





## Review

# Insights into the role of ERp57 in cancer

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## Abstract

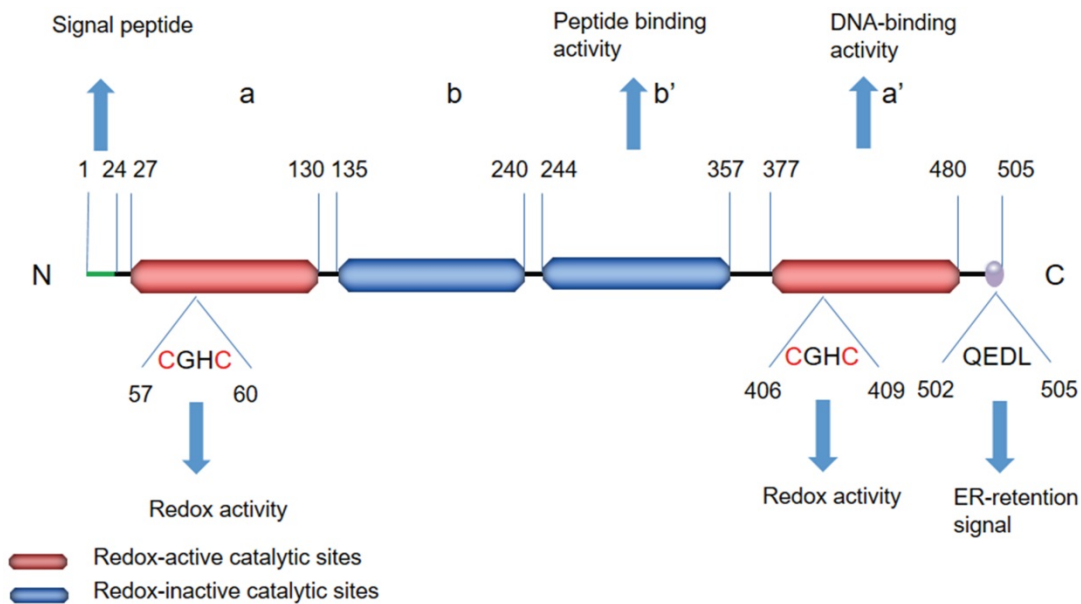
Endoplasmic reticulum resident protein 57 (ERp57) has a molecular weight of 57 kDa, belongs to the protein disulfide-isomerase (PDI) family, and is primarily located in the endoplasmic reticulum (ER). ERp57 functions in the quality control of nascent synthesized glycoproteins, participates in major histocompatibility complex (MHC) class I molecule assembly, regulates immune responses, maintains immunogenic cell death (ICD), regulates the unfolded protein response (UPR), functions as a 1,25-dihydroxy vitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D<sub>3</sub>) receptor, regulates the NF-κB and STAT3 pathways, and participates in DNA repair processes and cytoskeletal remodeling. Recent studies have reported ERp57 overexpression in various human cancers, and altered expression and aberrant functionality of ERp57 are associated with cancer growth and progression and changes in the chemosensitivity of cancers. ERp57 may become a potential biomarker and therapeutic target to combat cancer development and chemoresistance. Here, we summarize the available knowledge of the role of ERp57 in cancer and the underlying mechanisms.

Key words: ERp57/PDIA3, cancer, immune response, immunogenic cell death, unfolded protein response, DNA repair.

## Introduction

With cancer incidence and mortality rates increasing rapidly, cancer has become a global problem and is expected to become the leading cause of death worldwide in the 21st century according to the Global Cancer Statistics 2018 report [1]. To ease the burden of cancer, current research is focusing largely on molecular preventive trials, which are regarded as the priority study type; biomarkers are key determinants of molecular prevention that allow us to evaluate the natural history of cancer as well as the efficacy and toxicity of an agent [2]. Recent research regarding the expression of endoplasmic reticulum resident protein 57 (ERp57) in tumors revealed that ERp57 expression is upregulated in various cancers and participates in cancer initiation, progression and chemosensitivity [3-5]. Some evidence suggests that ERp57 can serve as a potential molecular marker and therapeutic target of cancer [6]. ERp57 has a molecular weight of 57 kDa and belongs

to the protein disulfide-isomerase (PDI) family; it is also referred to as protein disulfide-isomerase A3 (PDIA3), glucose regulatory protein 58 (GRP58) or ER60 protease and is mainly located in the endoplasmic reticulum (ER), with lower amounts in the cytoplasm and nucleus [7, 8]. Numerous studies have demonstrated that ERp57 is associated with multiple diseases, such as Alzheimer's disease [9], heart failure [10], thrombus formation [11, 12], neurodegenerative disease and cancer [13]. This review summarizes current knowledge relating to the key elements and mechanisms of ERp57 in various tumor functions, such as the regulation of T cell-mediated immune responses, regulation of immunogenic cell death, regulation of the unfolded protein response (UPR), regulation of DNA repair signaling and regulation of membrane-initiated signaling pathways.



**Figure 1.** Schematic representation of the structural features of Erp57. Erp57 has four thioredoxin-like site domains—termed a, b, b', and a'—and an acidic C-terminal tail. The C-terminus contains a QEDL sequence that serves as an ER retention signal. The redox-active catalytic sites in the a and a' domains are shown in red, while the redox-inactive catalytic sites in the b and b' domains are shown in blue. The redox-active catalytic sites involve a CGHC sequence. The a' domain has DNA-binding activity, and the b' domain has peptide-binding activity.

10	20	30	40	50
MRLRRLALFP	GVALLAAAR	LAAASDVLEL	TDDNFESRIS	DTGSAGMLLV
60	70	80	90	100
EFFAPWCGHC	KRLAPEYEA	ATRLKGIVPL	AKVDCTANTN	TCNKYGVSGY
110	120	130	140	150
PTLKIFRDGE	EAGAYDGPRT	ADGIVSHLKK	QAGPASVPLR	TEEFKKFIS
160	170	180	190	200
DKDASIVGFF	DDSFSEAHSE	FLKAASNLRD	NYRFAHTNVE	SLVNEYDDNG
210	220	230	240	250
EGIILFRPSH	LTNKFEDKTV	AYTEQKMTSG	KIKKFIQENI	FGICPHMTED
260	270	280	290	300
NKDLIQGGDL	LIAYYVDVYE	KNAKGSNYWR	NRVMMVAKKF	LDAGHKLNFA
310	320	330	340	350
VASRKTSFHE	LSDFGLESTA	GEIPVVAIRT	AKGEKFMQE	EFSRDGKALE
360	370	380	390	400
RFLQDYFDGN	LKRYLKSEPI	PESNDGPVKV	VVAENFDEIV	NNENKDVLI
410	420	430	440	450
FYAPWCGHCK	NLEPKYKELG	EKLSKDPNIV	IAKMDATAND	VPSPYEVGRF
460	470	480	490	500
PTIYFSPANK	KLNPKKYEGG	RELSDFISYL	QREATNPPVI	QEEKPKKKKK
AQEDL				

**Figure 2.** The amino acid sequence of Erp57 and the functional domains. Erp57 has a total of 505 amino acids including four thioredoxin-like site domains, two redox-active catalytic sites, two redox-inactive catalytic sites, and a C-terminal ER retention signal. The redox-active catalytic sites are shown with a red background, while the redox-inactive catalytic sites are shown with a blue background. The C-terminus contains a QEDL sequence shown in purple.

### Structure

The PDI family includes more than 20 members that catalyze cysteine-based redox reactions and play critical roles in productive protein folding [14, 15]. Erp57 is a highly conserved protein consisting of four thioredoxin-like site domains—termed a, b, b', and a'—and an acidic C-terminal tail (Figure 1). Domains a and a' contain the redox active site, whereas

domains b and b' are redox inactive. The two thioredoxin-like active domains a and a' each contain a Cys-Gly-His-Cys (CGHC) sequence (Figure 2), and the redox activity of the two domains is provided by the two cysteine residues of the CGHC motif [16, 17]. Erp57 exerts reduction, oxidation and disulfide isomerization effects in the ER through thioredoxin-like domains [16, 17]. The b' domain contains a ligand-binding site and exhibits

high-affinity binding with protein substrates, including both small and large peptide ligands. The b' domain is involved in simple isomerization reactions and directs noncovalent binding to substrates to destabilize the conformation of partially folded species [18]. The C-terminus contains a COOH-terminal Gln-Glu-Asp-Leu (QEDL) tetrapeptide that serves as an ER retention signal and acts in cooperation with other amino acid residues [13, 19-21]. ERp57 has two general functions: ERp57 binds to double-stranded DNA via recognition of a particular scaffold/matrix-associated region sequence and recruits proteins that localize to the nuclear matrix [22]. The DNA-binding properties are associated with the C-terminal region a' domain [23, 24]. The affinity of ERp57 for DNA fragments is strongly dependent on the redox state of the two thioredoxin-like sites (i.e., the oxidation of its cysteines) [23, 25]. There is a nuclear location sequence in close proximity to its C-terminus; thus, ERp57 can translocate to the nucleus from the cytosol to regulate the transcription of target genes [26, 27]. ERp57 exhibits proteolytic activity, degrades other ER proteins and is regulated by acidic phospholipids, including phosphoinositides [19].

### Clinical implications of ERp57 in cancer

Recent research from *in vitro* analyses and clinical trials support that ERp57 is overexpressed in a variety of cancers. ERp57 expression is significantly different between tumor tissues and normal tissues ( $P < 0.05$ ) in a wide variety of cancers, including stomach adenocarcinoma, colon adenocarcinoma, liver hepatocellular carcinoma (HCC), breast invasive carcinoma, and prostate adenocarcinoma, as shown in Figure 3. UALCAN analysis (<http://ualcan.path.uab.edu/analysis.html>) [28] was applied to demonstrate the difference in the mRNA expression of ERp57 between paratumor samples and tumor samples of The Cancer Genome Atlas (TCGA) genomics dataset.

Some studies have demonstrated that ERp57 is a primary cellular target that inhibits cancer cell proliferation [29]. ERp57 expression significantly differs among HCC patients, at-risk patients and healthy individuals, thereby potentially serving as a biomarker for the early diagnosis of HCC [6]. Evidence suggests that ERp57 is overexpressed in HCC, colorectal cancer [30] and breast cancer [31, 32] and participates in tumorigenesis and the progression of cancer [3, 4]. ERp57 expression is associated with the metastatic capacity of cancer cells. ERp57 is overexpressed in 73% of cervical cancers, especially in adenocarcinoma, and high expression indicates poor overall survival and high recurrence-free survival

rates in adenocarcinoma patients [33, 34]. *In vitro*, knockdown of ERp57 in HeLa cells inhibits cancer invasiveness and metastasis [33, 34]. ERp57 levels are also related to the malignant stages of prostate cancer [35]. Similarly, high levels of ERp57 in uveal melanoma may indicate that the tumor will metastasize [36]. However, ERp57 exerts the opposite effect on gastric cancer progression; its expression is significantly decreased in gastric cancer and metastases, and low levels of ERp57 are correlated with an increased depth of tumor invasion and advanced disease stage [37]. The results of retrospective analysis have shown that high expression indicates favorable overall survival in gastric cancer patients [38]. ERp57 is also related to gastric cancer treatment. Clinical trials have shown that ERp57 levels in the serum of patients with gastric cancer are decreased significantly after surgical treatment [39]. Taken together, these studies demonstrate that ERp57 is associated with tumor initiation and development; however, the implication of ERp57 in cancer is still debated. ERp57 may exert different functions depending on developmental and tissue-specific factors, but it is yet to be understood in detail. Thus, further study to uncover the mechanisms by which ERp57 modulates tumor tumorigenesis and progression is required. Here, we summarize the current research on the biological functions and mechanisms of ERp57 in cancer.

### Biological functions of ERp57 in cancer

#### Regulation of T cell-mediated immune responses

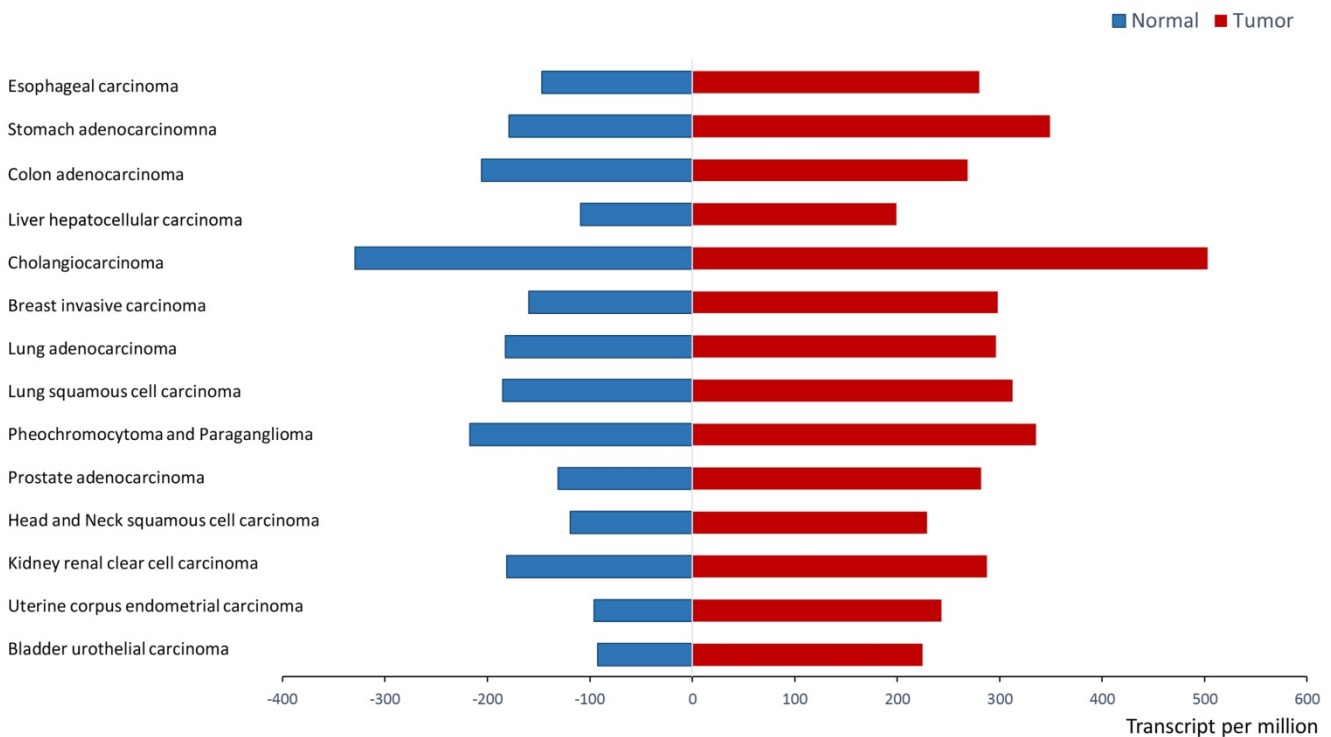
Calnexin (CNX) and calreticulin (CRT) predominantly act as lectins that specifically interact with nascently synthesized glycoproteins in the ER, and ERp57 forms complexes with these proteins to accomplish efficient folding and proper formation of intramolecular disulfide bonds in glycoproteins [40, 41]. ERp57 binding to substrates is dependent on CNX and CRT and is inhibited by the glucosidase inhibitor castanospermine (CST), an inhibitor of glucosidases I and II [42]. ERp57 mediates disulfide bond formation with heavy chains and complexes with CNX [43] to participate in major histocompatibility complex (MHC) class I molecule assembly [44]. ERp57 is indispensable for antigen processing and presentation, contributing to the activity of T cell-mediated immune responses. ERp57 is a component of the antigen processing complex that binds to nascently synthesized glycoproteins and facilitates peptide transport from the cytosol into the ER; afterwards, peptides bind to newly synthesized MHC class I molecules to form the MHC class I peptide-loading complex [45]. Stable

assembly of the MHC class I peptide-loading complex is impaired without ERp57, leading to decreased surface expression of MHC class I peptides [46]. Cell surface MHC I expression is essential for the induction of immune responses [47] because MHC class I molecules are involved in antigen presentation and display peptides to circulating CD8<sup>+</sup> cytotoxic T cells to enable tumor antigen recognition and induce CD8<sup>+</sup> T cell activation, eliciting antitumor immune responses and inducing cancer cell death [48]. If MHC class I surface expression is low, cancer cells fail to induce robust immune responses and exhibit weak immunogenicity [49], which is the major mechanism by which tumor cells escape immune attack [50]. Moreover, ERp57 expression is associated with CD8<sup>+</sup> cytotoxic T lymphocyte dysfunction. The antitumor activity of CD8<sup>+</sup> T cells is enhanced when ERp57 is knocked out in human CD8<sup>+</sup> T cells because ERp57 knockout in CD8<sup>+</sup> T cells regulates the expression of multiple immune regulators and effectors on the cell surface [51]. Hence, these reports suggest that ERp57 has a critical role in maintaining antitumor immune responses; thus, it may emerge as a potential cancer therapeutic target for the treatment of tumors for which prior treatment failed to induce strong T cell-mediated immune responses. The mechanism by which ERp57 regulates immune responses and the activity of CD8<sup>+</sup> T cells need to be explored in detail to

expand the utility of ERp57 in cancer immunotherapy strategies.

### Regulation of immunogenic cell death

Immunogenic cell death (ICD), a type of regulated cell death (RCD), induces adaptive immune responses to kill cells directly [52, 53]. CRT exposure on the cell surface triggers immune responses and facilitates recognition and removal of apoptotic cells [54, 55]. ER stress responses are required for ERp57/CRT exposure on the plasma membrane [56]. Knockdown of ERp57 simultaneously inhibits CRT translocation to the surface and exposure, preventing the restoration of tumor cell immunogenicity [57, 58]. Many studies have shown that radiation therapy and some chemotherapeutics, in particular anthracycline agents, can induce immune responses and lead to ICD [52, 59]. ERp57-deficient cancer cells treated with anthracyclines are unable to elicit anticancer immune responses and become resistant to anthracycline chemotherapy *in vivo* because CRT translocation is inhibited and immunogenic cell death is abolished [58]. These studies demonstrate that ERp57 is indispensable for maintaining the immunogenicity of cancer cells and inducing ICD in chemotherapy-treated cells. ERp57 is likely to be a potential indicator of the efficacy of cancer immunotherapy.



**Figure 3.** ERp57 expression in normal samples and tumor samples in the TCGA (UALCAN). ERp57 expression is significantly different between tumor samples and normal samples ( $P < 0.05$ ) according to TCGA genomics data for a wide variety of cancers. The difference in mRNA expression was assessed by Student's t-test.

## Regulation of the UPR

Due to its disulfide isomerase activity, ERp57 forms a complex with CNX and CRT to specifically modulate the folding of newly synthesized glycoproteins by facilitating the formation of native disulfide bonds [60, 61]. In response to intrinsic (oncogene activation) and extrinsic (hypoxia, chemicals or nutrient deficiency) stressors, unfolded and misfolded proteins accumulate in the ER lumen [62]. To ease the burden of the ER lumen, the UPR, a finely regulated program, is activated to maintain ER homeostasis and prevent ER stress from inducing death [63]. ERp57, as one of the key chaperones of the UPR, is required for this process. Knockdown of ERp57 enhances the ER stress response and facilitates the activation of ATF4/XBP-1 cascades [64]. Recent studies have provided evidence that ERp57 maintains the redox state of PDI and that knockdown of ERp57 facilitates PDI oxidation and activates PERK/CHOP cascades to induce p53-dependent apoptosis [65]. Moreover, the redox state of ERp57 is very significant. Evidence shows that the action of ERp57 is modulated by ROS because it can induce the oxidative modification of ERp57 and reverse the inhibitory effect on HCC progression [66]. In a breast cancer mammosphere model employing SUM159PT cells, mammosphere survival and growth were partially inhibited when ERp57 was knocked down because the effects of the ER protein folding machinery were decreased [67]. ER stress plays a critical role in tumor proliferation, progression and resistance, and the UPR alleviates cellular stress and promotes cell survival [68, 69]. Recent progress has revealed that ERp57 regulates the UPR, providing valuable information for disrupting the chronic ER stress conditions of cancer. An increasing body of evidence indicates that the UPR may be a target for anticancer therapeutics [70]. Studies have reported that ERp57 may be a regulator of the UPR. However, the functional role of ERp57 in the modulation of the UPR in cancer depends on some elements, including the oxidative modification of ERp57, the tumor type, the ER stress conditions and other undetermined factors; thus, more research is required for a deeper understanding.

## Regulation of DNA repair signaling

Recent data suggest that ERp57 plays an important role in the DNA repair process. ERp57, accompanied by high mobility group proteins 1 and 2 (HMGB1 and HMGB2), acts as a component of a complex that detects damaged DNA, inactivates the mismatch repair system and decreases the sensitivity of cells to thiopurine treatment [71, 72]. Inhibition of ERp57 significantly abrogates the phosphorylation of

H2A $\chi$  and suppresses the induction of the DNA damage response by cytarabine in A549 and UO31 human carcinoma cells [73]. Ref-1, a potent activator of p53 [74], can regulate p53-mediated base excision repair [75]. ERp57 interacts with Ref-1 through its thioredoxin-like domains and cooperates with it to regulate redox-sensitive transcription factor activation, ultimately yielding a protective effect against oxidative insult [76]. ERp57, vimentin and the nuclear proteins nucleophosmin (NPM1) and nucleolin (NCL) are major proteins exposed after cell injury; these proteins are necessary for the repair of plasma membrane damage and function as wound-associated proteins [77]. Vimentin can protect cells from DNA damage [78], and NPM1 and NCL are DNA damage proteins that directly participate in DNA repair [79, 80]. ERp57 has been found to form a complex with vimentin [5], NPM1 and NCL to regulate cell division and cancer development [81]; however, the underlying mechanism has not been fully illustrated so far. In addition, ERp57 has roles in chromosome cohesion and segregation; it complexes with  $\beta$ -actin and III  $\beta$ -tubulin (TUBB3) in the nuclear compartment, participating in the regulation of actin conformation states [81] and the attachment of microtubules to chromosomes, which plays a key role in paclitaxel sensitivity [82].

Taken together, the evidence indicates that ERp57 has a protective effect on the survival of tumor cells due to its contribution to the DNA repair process, which regulates the sensitivity of the tumor to DNA-modifying chemotherapy. Thus, it may become a biomarker to predict therapeutic failure and success. However, further studies are required to confirm these findings and identify potential antitumor targets.

## Regulation of membrane-initiated signaling pathways

1,25(OH) $_2$ D $_3$  is the active form of vitamin D, and its analogs exert inhibitory effects on the proliferation and progression of multiple cancers, including melanoma [83], prostate cancer, and leukemia [83, 84]. ERp57 acts as a 1,25D $_3$ -membrane-associated, rapid response to steroid binding (1,25D $_3$ -MARRS) receptor, mainly located on the plasma membrane and Golgi/ER [85-87]. It binds to secosteroid 1,25(OH) $_2$ D $_3$  to form a ligand-receptor complex to mediate several rapid signal transduction cascades; for example, it regulates STAT3 [88] and the NF- $\kappa$ B pathway [89], promotes the formation of complexes involving ERp57 and other proteins, and translocates to the nucleus to regulate gene expression [27]. ERp57 complexes with NF- $\kappa$ B to activate downstream cascades to regulate leukemia cell differentiation [89].

ERp57 regulates the transcription and translation of STAT3 through binding to STAT3 DNA and protein [90] and regulates the level of STAT3 phosphorylation to modulate the transcriptional activity of STAT3, which affects gene expression [91, 92]. The ERp57/STAT3 complex translocates to the nucleus to induce MCOLN3 expression and enhance  $\text{Ca}^{2+}$  release from lysosomes to activate autolysosomal degradation [93]. *In vitro* studies have revealed that knockdown of ERp57 inhibits HCC cell proliferation [92] and enhances the paclitaxel sensitivity of paclitaxel-resistant SKOV3/tax cells by blocking the STAT3 pathway [5]. Furthermore, a study reported that knockdown of ERp57 prevents EGFR-mediated cancer proliferation by inhibiting the internalization and phosphorylation of the EGF receptor [94]. EGFR amplification or mutation facilitates tumor proliferation, invasion, migration and apoptosis inhibition by regulating multiple downstream cascades, and EGFR inhibitors provide an effective therapeutic target for EGFR-mediated cancer [95]. Thus, analysis of the inhibitory function of ERp57 on EGFR-mediated cancer could open a new avenue to further explore optimized treatment options.

### Regulation of other signal transduction pathways

Mitomycin C (MMC) exerts anticancer effects by inducing DNA cross-linking in cancer cells [96]. ERp57 functions as a reductase, catalyzes the metabolic reduction of MMC and induces DNA cross-linking via its two thioredoxin-like domains [97], leading to increased MMC cytotoxicity [96]. MMC cytotoxicity induced by DNA cross-linking and breakage is also associated with numerous side effects, such as lack of appetite, weight loss, and renal toxicity, which are alleviated after inhibition of ERp57 [98].

Affymetrix microarray results suggest that cytoskeletal remodeling and the Wnt signaling pathway are the two of the top pathways disrupted by ERp57 silencing in HeLa cells [99]. The present data demonstrate that  $\beta$ -catenin participates in the mechanisms of cell adhesion, cytoskeleton remodeling and the canonical Wnt signaling pathway [100]. Stable knockdown of ERp57 induces  $\beta$ -catenin accumulation and inhibits the migration of HeLa cells [99], and resveratrol can increase the interaction between ERp57 and  $\beta$ -catenin [101]. In addition, ERp57 can regulate the proliferation, invasion and migration of cancer via the MAPK signaling pathway. Downregulation of ERp57 suppresses JNK, ERK and p38 phosphorylation [102], ERp57 expression requires ERK and p38, and inhibition of the ERK/p38 MARK

pathway suppresses ERp57 expression [98]. Little is known regarding the regulatory role of ERp57 in these pathways, and more research is needed to confirm these findings.

### Conclusions

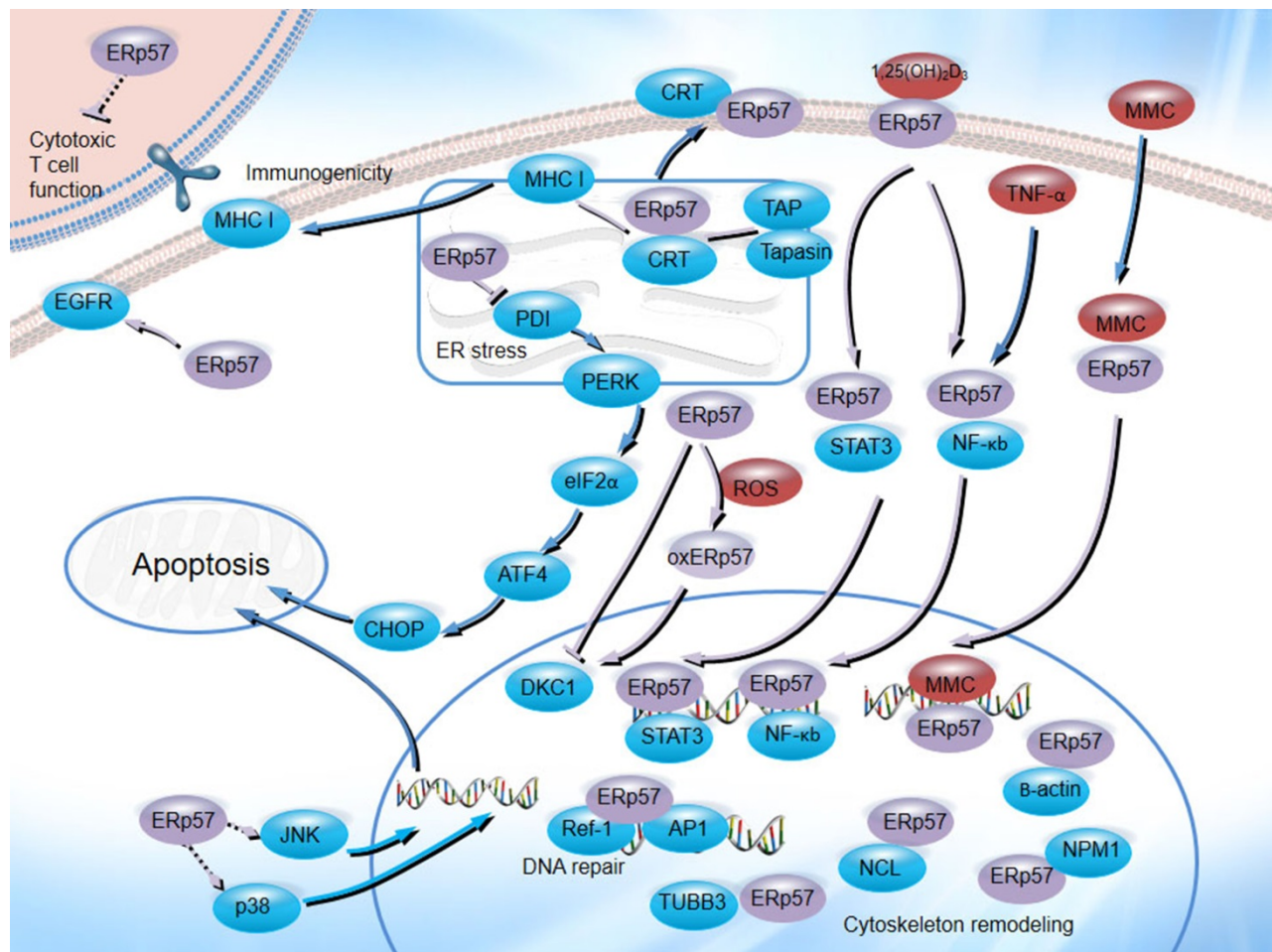
ERp57 plays an important role in the natural history of cancer and the therapeutic process. As an ER chaperone, ERp57 is associated with CRT and CNX, participates in MHC class I molecule assembly [103, 104], regulates tumor cell immunogenicity [105], facilitates new glycoprotein synthesis and enhances oxidative refolding of denatured cells [106], functions as a  $1,25\text{D}_3$ -MARRS receptor [107], regulates gene transcription, binds to STAT3 and NF- $\kappa$ B, enhances MMC-induced DNA cross-linking and is involved in DNA repair processes and cytoskeletal remodeling (Figure 4). Numerous studies have demonstrated that ERp57 plays a significant role in tumor development and chemoresistance in a wide variety of cancers. These identified crucial roles and their regulatory pathways may provide a framework for the comprehensive understanding of ERp57 in cancer, which might indicate its potential as a potential therapeutic target for cancer treatment.

### Abbreviations

ERp57: Endoplasmic reticulum resident protein 57; PDIA3: protein disulfide-isomerase A3; PDI: protein disulfide-isomerase; ER: endoplasmic reticulum; MHC: major histocompatibility complex; ICD: immunogenic cell death; UPR: unfolded protein response;  $1,25(\text{OH})_2\text{D}_3$ : 1,25-dihydroxy vitamin  $\text{D}_3$ ; GRP58: glucose regulatory protein 58; CGHC: Cys-Gly-His-Cys; QEDL: Gln-Glu-Asp-Leu; HCC: hepatocellular carcinoma; TCGA: The Cancer Genome Atlas; CNX: calnexin; CRT: calreticulin; CST: castanospermine; RCD: regulated cell death; HMGB1: high mobility group proteins 1; HMGB2: high mobility group proteins 2; NPMI: nucleophosmin; NCL: nucleolin; TUBB3: III  $\beta$ -tubulin;  $1,25\text{D}_3$ -MARRS:  $1,25\text{D}_3$ -membrane-associated, rapid response to steroid binding; MMC: Mitomycin C.

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**Figure 4.** The biological functions of ERp57 in cancer. ERp57 regulates diverse signal transduction pathways: ERp57 is associated with CRT and CNX, participates in MHC class I molecule assembly, inhibits T cell-mediated immune responses, regulates the UPR, functions as a receptor for 1,25(OH)<sub>2</sub>D<sub>3</sub>, binds to STAT3 and NF-κB, enhances MMC-induced DNA cross-linking, and participates in DNA repair processes and cytoskeletal remodeling.

## Competing Interests

The authors have declared that no competing interest exists.

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