxaliplatin treatment of colon cancers actually boosted the abundance of CSCs by more than 10 times [11]. It is clear that a more complete understanding of the properties and characteristics of CSCs is a key to future success in cancer treatment. To improve the outcome of cancer treatments, CSCs must be effectively targeted and eradicated.

CANCER STEM CELLS

In adult organisms, normal stem cells can be found in different tissue types and function as an internal repair system, dividing to replenish specialized cells and also maintaining normal turnover of regenerative organs, such as blood, skin, or intestinal tissues [12]. Similar to normal stem cells, CSCs have been suggested to maintain the tumors and the abnormal regulation of CSCs is implicated in the generation and progression of malignant tumors. CSCs are defined by their ability to efficiently regenerate the original phenotype of the tumor upon inoculation into immune deficient mice [13]. This functional definition is often complemented by including the expression of cell-surface markers that are also expressed by the normal stem cells in the tissue of origin [14,15]. CSCs, also called tumor-initiating cells, were initially identified in the hematopoietic system [16,17]. Later, they were also found in solid tumors, including those arising in the breast, lung, prostate, colon, brain, head and neck, and pancreas [14,16,18,19]. Likewise, epithelial-mesenchymal

transition (EMT), which is critical during normal development, fibrosis and wound healing, has also been implicated as a means by which transformed epithelial cells can acquire the abilities to invade, resist apoptosis, and disseminate, thus contributing to tumor invasion and metastasis[20-23]. Recently, the link between activation of the EMT program and the genesis and maintenance of cells with stem cell-like properties has been confirmed [24-26]. This connection may generate more aggressive cell behaviors, hence demanding the development of therapeutic strategies designed to interfere with EMT and CSC activity within tumors.

CRIPTO-1 AND EMT

The Teratocarcinoma-Derived Growth Factor-1, *Tdgf-1* or *Cripto-1* gene, a member of the TGF-β super family, plays a fundamental role in normal development as well as during the regulation of self-renewal and pluripotency of mouse and human embryonic stem cells. Furthermore, Cripto-1 represents a clear example of an embryonic signaling molecule which when reactivated in an uncontrolled manner can drive cell transformation and tumor progression in adult tissues [27]. Interestingly Cripto-1 effects multiple signaling pathways known to be EMT triggers such as transforming growth factor (TGF)-β, fibroblast growth factors (FGFs), Wnts and Notch [28]. Multiple studies showed that Cripto-1 over expression in mammary epithelial cells and multiple cancer cell lines leads to their enhanced migration and invasion capacity. HC-11 mouse mammary epithelial cells over expressing Cripto-1 undergo EMT, as shown by a decrease in E-cadherin expression and an increase in vimentin, N-cadherin, and Snail expression [29]. Also over expression of Cripto-1 in MCF-7 breast cancer cells, Caski human cervical carcinoma cells and LS174-T colon cancer cells show a significant increase in their migration and invasion behaviors compared with parental cell lines. Our previous study showed that mammary tumors from MMTV–Cripto-1 transgenic mice exhibit areas of morphological changes associated with EMT such as reduction of intercellular adhesion proteins, e.g. E-cadherin, and an increase in the expression of mesenchymal markers, including N-cadherin and vimentin. Moreover, we detected increased expression of several integrins, including integrins β3, β5, β1 and β4 [29], also linked to EMT and cell spreading. Markers of EMT could also be detected in uterine leiomyosarcomas that develop in approximately 20% of nulliparous or multiparous MMTV–Cripto-1 mice [30].Since Cripto-1 has been found to promote EMT *in vitro* and *in vivo* in mouse mammary epithelial cells, cancer cell lines and mouse mammary tumors [28], it is possible that this gene is involved in driving an EMT program in breast cancer stem-like cells thereby supporting their self-renewal and metastatic abilities [31].

Cripto-1 expression is not restricted to malignant breast tissues.Cripto-1 is over expressed in a variety of human tumors and its expression has been associated with more aggressive behavior in several types of cancers [28]. Increased Cripto-1 expression and decreased E-cadherin expression have been positively associated with tumor progression, poor prognostic factors (e.g. tumor size, depth of invasion, lymph node metastasis, liver metastasis, and TNM stage) in patients with gastric, breast and colon cancers [32,33].Several reports have showed that Cripto-1 might also play a role in human melanomas [34, 35]. Cripto-1 expression was detected in 43% of primary human cutaneous melanomas and in 57% of melanoma cell lines. In melanomas, Cripto-1 strongly enhanced the motility of melanoma cell lines and blocking of Cripto-1 expression using small-interfering RNAs significantly inhibited growth and the invasive ability of melanoma cells [34].

CRIPTO-1 AND CANCER STEM CELLS

Cripto-1 is known to be involved in stem cell maintenance and pluripotency [31]. Furthermore, Cripto-1 contributes to the tumorigenicity of invasive cancer cells with stem-like characteristics [36] and multiple groups have detected stem cell markers in Cripto-1-positive human cancer cells. Cripto-1 has been demonstrated to be a potential marker for the identification of CSCs in human malignant melanomas [37]. Strizzi et al, using Fluorescence-activated Cell Sorting (FACS),isolated from a human melanoma cell line a subpopulation of cells that expresses Cripto-1 on the cell surface and possesses stem-like characteristics [37]. Although the Cripto-1-positive subpopulation represented a relatively small fraction of the population, it showed a more spindle-shaped morphology, and exhibited increased expression of embryonic stem cell-associated transcription factors, such as Oct-4 and Nanog, as compared to the parental melanoma cells [37]. In another study, Cripto-1 was identified together with Oct-4 and SUZ-12 in a small subpopulation of stem-like cells in both hormone-responsive and non-responsive human prostate tumor cells [38]. Furthermore, Watanabe and colleagues reported that Cripto-1 is heterogeneously expressed in human embryonal carcinoma (EC) cells, which are pluripotent stem cells derived from germ cell teratocarcinomas (the malignant counterpart of embryonic human stem cells). In accordance with Cripto-1 expression on the cell surface, two populations of EC cells were isolated that expressed high and low levels of Cripto-1. The Cripto-1 high subpopulation formed significantly more tumor spheres *in vitro* under serum-free conditions than the Cripto-1 low-expressing cells. Additionally, by injecting Cripto-1 high expressing cells subcutaneously into nude mice, the authors observed that these cells were able to generate significantly larger tumors with shorter latency period when compared with tumors derived from Cripto-1 low expressing cells[39]. In addition, Cripto-1/GRP78 (heat shock 78kDa glucose-regulated protein) signaling has been suggested as an important pathway that regulates hematopoietic stem cell quiescence [40]. Under hypoxic conditions, Cripto-1 expression was essential in regulating the lineage specification of a CD34/GRP78 myeloid progenitor population in the hematopoietic stroma niche of the bone marrow [40]. Finally, the Nodal/Cripto-1 signaling pathway has been shown to maintain self-renewal and *in vivo* oncogenic capacity of pancreatic CSCs [41]. Inhibition of this signaling by blocking the Alk4/7 receptor reversed the chemoresistance of orthotopically engrafted pancreatic CSCs, suggesting a novel therapeutic approach to target pancreatic CSCs. All these novel findings suggest that Cripto-1 may represent an important marker for the identification of a cancer cell subpopulation with stem-like properties within aggressive tumors that are resistant to conventional therapy.

MULTIPLE MODALITIES TO TARGET CRIPTO-1

As Cripto-1 may be expressed in a population of CSCs and contribute to CSC self-renewal and EMT, it is potentially an attractive therapeutic target. Beyond the potential role of Cripto-1 in the induction or maintenance of CSCs, the role of Cripto-1 in

the tumor microenvironment makes it a potential therapeutic target since it also assists in sustaining the niche in which the tumor thrives. Our laboratory and others have successfully targeted Cripto-1 *in vitro* in various types of cancer cell lines and *in vivo* in several types of xenograft tumor model systems thereby abrogating its effects on tumor growth and metastasis [36]. There are various methods that have been shown to counteract the oncogenic effects of Cripto-1 by targeting either Cripto-1 mRNA or protein. Interference of Cripto-1 expression has been effective by using antisense oligonucleotides against Cripto-1 *in vitro* in breast, colon and ovarian cancer cells, and *in vivo* in colon cancer xenografts [42-45]. Recently, it has been shown that micro RNAs (miRNA), small non-coding RNA molecules that inhibit mRNA translation, are involved in the regulation of Cripto-1 expression. In particular, miR-15a -16 was shown to down-regulate Cripto-1 expression and disrupt Cripto-1-mediated invasion of non-small cell lung cancer cells (NSCLC) *in vitro* [46]. Also, miR-15a -16 was able to reduce the tumor volume of NSCLC xenograft tumors [46]. Using proper delivery systems, this strategy could prove useful in targeting Cripto-1 expressing cells refractory to normal therapy.Cripto-1-neutralizing monoclonal antibodies and small molecule compounds that target the various domains of Cripto-1 have shown to be efficacious by inhibiting the proliferation of multiple cancer cell lines, blocking the growth of tumor xenografts, enhancing the effects of chemotherapeutic regimens and inducing apoptosis [47-51]. Antibodies directed against the EGF-like domain of Cripto-1 have prevented the activation of Smad signaling by interfering with Nodal-mediated Alk4 activation [48]. Antibody neutralization of the EGF-domain and its interactions can also impair the activation of Akt leading to apoptosis as seen in a multi-drug resistant leukemia model [49]. An antibody directed against GRP78 is also able to prevent Cripto-1-mediated activation of MAPK and Akt [52]. Antagonists of Cripto-1's CFC domain, such as monoclonal antibodies[47], Alantolactone (a natural small molecule compound) [53], and a synthetic Cripto-1-binding peptide [54] have been shown to disrupt Cripto-1/Nodal binding and suppress Cripto-1-mediated inhibition of TGF-β/Active in growth inhibition. Also, a kinase-deficient soluble version of Alk4 has recently been shown to be efficacious in blocking Cripto-1 activation of Akt [55]. Cripto-1 as a possible marker for CSCs provides the potential of specifically delivering nanomedicines to Cripto-1-expressing cells using non-neutralizing Cripto-1 antibodies, similar to a recently concluded phase I clinical trial using a cytoxin-conjugated antibody directed against the amino-terminal region of Cripto-1[50], thereby eliminating Cripto-1-positive CSCs.

Taken together, these data show that targeting Cripto-1 in a therapeutic setting can be quite advantageous due to its role in multiple processes of tumor formation and metastasis. The combination of therapies directed against Cripto-1 along with treatments against the bulk tumor could provide not only success against a primary tumor, but prevent metastasis and relapse.

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