

Role of [ERp57 \[PDIA3\]](#) in the signaling and transcriptional activity of [STAT3 \[STAT3\]](#) in a [melanoma cell line](#). 19995546

The [Stat3 \[STAT3\]](#) and [GRP58 \[PDIA3\]](#)-containing [plasma membrane](#) fraction also contained Stat1, Stat5b, and gp130. 12060494

Using differential sedimentation and density equilibrium flotation methods, [Stat3 \[STAT3\]](#) and [GRP58 \[PDIA3\]](#) were observed to be coassociated with [cytoplasmic membranes](#) enriched for the [plasma membrane](#) marker 5' nucleotidase but not with those containing the [endoplasmic reticulum](#) marker BiP/GRP78. 12060494

We suggest that the chaperone [GRP58 \[PDIA3\]](#) may regulate signaling by sequestering inactive and activated [Stat3 \[STAT3\]](#). 12060494

[Chromatin immunoprecipitation](#) in [M14 melanoma](#) cells showed that the protein [ERp57 \[PDIA3\]](#) ([endoplasmic reticulum](#) protein 57) binds to DNA in the proximity of [STAT3 \[STAT3\]](#) in a subset of [STAT3 \[STAT3\]](#)-regulated genes. 19995546

Both cytosolic [Stat3 \[STAT3\]](#) and [GRP58 \[PDIA3\]](#) eluted during Superose-6 [gel-filtration chromatography](#) in complexes of size 200-400 kDa (statosome I), and anti-[Stat3 \[STAT3\]](#) pAb cross-immunoprecipitated GRp58 from these FPLC elution fractions. 12060494

Upon depletion of [ERp57 \[PDIA3\]](#) by [RNA interference](#), the [phosphorylation](#) of [STAT3 \[STAT3\]](#) on [tyrosine \[?\]](#) 705 was decreased, and the IL-6-induced activation of CRP expression was completely suppressed. 19995546

Association of the chaperone glucose-regulated protein 58 ([GRP58 \[PDIA3\]](#)/[ER-60 \[PDIA3\]](#)/[ERp57 \[PDIA3\]](#)) with [Stat3 \[STAT3\]](#) in [cytosol](#) and [plasma membrane](#) complexes. 12060494

Likewise, excess exogenous recombinant human [GRP58 \[PDIA3\]](#) prepared using a [baculovirus](#) expression system preferentially [inhibited](#) [Stat3 \[STAT3\]](#) DNA-binding activity in the S100 [cytosol](#), suggesting that [GRP58 \[PDIA3\]](#) may sequester [activated Stat3 \[STAT3\]](#). 12060494

The new data confirm the association between [GRP58 \[PDIA3\]](#) and [Stat3 \[STAT3\]](#) in cytosolic 200-400-kDa statosome I [complexes](#) and show that both [GRP58 \[PDIA3\]](#) and Stat [family members](#) coassociate in the [plasma membrane](#) compartment. 12060494

In the S100 [cytosol](#) fraction, three different anti-[GRP58 \[PDIA3\]](#) polyclonal antibodies (pAb) cross-immunoprecipitated [Stat3 \[STAT3\]](#) (but not Stat1), and, conversely, anti-[Stat3 \[STAT3\]](#) pAb cross-immunoprecipitated [GRP58 \[PDIA3\]](#). 12060494

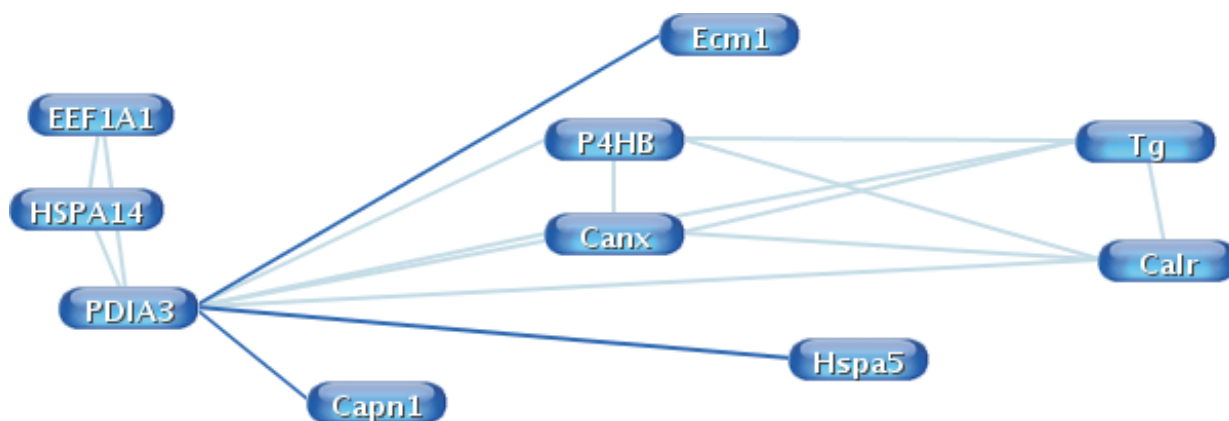
[In vitro](#) experiments showed that [ERp57 \[PDIA3\]](#) is also required for the [binding](#) of [STAT3 \[STAT3\]](#) to its [consensus sequence](#) on DNA. 19995546

Thus [ERp57 \[PDIA3\]](#), previously shown to associate with [STAT3 \[STAT3\]](#) in the [cytosol](#) and in the nuclear [STAT3 \[STAT3\]](#)-containing enhanceosome, is a necessary cofactor for the regulation of at least a subset of [STAT3 \[STAT3\]](#)-dependent genes, probably intervening both at the site of [STAT3 \[STAT3\]](#) [phosphorylation](#) and at the nuclear level. 19995546

In the present study, the association between [GRP58 \[PDIA3\]](#) and [Stat3 \[STAT3\]](#) in different cytoplasmic compartments was evaluated using cross-immunoprecipitation and [cell-fractionation](#) techniques. 12060494

- The [HLA-C \[HLA-C\]](#) ✨ specific receptors are represented by two 58 Kd ([p58 \[PDIA3\]](#) ✨) molecules that are highly homologous, as shown by both biochemical analysis and by the comparison of the corresponding genes. 7579196
- [Calnexin \[CANX\]](#) ✨ and [ERp57 \[PDIA3\]](#) ✨ facilitate the assembly of the neonatal Fc receptor for IgG with beta 2-microglobulin in the [endoplasmic reticulum](#). 16002696
- [ERp57 \[PDIA3\]](#) ✨ was found to **interact** with class III beta-tubulin ([TUBB3 \[TUBB3\]](#) ✨), involved in [paclitaxel \[?\]](#) resistance in ovarian and other cancers. 19714814
- We found that [ERp57 \[PDIA3\]](#) ✨ **binds** to the **P**-domain of [calreticulin \[CALR\]](#) ✨, an independently folding domain comprising residues 189-288. 11842220
- In addition, [ER-60 \[PDIA3\]](#) ✨ is part of the late assembly **complexes** consisting of [MHC \[HLA-E\]](#) ✨ class I, [tapasin \[TAPBP\]](#) ✨, TAP, [calreticulin \[CALR\]](#) ✨ and [calnexin \[CANX\]](#) ✨. 9545232
- Our results clearly show that [ERp57 \[PDIA3 / Pdia3\]](#) ✨ must be physically **associated** with the [calnexin \[CANX\]](#) ✨ cycle to catalyze isomerization reactions with most of its substrates. 19054761
- [Tapasin \[TAPBP\]](#) ✨ and [ERp57 \[PDIA3\]](#) ✨ form a stable disulfide-linked dimer within the MHC class I peptide-loading complex. 16193070
- We examined interactions between the [endoplasmic reticulum](#) (ER) chaperones [calnexin \[CANX\]](#) ✨ ([CN \[CANX\]](#) ✨), [ERp57 \[PDIA3\]](#) ✨, and immunological heavy chain-binding protein (BiP) and nicotinic acetylcholine receptor (nAChR) subunits. 17728248
- A ternary complex between heavy chain, [ERp57 \[PDIA3\]](#) ✨, and [tapasin \[TAPBP\]](#) ✨ was observed and shown to be **stabilized** by a disulfide between both tapasinheavy chain and [tapasin \[TAPBP\]](#) ✨ -[ERp57 \[PDIA3\]](#) ✨. 18039656
- On the basis of these data, we propose a model where the region of [ERp57 \[PDIA3\]](#) ✨ equivalent to the primary substrate **binding site** of archetypal [PDI \[P4HB\]](#) ✨ is occupied by calreticulin and suggest that the ER lectins act as adaptor molecules that define the [substrate specificity](#) of [ERp57 \[PDIA3\]](#) ✨. 14871899
- Specific [ERp57 \[PDIA3\]](#) ✨/[calreticulin \[CALR\]](#) ✨ complexes exist in canine pancreatic [microsomes](#), as demonstrated by [SDS-PAGE](#) after cross-linking, and by native electrophoresis in the absence of cross-linking. 10436013
- [ER-60 \[PDIA3\]](#) ✨ is a [thiol](#) oxidoreductase family protein of the [endoplasmic reticulum](#) that facilitates the oxidative folding of glycoproteins via interaction with [calnexin \[CANX\]](#) ✨ ([CNX \[CANX\]](#) ✨) and [calreticulin \[CALR\]](#) ✨ ([CRT \[CALR\]](#) ✨). 15236594
- We conclude that [ERp57 \[PDIA3\]](#) ✨ forms **complexes** with both [calnexin \[CANX\]](#) ✨ and [calreticulin \[CALR\]](#) ✨ and propose that it is these complexes that can specifically modulate glycoprotein folding within the ER lumen. 10436013
- [ERp57 \[PDIA3\]](#) ✨ **functions** as a subunit of specific **complexes** formed with the ER lectins [calreticulin \[CALR\]](#) ✨ and [calnexin \[CANX\]](#) ✨. 10436013
- Furthermore, the [thiol](#) oxidoreductase [ERp57 \[PDIA3\]](#) ✨ was detected in FcRn-[CNX \[CANX\]](#) ✨ complexes, suggesting its role in disulfide bond formation of the FcRn **H** chain. 16002696
- The genes [MAP3K5 \[MAP3K5\]](#) ✨ and [PDIA3 \[PDIA3\]](#) ✨ are **associated** with malignant stages of [prostate cancer \[GDEP\]](#) and therefore provide novel potential biomarkers. 20035634
- Here, we analyzed the cooperation of [ER-60 \[PDIA3\]](#) ✨ and [BiP \[HSPA5\]](#) ✨ in the oxidative refolding of denatured proteins [in vitro](#). 16428306

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[ERp57 \[Pdia3\]](#) ⭐-associated mitochondrial micro-[calpain \[Capn1\]](#) ⭐ truncates apoptosis-inducing factor. 18559257

[1,25-Dihydroxy vitamin D3](#) is an autocrine regulator of [extracellular matrix \[ECM1 / Ecm1\]](#) turnover and growth factor **release** via [ERp60 \[Pdia3\]](#) ⭐-activated matrix vesicle matrix metalloproteinases. 18765931

Using peptide mass fingerprinting by matrix-assisted laser desorption/ionization-time of flight **mass spectrometry**, we identified five of these spots as [protein disulfide isomerase A3 \[PDIA3 / Pdia3\]](#) ([PDA3 \[PDIA3 / Pdia3\]](#)), one as 60 kDa heat shock protein ([HSP60 \[HSPA14\]](#)) and two as [elongation factor Tu \[Eef1a1 / EEF1A1\]](#) ⭐ ([EF-Tu \[Eef1a1 / EEF1A1\]](#) ⭐). 12872233

Mixed-disulfide folding intermediates between [thyroglobulin \[Tg / TG\]](#) ⭐ and [endoplasmic reticulum resident oxidoreductases ERp57 \[Pdia3\]](#) ⭐ and [protein disulfide isomerase \[P4hb / P4HB\]](#) ⭐. 16260597

Overexpression of [ERp57 \[PDIA3 / Pdia3\]](#) ⭐ also augmented [tunicamycin \[?\]-induced](#) caspase-3 activation and reduced [BiP \[HSPA5 / Hspa5\]](#) ⭐/[GRP78 \[HSPA5 / Hspa5\]](#) ⭐ induction. 19411306

These data point towards mixed disulfides with the [ERp57 \[Pdia3\]](#) ⭐ oxidoreductase in conjunction with [calreticulin \[Calr\]](#) ⭐/[calnexin \[Canx\]](#) ⭐ chaperones acting as normal early [Tg \[Tg / TG\]](#) ⭐ folding intermediates that can be "substituted" by [PDI \[P4hb / P4HB\]](#) ⭐ adducts only at the expense of lower folding efficiency with resultant ER stress. 16260597

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