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REVIEW

Calreticulin and Cancer

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Abstract Calreticulin (CRT) as a multi-functional endoplasmic reticulum protein is involved in a spectrum of cellular processes which ranges from calcium homeostasis and chaperoning to cell adhesion and finally malignant formation and progression. Previous studies have shown a contributing role for CRT in a range of different cancers. This present review will focus on the possible roles of CRT in the progression of malignant proliferation and the mechanisms involved in its contribution to cancer invasion.

Keywords Calreticulin · Endoplasmic reticulum · Cancer · Malignant progression · Invasion · Metastasis

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Calreticulin

Calreticulin (CRT), as a multifunctional protein resides in the endoplasmic reticulum (ER) [1] as well as other cellular compartments such as the cell membrane, cytoplasm and nucleus [2]. The CRT structure includes the N and C terminals and three different domains [3] (Fig. 1). The N-terminal is a cleavable amino acid signal sequence while the C-terminal includes a KDEL ER retrieval signal. These specific sequences of amino acids are responsible for the different functions of CRT such as chaperoning [4], integrin binding [5], attachment to steroid hormone receptors [6], Ca^{2+} binding and interacting with other chaperones like calnexin [7].

Biological Functions

Molecular chaperoning and calcium homeostasis are two main physiological role of CRT inside the ER. It is also present on the membrane of other cellular organelles, cell surface and in the extracellular environment where it contributes to different physiological and pathological roles such as cell adhesion, transcriptional activities and gene expression regulation as well as recognition and elimination of apoptotic cells [8, 9]. Finally, new roles of CRT in the extracellular space such as the involvement in cutaneous wound healing [10] and possible diagnostic applications of CRT in blood [11] or urine [12] have emerged.

Transcriptional Regulation of CRT

The human CRT gene is located on chromosome 19 [13] and its promoter region includes multiple regulatory sites such as AP-1, AP-2 and GC rich areas (H4TF-1) [14] which are usually present in actively transcribed genes during cellular proliferation [1]. Calcium depletion is one of the most

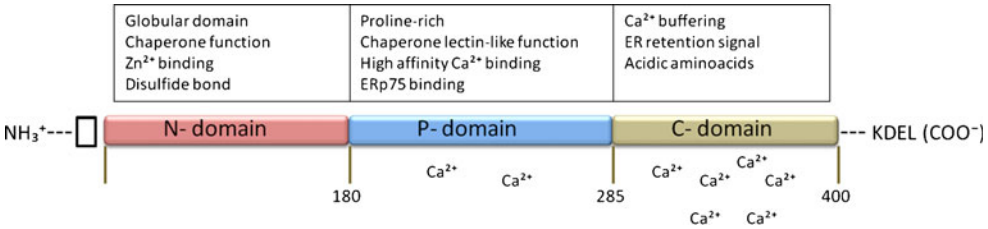

Fig. 1 Calreticulin protein structure and functions

important activators of the CRT gene promoter [15, 16]. A number of transcription factors have been identified so far as the modulators of CRT gene which seem to be critical during embryonic development or pathological conditions [17].

Nkx2.5, COUP-TF1, GATA6, Evi-1 and MEF2C have been introduced as important regulators of CRT expression during embryonic cardiogenesis [18–20]. Regulators of CRT expression during pathologic conditions, especially modulators of CRT overexpression in cancer are less characterized. Depletion of Ca^{2+} stores, an intracellular stress indicator, is able to induce CRT gene expression in vitro and in vivo [15]. A recent study revealed that TNFα works as a negative regulator of CRT expression through the suppression of C/EBPα [21].

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CRT has been found to be up-regulated in proliferating myoblasts [22] while its nuclear/ER expression ratio is increased in malignant liver cells [23]. Furthermore, CRT as a major calcium homeostasis regulator is possibly engaged in cellular invasion and metastasis through the induction of cell migration [24] as migratory and invasive potentials of cancer cells are associated with dynamic intracellular Ca^{2+} signaling events [25]. It is also known that CRT is capable of preventing anoikis [26], although Akt modification was reported as a major contributor in CRT-associated apoptosis [27–29].

An association between the presence of CRT and tumorigenesis has been the focus of recent studies where they have mostly reported positive correlations as summarized in Tables 1 and 2. In brief, CRT over expression has been reported in ductal carcinoma of the breast [30, 31], bladder cancer [32], prostatic adenocarcinoma [33], hepatocellular carcinoma [23, 34], pancreatic malignancies [35], esophageal cancer [36, 37], gastric cancer [38], colon cancer [39], melanoma [40, 41] and leukemia [42]. In addition, CRT expression is also associated with a more invasive and advanced malignant processes as well as poorer prognosis, as have been reported in esophageal cancer [36], gastric cancer [43] and ductal carcinoma of the breast [44–46]. In bladder cancer cells, CRT knockdown suppressed proliferation, migration and attachment while its overexpression induced cell migration and attachment [47]. This was accompanied by a reduction in pulmonary metastatic formation in CRT-knockdown cells [48].

Table 1 CRT expression in various cancers

Cancer type	CRT expression	Molecular/cellular finding	Clinical findings	Reference no.
Pancreas	↑	↑mRNA, ↑CRT-Ab	–	[35]
Liver	↑	↑CRT protein in nuclear matrix	–	[23]
Esophagus	↑	↑mRNA, ↑CRT protein	↓survival	[37, 66]
Stomach	↑	↑CRT protein	↑invasion, ↑metastasis, ↓survival	[43]
Colon	↑	↑CRT protein in nuclear matrix	–	[39]
Breast	↑	↑mRNA, ↑CRT protein	↑invasion, ↑metastasis, ↓survival	[30, 31, 44, 45]
Skin (melanoma)	↑	Active proliferation/↑migration	–	[40, 41]
Blood (AML)	↑(inductive)	↓ cellular differentiation	–	[42, 46]
Connective tissue	↑	↑cellular motility	↑lung metastasis	[48]
Bladder	↑	↑mRNA, ↑CRT protein	↑urinary CRT	[32]
Bladder	↑	↑mRNA, ↑CRT protein	↑lung metastasis	[47]
Prostate	↑	↑CRT protein	–	[33]
Prostate	↓	↓CRT protein	–	[50]
Prostate	↑(inductive)	↓tumor formation	–	[50]

↑: increased, ↓: decreased

The table shows the correlation between CRT expression and molecular/cellular outcomes as well as clinical consequences in different cancers

Table 2 Possible mechanisms involving CRT during tumorigenesis

Pathway	Cancer/cell type	Cancer related function	Possible CRT action	Consequence	Reference no.
E-cadherin	Madin-Darby Canine Kidney Cell	Inhibition of invasion	↑Slug	Inhibition of E-cadherin	[60]
PI3K-Akt	Esophageal squamous cell carcinoma	Cell cycle progression, ↑cell survival, ↑ cell growth	↑STAT3/CTTN	↑motility, ↓anoikis	[66]
ERα	Breast cancer cell line	↑proliferation, ↓invasion	attachment to KxFF[K/R]R motif	↑invasion	[69]
Ca^{2+}	HeLa cells	↑cell motility	↑Ca^{2+} release from ER	↑cellular migration	[77]
TSP1	Mouse embryonic fibroblast	↑cell motility, ↓cell adhesion	LRP1	↑motility, ↑invasion	[26]
VEGF	Gastric cancer cells	↑proliferation, ↑cell motility	↑VEGF	↑invasion	[43]
Focal adhesion complex	Bladder cancer cells	↑proliferation, ↑cell motility	↑Paxillin, ↑focal adhesion kinase	↑invasion, ↑metastasis	[47]

The table shows the possible roles for CRT in candidate signaling pathways and the probable actions through which the pro-cancer effects are achieved

In the prostate, CRT acts as an androgen-modulated intracellular Ca^{2+} regulator. CRT expression is higher in prostatic epithelial cells which implies that CRT is a direct androgen responsive gene [49]. In prostate cancer, the role of CRT remains contradictory. Significant over-expression of CRT was reported in prostatic adenocarcinoma when compared to benign hyperplasia [33]. However, a recent study confirmed that fewer malignant colonies as well as the inhibition of xenograft tumor formation following over-expression of exogenous CRT in prostate cancer cells. CRT down-regulation was also reported in human prostate cancer tissues [50].

CRT Role in Cancer Immunogenic Cell Death

CRT has been reported to be activated in peripheral T cells [51]. It is also found abundant inside the granules of cytotoxic lymphocytes [52] suggesting its potential role as a modulator of cytotoxic activity of these granule proteins [53, 54]. It is now also well-known that CRT can be a key player in the detection and engulfment of dying tumor cells by macrophages [55]. This explains why drugs with the potential of triggering CRT exposure when combined with conventional chemotherapy are able to activate the immune system and therefore promote cancer immunogenic cell death [56] as reported in colon cancer cells treated by pro-apoptotic drugs such as anthracyclines [55]. In this process, CRT was reported to be recognized by LRP and C1q [57]. The same process has been reported in clonal plasma cells of patients with systemic light chain amyloidosis, in which, CRT expression has been correlated with response to high-dose therapy [58]. The ability of CRT in maximizing cancer cell death through its immunogenic function makes it a putative biomarker for the evaluation of therapeutic response [57].

Probable Mechanisms of CRT Contribution to Cancer Invasion

Previous studies have introduced or proposed several functional pathways through which CRT may exert its enhancing effects on pro-cancer/pro-invasive processes during malignant formations (Fig. 2). Some of these pathways are discussed.

Slug/E-Cadherin Pathway

E-cadherin suppresses invasion and metastasis in carcinoma cells and its inhibition is a key step for gaining the hallmarks of malignant cells [59]. Canine kidney CRT over-expressing cells have shown significant down regulation in E-cadherin expression and enhanced migratory potential [60]. Furthermore, these cells demonstrated higher expression of Slug which is a suppressor of E-cadherin promoter. Thus, a regulatory function for CRT in epithelial cell-cell interactions including changes in adhesion and migratory potentials due to modulation of Slug/E-cadherin pathway is proposed [60].

CTTN–PI3K–Akt-Signaling Pathway

Activated Akt, a major regulator of important cellular processes such as cell cycle progression, growth and survival is produced following the transfer to the inner cell membrane and via interactions with phosphatidylinositol-3 kinase (PI3K) [61]. The signal transducer and activator of transcription 3 (STAT3) is a modulator of Akt expression [62] through which it induces proliferation, survival and invasion of tumor cells [63]. Finally, cortical actin binding protein (CTTN) is a modulator of PI3K–Akt signaling pathway where it induces cell motility as well as resistance to anoikis [64, 65]. It is now confirmed that in esophageal squamous

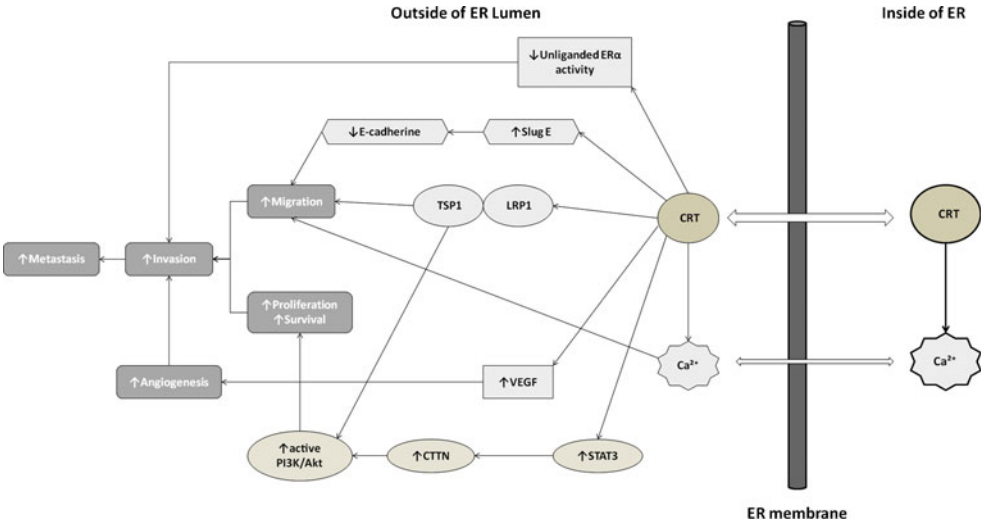

Fig. 2 Cancer related functions of calreticulin. CRT is proposed to contribute to the course of cancer through different functional pathways which will ultimately lead to increased cancer cell proliferation, migration and survival. Therefore, CRT induces cancer invasion and metastatic processes

cell carcinoma, CRT works as the upstream regulator of STAT3 and enhances CTTN transcription which indirectly accelerates PI3K/Akt pathway and ultimately will increase the motility of cancer cells and their resistance to anoikis [66].

Estrogen Receptor Alpha

CRT is believed to reverse estrogen receptor α (ERα) inhibition of invasion through its unliganded mechanism of action [67]. As mentioned, CRT is also involved in regulation of gene expression through interaction with the consensus motif KxFF[K/R]R located in the DNA binding domain of all nuclear receptors [67]. In estrogen receptors, this motif is necessary for the binding specificity of the estrogen receptor element [68]. In breast cancer cells, CRT is a potential regulator of ERα function where it prevents ERα activity of estrogen independent inhibition of invasion and therefore, it possibly activates invasion by blocking ERα linkage [69].

Calcium, Cell Motility and Calreticulin

Calcium regulates various aspects of amoeboid cell motility and induces the membrane localization of myosin II which ultimately leads to an efficient cellular migration [70]. Cellular speed is mainly regulated by calcium release from internal stores and its entrance through the plasma membrane [71]. In addition, KCa2.3 channels (the calcium-activated, voltage-gated SK3 potassium channel) which functions as a major regulator of Ca^{2+}transport through the cell membrane are important contributors to malignant cell motility [72]. Hence, regulation of intra-cellular calcium is a major determinant in the process of cellular migration [73]. As mentioned, CRT has a key role in calcium binding and buffering [1] by acting in various processes that interacts with calcium homeostasis including intra-ER Ca^{2+}storage [74], Ca^{2+}release from the ER [74, 75] and SERCA function [76]. In addition, CRT has been shown to activate the process of store-operated Ca^{2+}influx in HeLa cells [77]. Taken together, CRT can possibly induce cell migration and malignant invasion through its effects on intra- and extracellular calcium homeostasis.

TSP1-CRT-LRP1 Signaling Pathway

Thrombospondin 1 (TSP 1) is a major regulator of cellular adhesion and motility [26] and these effects are achieved through the attachment of its N-domain to the CRT-LRP1 (low density lipoprotein receptor-related protein) receptor co-complex [78]. This will ultimately lead to down regulation of signals involved in cell adhesion and finally increase cell motility via disassembly of focal adhesions. In mouse embryonic fibroblasts, TSP1-CRT-LRP1 pathway activates pro-survival signals such as PI3-K and Akt which precedes the inhibition of apoptosis [26, 79].

Other Pathways

A correlation has been reported between CRT over-expression and the up-regulation of vascular endothelial growth factor (VEGF) in gastric cancer cells at both mRNA and protein levels [43]. This proangiogenic role could be a possible mechanism of CRT-dependent invasive and metastatic potential in cancers. Finally, breast cancer patients with CRT over-

expression have shown a greater risk in the post-operative course of treatment. Interestingly, the risk for development of post-operative distant metastasis in breast cancer patients with CRT over-expression is much higher when the tumors were also positive for the expression of Her2/neu [45], suggesting Her2/neu as another possible target or contributor to the CRT pro-malignant effects.

Summary

CRT has a broad spectrum of functions in the ER, nucleus, cytosol, as well as outside the cell. While, calcium homeostasis and chaperoning are the most important CRT functions inside the ER, cell adhesion and regulation of gene expression seem to be its most important extra-ER functions. In addition to its physiological roles, CRT over-expression or its absence are linked to various pathological conditions such as malignant evolution and progression. Evidence from numerous studies suggests that CRT overexpression is a protumorigenic event in various cancers. However the exact role(s) of CRT is yet be clarified due to its diverse interactions into various cellular processes and signaling pathways. With the use of high-throughput global profiling platforms, further elucidation is possible. Future work should be focused on delineating the mechanisms involved in pro-malignant and pro-invasive effects of CRT as well as determining the probable interacting genes and signaling pathways.

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