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Gene Section

Review

CALR (calreticulin)

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Abstract

Calreticulin (CALR) is a multifunctional protein involved in molecular chaperoning and calcium homeostasis. CALR has also been associated with proliferation, cell cycle progression, migration, invasion and anoikis resistance in cancer cells. The prognostic impact of CALR expression is yet to be elucidated, however in some types of cancer, high CALR expression has been related to worse clinical outcomes. Notably, the discovery of recurrent mutations in the exon 9 of the CALR gene in myeloproliferative neoplasms has opened a new round of investigations. The present review contains data on CALR DNA/RNA, protein encoded and function.

Keywords
CALR; chromosome 19; calcium homeostasis; chaperone; cancer

Identity

Other names: CRT, HEL-S-99n, RO, SSA, cC1qR

HGNC (Hugo): CALR

Location : 19p13.13

DNA/RNA

Description

The entire CALR gene is approximately 5.9 Kb (start: 12938578 and end: 12944489 bp; orientation: Plus strand) and contains 9 exons. The CALR cDNA contains 1.9 Kb.

Protein

Description

CALR protein consists of 417 aminoacids with a molecular weight of 46 kDa and has a conserved P-domain, N-domain and C-domain. A KDEL (lysine, aspartic acid, glutamic acid and leucine) motif, which prevent secretion from endoplasmic reticulum, this protein is found in the C-terminal region. The representation of the primary structure of CALR protein is illustrated in Figure 1.

Expression

Ubiquitous.

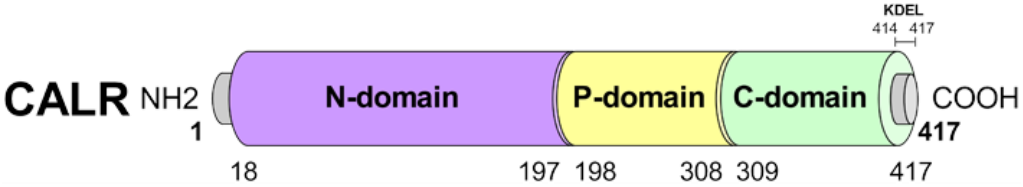

Figure 1. Schematic primary structure of CALR protein. The conserved P-domain, N-domain and C-domain and KDEL motif are illustrated. Amino acid (aa) positions are indicated.

Localisation

CALR is predominantly found in the cytoplasm and endoplasmic reticulum. Nuclear, membrane and cell surface localization has also been frequently reported.

Function

CALR is a multifunctional protein, and molecular chaperoning and calcium homeostasis are the two most well-characterized functions of this protein. In the endoplasmatic reticulum, CALR binds to calcium, participates on folding of newly synthesized proteins and glycoproteins, and interacts with other chaperones as CANX (calnexin) (Gelebart, et al. 2005; Lu, et al. 2015; Zamanian, et al. 2013). Recently, evidence of the CALR participation in cell signaling networks has grown. CALR has been pointed out as a regulator of STAT3, STAT5, AKT, MAPK and PTK2 (FAK) cell signaling, promoting proliferation, cell cycle progression, migration, invasion and anoikis resistance (Chiang, et al. 2013; Du, et al. 2009; Feng, et al. 2015; Shi, et al. 2014; Wang, et al. 2013). CALR has also been described as a VEGFA and HIF1A inductor (Chen, et al. 2009; Weng, et al. 2015).

Under stress conditions, CALR translocates onto the plasma membrane surface as a result of the CALR transport from endoplasmic reticulum to the Golgi apparatus, followed by exocytosis of CALR-containing vesicles, which acts as an "eat-me" signal (Zitvogel, et al. 2010).

This process has been associated with immunogenic cell death (Apetoh, et al. 2007; Obeid, et al. 2007).

In myeloproliferative neoplasms, mutated-CALR (exon 9 indel mutations) has been related to activation of MPL and JAK2 /STAT signaling, leading to cell proliferation and survival (Araki, et al. 2016; Balligand, et al. 2016; Chachoua, et al. 2016; Elf, et al. 2016; Marty, et al. 2016; Nivarthi, et al. 2016).

A potential model for CALR network is summarized in Figure 2.

Homology

CALR belongs to the calreticulin family, which is comprised of endoplasmic reticulum calcium-binding chaperones. CALR shares high homology among different species (Table 1).

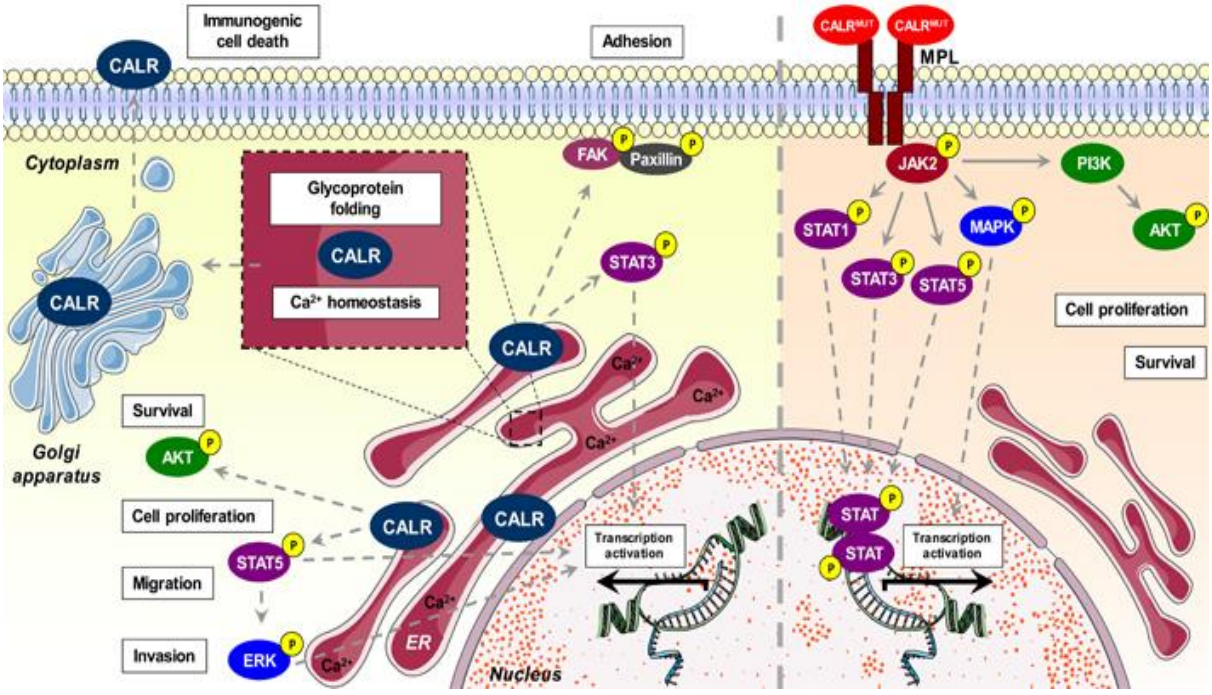

Figure 2. A potential model for CALR network signaling. (Left panel) CALR binds to calcium, participates in the folding of newly synthesized glycoproteins, and interacts with other chaperones in the endoplasmatic reticulum. CALR regulates STAT3, STAT5, AKT, MAPK and FAK cell signaling, promoting proliferation, cell cycle progression, migration, invasion and anoikis resistance. Under stress condition, CALR translocates onto the plasma membrane by Golgi apparatus-mediated exocytosis, which participates in immunogenic cell death. **(Right panel)** Mutated-CALR (exon 9 indel mutations) induces activation of MPL and JAK2/STAT signaling, promoting cell proliferation and survival in myeloproliferative neoplasm cells. Abbreviations: ER, endoplasmic reticulum; Ca2+, calcium; MUT, mutated; P, phosphorylation. The Figure was produced using Servier Medical Art (http://www.servier.com/Powerpoint-image-bank).

% Identity for: *Homo sapiens* CALR	Symbol	Protein	DNA
vs. P. troglodytes	CALR	100	99.9
vs. M. mulatta	CALR	99.8	97.6
vs. C. lupus	CALR	96.6	90.6
vs. B. taurus	CALR	94.8	89.6
vs. M. musculus	Calr	95.7	88.2
vs. R. norvegicus	Calr	95.7	87.7
vs. G. gallus	CALR3	65.4	66.4
vs. X. tropicalis	calr	83.1	76.6
vs. D. rerio	Calrl2	80.0	73.7
vs. D. melanogaster	Crc	72.4	69.9
vs. A. gambiae	AgaP_AGAP004212	71.5	69.3
vs. C. elegans	crt-1	67.1	67.4
vs. A. thaliana	CRT1a	56.0	61.6
vs. A. thaliana	CRT1b	57.1	59.6
vs. O. sativa	Os03g0832200	56.5	62.9
vs. O. sativa	Os07g0246200	59.1	62.8

Table 1. Comparative identity of human CALR and other species s (Source: http://www.ncbi.nlm.nih.gov/homologene)

Mutations

Somatic

Mutations in exon 9 of the CALR gene have been described in 56 to 88% of non-mutated JAK2 and MPL myeloproliferative neoplasm (essential thrombocythemia and primary myelofibrosis) patients (Klampfl, et al. 2013; Nangalia, et al. 2013). Excluding myeloproliferative neoplasms, recurrent mutations in the CALR gene are rare. A total of 53 substitution missense, 7 substitution nonsense, 22 substitution synonymous, 798 insertion frameshift, 7 deletions inframe, 1493 deletion frameshift, 50 complex and 553 other mutations are reported in COSMIC, being 2939 mutations in hematopoietic and lymphoid cancers (Catalogue of somatic mutations in cancer; http://cancer.sanger.ac.uk/cancergenome/projects/cosmic).

Implicated in

Myeloproliferative neoplasms

In December 2013, two independent groups identified somatic mutations in the CALR gene in essential thrombocythemia and primary myelofibrosis patients with non-mutated JAK2 and MPL (Klampfl, et al. 2013; Nangalia, et al. 2013). CALR was also identified in a subset of patients with refractory anemia with ringed sideroblasts associated with marked thrombocytosis, but not in other hematological malignancies (Klampfl, et al. 2013). These finding were confirmed by several research groups (Grinsztejn, et al. 2016; Haslam, et al. 2016; Labastida-Mercado, et al. 2015; Li, et al. 2015; Lin, et al. 2015; Machado-Neto, et al. 2015; Monte-Mor, et al. 2016; Nunes, et al. 2015; Shirane, et al. 2015; Wojtaszewska, et al. 2015; Wu, et al. 2014). Over fifty different CALR mutations in exon 9 have been described, however the most frequent mutations (approximately 80%) are classified as type-1 (L367fs*46, deletion of 52bp) and type-2 (K385fs*47, insertion of 5bp). Patients with CALR-mutated myeloproliferative neoplasms have a lower age of disease onset, lower hemoglobin and platelet counts, and a better overall survival than either JAK2-mutated or CALR/JAK2/MPL wild-type patients (Chen, et al. 2014; Li, et al. 2014; Tefferi, et al. 2014b). In essential thrombocythemia, Pietra and colleagues (Pietra, et al. 2016) observed that CALR type 1-like mutations were mainly associated with a myelofibrosis phenotype and a higher risk of fibrotic transformation, whereas CALR type 2-like mutations were associated with an essential thrombocythemia phenotype, lower risk of thrombosis and an indolent clinical course. However, in primary myelofibrosis patients, CALR type 1-like mutations presented a better prognosis than patients with CALR type 2-like or JAK2 mutations (Guglielmelli, et al. 2015; Tefferi, et al. 2014a). CALR mutations were also reported in some cases of familial myeloproliferative neoplasms, but are rare in childhood essential thrombocythemia (Langabeer, et al. 2014; Lundberg, et al. 2014; Maffioli, et al. 2014). Gene expression signature studies on myeloproliferative neoplasm pathogenesis indicate a central role of the JAK/STAT signaling pathway in both JAK2 and CALR mutations, (Rampal, et al. 2014). Using a large panel of cancer cell lines, Kollmann and colleagues (Kollmann, et al. 2015) identified MARIMO as a leukemia cell line presenting a CALR

mutation (61-bp deletion; c.1099_1159del; L367fs*43); surprisingly, this cell line showed neither JAK/STAT activation nor response to the treatment with the JAK1/2 inhibitor ruxolitinib.

Acute myeloid leukemia

Balkhi and colleagues (Balkhi, et al. 2006) observed that CALR is acetylated in acute myeloid leukemia with t(8;21)(q22;q22). Previous studies also suggested that high CALR expression may be involved in repression of CEBPA in leukemia cells with inv(16) (p13q22) or t(8;21) (Helbling, et al. 2004; Helbling, et al. 2005). High CALR expression was observed in a subset of AML patients that are positive for XBP1s, a marker of unfolded protein response (Schardt, et al. 2009). Chemotherapy-independent CALR exposure at the cell surface was found in some acute myeloid leukemia patients, which was associated with low CD47 expression and enhanced cellular immune response against tumor antigens (Wemeau, et al. 2010). In samples from acute myeloid leukemia patients, CALR expression was increased in relation to samples from benign conditions, acute lymphoblastic leukemia and myeloproliferative neoplasms, however no association was observed with clinical and laboratorial characteristics (Park, et al. 2015).

Chronic lymphocytic leukemia

CALR is highly expressed by stromal cells, which participate in the protective effect that stroma exerts on chronic lymphocytic leukemia cells by B-cell antigen receptor stimulation (Binder, et al. 2010). Molica and colleagues (Molica, et al. 2016) reported similar concentrations of CALR in serum from chronic lymphocytic leukemia and from healthy donors. However, elevated serum CALR was associated with higher peripheral blood lymphocytosis, Rai sub stages I-II and shorter treatment-free survival.

Lymphoma

Vasostatin, a fragment of CALR (amino acids 1-180), was found to inhibit tumor formation capacity of the Burkitt lymphoma -cell line CA46 (Pike, et al. 1998). Similar results were found using a CALR fragment of amino acids 1-120 or 120-180 that also inhibits endothelial cell proliferation in vitro and Burkitt tumor growth (Pike, et al. 1999).

Breast cancer

Using two-dimensional gel electrophoresis, Franzen and colleagues (Franzen, et al. 1997; Franzen, et al. 1996) observed an increase of CALR expression in high proliferative lesions from breast carcinoma compared to fibroadenoma (benign tumor) cells. Similar findings were reported by other research groups (Bini, et al. 1997; Chahed, et al. 2005; Kabbage, et al. 2013; Song, et al. 2012; Zamanian, et al. 2016) that also observed high CALR expression in breast cancer samples compared to histologically normal tissues using proteomics analysis. CALR overexpression was also correlated with lymph node metastasis and with postoperative appearance of distant metastases in ERBB2 (Her2/neu) positive breast cancer (Eric, et al. 2009). A multivariate analysis indicated that CALR expression is an independent predictor of tumor size and the occurrence of distant metastasis in a cohort of 228 breast cancer patients (Lwin, et al. 2010). Abundant CALR protein was found in breast tumor interstitial fluid compared to normal breast interstitial fluid (Gromov, et al. 2010). Serum levels of IgA of anti-calreticulin antibodies were higher in breast cancer patients compared to healthy donors (Eric-Nikolic, et al. 2012). mRNA and protein CALR expression was found to be expressed at higher levels in the breast cancer MDA-MB-231 cell line (more aggressive model) compared to breast cancer MCF7 cell line (less aggressive model) (Lwin, et al. 2010). CALR-silenced MCF-7 cells presented lower migration and invasion, and global gene expression profiling indicated a participation of TP53 and MAPK signaling pathways in these processes (Zamanian, et al. 2016).

Ovarian cancer

Increased CALR expression, at the mRNA and protein levels, was observed in samples from ovarian cancer patients compared to samples from normal ovaries, benign tumors, and borderline tumors (Vera, et al. 2012). In ovarian cancer HOSE and A2780 cell lines, NGF (nerve growth factor) treatment resulted in induction of CALR expression, which was abolished by GW441756 treatment, a tropomyosin receptor kinase A selective inhibitor (Vera, et al. 2012). Overexpression of CALR was observed in solid metastases in comparison to effusions and primary ovarian carcinomas. High CALR expression in ovarian carcinoma effusions was associated with a better response to chemotherapy at diagnosis (Vaksman, et al. 2013).

Prostate cancer

n prostate cancer cell lines, CALR is a hormone responsive gene and CALR inhibition, by antisense oligonucleotide, increases the sensitivity to calcimycin (A23187)-induced apoptosis (Zhu, et al. 1999). Using two-dimensional gel, a high expression of CALR was found in prostate carcinoma compared to prostate hyperplasia (Alaiya, et al. 2000). On the other hand, Alur and colleagues (Alur, et al. 2009) observed that CALR is downregulated in cancer cells compared to adjacent benign glandular epithelial cells using immunohistochemical analysis. In the prostate cancer LNCaP cell line, induction of neuroendocrine differentiation reduces CALR expression and modulates intracellular Ca^{2+} homeostasis (Vanoverberghe, et al. 2004). In

contrast, CALR was downregulated in poorly-differentiated tumors, though not in well-differentiated tumors in a murine prostate cancer model (Ruddat, et al. 2005). Increased CALR expression was observed in 1E8-H cells (prostate cancer cell line with high metastatic potential) compared to 2B4-L (prostate cancer cell line with low metastatic potential) (Wu, et al. 2007). In the human prostate cancer PC3 cell line, induction of CALR expression resulted in lower clonogenic capacity and xenograft tumor growth (Alur, et al. 2009). In rat Dunning AT3.1 prostate cancer cell line, induction of CALR overexpression did not modulate tumor growth, but reduced lung macrometastasis (Alur, et al. 2009). Docetaxel-resistant PC3 cells presented high levels of CALR compared to docetaxel-sensitive PC3 cells (Zu, et al. 2015).

Bladder cancer

Using proteomic analysis, Kageyama and colleagues (Kageyama, et al. 2004) reported an increased expression of CALR in bladder cancer compared to normal urothelium, and suggested that CALR may be a biomarker for bladder cancer with a sensitivity of 73% and a specificity of 86%. Latterly, the same research group led by Yoshiki (Iwaki, et al. 2004) validated these findings in a larger cohort of bladder cancer patients and controls (112 and 230, respectively), and CALR expression combined with other markers (SNCG (synuclein gamma) and COMT (catechol-o-methyltransferase)) displayed a sensitivity of 76.8% and a specificity of 77.4% as bladder cancer biomarkers (CALR alone presented a sensitivity of 71.4% and a specificity of 77.8%). Yoshiki's group (Kageyama, et al. 2009) also reported that CALR was highly expressed in urine samples from bladder urothelial carcinoma patients compared to urological patients without urothelial carcinoma and non-urological patients, and suggested that urinary CALR concentration may be a useful biomarker for bladder urothelial carcinoma with a sensitivity of 67.9% and specificity of 80.0%. In another study, urinary CALR was indicated as a potential biomarker for urothelial urinary bladder carcinoma (Soukup, et al. 2015). In the human bladder cancer J82 cell line, CALR silencing reduced cell viability, cell cycle progression, adhesion, migration, PXN (Paxillin)/FAK axis activation, FUT1 expression and in vivo tumor growth and metastasis (Lu, et al. 2014b; Lu, et al. 2011).

CALR expression was increased in urine from urothelial transitional cell carcinoma compared to healthy donors (Lu, et al. 2014a).

Oral squamous cell carcinoma

High prevalence of CALR expression positivity was observed in oral squamous cell carcinoma samples (96%) compared to non-cancerous matched tissue (32%). Similarly, oral squamous cell carcinoma cell lines (Ca9-22,CAL-27, HSC-3, SCC-9, SAS and FaDu) presented higher CALR expression than human oral keratinocytes (Chiang, et al. 2013). In SAS cells, CALR knockdown reduced cell proliferation, clonogenicity, anchorage-independent growth, migration, and Paxillin/FAK and MAPK activation (Chiang, et al. 2013).

Esophageal squamous cell carcinoma

CALR upregulation was observed in esophageal squamous cell carcinoma compared to adjacent nonmalignant tissue by two dimensional electrophoresis and mass spectrometry analysis (Jazii, et al. 2006; Nishimori, et al. 2006). In agreement, Du and colleagues (Du, et al. 2007) observed an increased CALR expression in esophageal squamous cell carcinoma samples compared to matched adjacent normal tissue, using two dimensional electrophoresis, western blot and/or immunohistochemistry, which was associated with a poorer prognosis by univariate analysis. Latterly, Du and colleagues (Du, et al. 2009), in an elegant mechanistic study, demonstrated that CALR inhibition reduced cell migration and invasion, clonogenic potential and in vivo tumor growth, and induced anoikis in esophageal squamous cell carcinoma cell lines. In the esophageal squamous cell carcinoma KYSE450 cells, CALR silencing reduces CTTN expression, and AKT and STAT3 activation (Du, et al. 2009). The same research group showed that CALR regulates PTPN1 (PTP1B) and NRP1 expression, at mRNA and protein levels, and STAT5 and ERK activation (Shi, et al. 2014; Wang, et al. 2013).

Gastric cancer

High CALR expression was observed in 20 out of 30 gastric cancer patients comparing matched tumor and non-tumor specimens (Chen, et al. 2009) using cDNA microarray (discovery cohort). Similar results were observed in an independent cohort of validation (enrolling 79 gastric cancer patients), in which high CALR expression was associated with high microvessel density, positive serosal invasion, lymph node metastasis, perineural invasion and poor survival (by multivariate analysis) (Chen, et al. 2009). Functional analysis using AGS human gastric cancer cell line denoted that CALR overexpression resulted in increased proliferation, cell cycle progression, migration and PIGF and VEGF secretion, whereas CALR inhibition resulted in the opposite effect (Chen, et al. 2009).

Colorectal adenocarcinoma

Using high-resolution two-dimensional gel analysis, CALR was found to be an abundant protein in the

nuclear matrix of colon cancer cells, though not of normal colon tissue (Brunagel, et al. 2003). Low CALR expression was observed in colon cancer compared to normal colon tissue (Alfonso, et al. 2005; Toquet, et al. 2007). Similarly, Peng and colleagues (Peng, et al. 2010) observed reduced expression of CALR in colon tumors in relation to adjacent normal epithelium; of note, CALR expression was associated with T-cell infiltration and better survival rates in colon cancer patients by univariate analysis. CALR downregulation was also observed in colonic cancer cell lines (SW1116, SW620, SW480, HT29, HT29-Cl.19A, HT29-Cl.16E and Colo320 cells) compared to primary normal colonic epithelial cells (Toquet, et al. 2007). In contrast, Vougas and colleagues (Vougas, et al. 2008) reported high CALR expression in colon cancer compared to the matched mirror biopsy tissues, especially in highly malignant and poorly differentiated tumors.

In sera, anti-calreticulin antibodies were found in 57% of colorectal adenocarcinoma patients and in 2% of healthy donors (Pekarikova, et al. 2010). High MIR27A -expressing cells displayed less CALR on the cell surface (Colangelo, et al. 2016b), which impaired the kinetics of apoptosis in drug-induced immunogenic cell death of human colorectal cancer HCT116 cells (Colangelo, et al. 2016a).

Hepatocellular carcinoma

Yoon and colleagues (Yoon, et al. 2000) researching for nuclear matrix proteins differently expressed in hepatocellular carcinoma found CALR to be present in the nuclear matrix fraction of carcinomas, though not in the nonmalignant liver tissue. Increased CALR expression was also reported in the human hepatoma cell line BEL-7404 compared to normal human liver cell line L-02 (Yu, et al. 2000). The investigation of differentially expressed proteins in high (MHCC97-H) and low (MHCC97-L) metastatic hepatocellular carcinoma cell lines found that CALR is downregulated in high metastatic hepatocellular carcinoma MHCC97-H cell line compared to MHCC97-L cells (Ding, et al. 2004). CALR protein fragments were detected at higher levels in the serum from hepatocellular carcinoma patients in relation to the serum from healthy individuals, from chronic hepatitis patients, or from cirrhosis patients, suggesting that serum CALR fragments may be biomarkers for hepatocellular carcinoma (Chignard, et al. 2006). Serum anti-calreticulin antibodies have been found in 63% of hepatocellular carcinoma patients, suggesting that CALR is a molecular target for B cell molecular in this malignancy (Pekarikova, et al. 2010). In the hepatocellular carcinoma SMMC7721 and HepG2 cell lines, CALR silencing reduced cell viability, cell cycle progression, invasion and AKT activation (Feng, et al. 2015).

Pancreatic adenocarcinoma

Anti-calreticulin antibodies were found in 47% of sera from pancreatic adenocarcinoma patients compared to 2% from healthy donors (Pekarikova, et al. 2010). Higher CALR expression was found in pancreatic tumors in comparison to paired non-cancerous pancreatic ductal tissues, and was associated with more advanced lymph node metastasis, high grade stage and worse overall survival (by univariate analysis) (Sheng, et al. 2014). In pancreatic cancer cell lines, CALR silencing reduced proliferation, migration, ERK activation, and did not modulate TP53, MDM2 , phospho-AKT, phospho-JUNK and phospho-p38 MAPK, wheras CALR overexpression increased migration and ERK activation, but did not modulate TP53, MDM2 and phospho-AKT expression (Sheng, et al. 2014).

Xenograft pancreatic tumors treated with adenovirus expressing vasostatin presented lower tumor size and reduced angiogenesis compared to those treated with a control adenovirus (Li, et al. 2006). On the other hand, vasostatin-expressing BON cells, a pancreatic carcinoid tumor cell line, showed enhanced cell proliferation, invasion and in vivo tumor formation (Liu, et al. 2005). Using two-dimensional gel electrophoresis, increased CALR expression was observed in pancreatic cancer samples compared to matched non-cancerous pancreatic samples (Wang, et al. 2012), and in serum from pancreatic cancer patients compared to serum from healthy donors (Hong, et al. 2004).

Lung cancer

CARL protein levels were significantly higher in serum samples of lung cancer patients compared to healthy individuals. Immunohistochemistry analysis showed an increased CALR expression in lung cancer cells in comparison to normal lung cells, which was associated with tumor pathological grade (Liu, et al. 2012). In a large cohort of lung cancers (270 patients), CALR expression was heterogeneous, found in cytoplasm and at the surface of tumor cells and was not associated with tumor stage (Fucikova, et al. 2016). High CALR expression was associated with tumor infiltration by immune cells and low CALR expression impacted negatively on overall survival by univariate and multivariate analysis (Fucikova, et al. 2016). Pemetrexed-resistant A549 adenocarcinomic human alveolar basal epithelial cells presented elevated levels of CALR compared to pemetrexed-sensitive A549 cells. CALR silencing rescued, at least in part, sensibility to pemetrexed treatment in pemetrexed-resistant A549 cells, whereas induction of increased CALR expression reduced sensibility to pemetrexed treatment of pemetrexed-sensitive A549 cells (Chou, et al. 2015).

Glioblastoma

Okunaga and colleagues (Okunaga, et al. 2006) reported that the neuroglioma H4 cell line (radiosensitive cells) expressed high levels of CALR compared to the glioblastoma cell lines U251MG and T98G (radioresistant cells).

The authors also observed that the induction of CALR expression by transfection enhanced radiation-produced apoptosis in U251MG cells (Okunaga, et al. 2006). In glioma patients, CALR expression was reduced compared to normal brain tissue, and negative CALR expression was associated with higher grade disease and reduced overall survival by univariate analysis (Gao, et al. 2013). CALR expression was increased in 5 out of 9 relapsed glioblastoma patients that presented low levels of CALR expression(Muth, et al. 2016).

Neuroblastoma

Using immunohistochemical, Hsu and colleagues (Hsu, et al. 2005) observed that 47% of neuroblastoma samples were positive for CALR expression, which associated with age at diagnosis ≤1 year, early clinical stage, differentiated tumors and non-amplified MYCN.

The authors also showed that positive CALR expression was an independent factor for better overall survival by multivariable analysis (Hsu, et al. 2005). In neuroblastoma cell lines (SH-SY5Y, SK-N-DZ and stNB-V1), CALR inhibition resulted in VEGFA and HIF1A downregulation, whereas CALR overexpression led to increased levels of VEGFA and HIF1A (Weng, et al. 2015).

Melanoma

Increased CALR expression was found upon ionizing radiation and associated with radio resistance of the melanoma cell line SQ-20B (Ramsamooj, et al. 1995).

In melanoma samples, a similar profile of CALR expression was observed between primary tumors and metastatic lesions (Dissemond, et al. 2004). Using a proteomic approach, a higher CALR expression was observed in the melanoma 526 cell line compared to melanocytes (FOM78) (Caputo, et al. 2011).

Liposarcoma

CALR was expressed in both dedifferentiated areas and atypical stromal cells and/or lipoblasts in the well-differentiated areas in liposarcomas, thought not in normal fat tissue (Hisaoka, et al. 2012). The authors associated CALR upregulation with the downregulation of MIR1275 , a putative microRNA that targets CALR. In addition, CALR silencing reduces cell proliferation and induces adipogenesis in the dedifferentiated liposarcoma FU-DDLS-1 cell line (Hisaoka, et al. 2012).

Fibrosarcoma

Using fibrosarcoma murine cell line models that present regressive (QR-32 cells) and progressive (QRsP-11 cells) tumor formation in mice, Hayashi and colleagues reported that QRsP-11 cells presented higher expression of CALR compared to QR-32 cells (Hayashi, et al. 2005).

Thyroid cancer

Thyroid cell lines transformed by mutant TP53 presented CALR downregulation (Paron, et al. 2005). CALR expression was found to be lower in malignant follicular thyroid carcinoma compared with benign follicular thyroid adenoma using proteomics analysis validated by immunohistochemistry (Netea-Maier, et al. 2008).

Adrenocortical carcinomas

Elevated CALR expression was identified in adrenocortical carcinomas compared to adjacent normal adrenocortical tissues, which was associated with higher grade tumors (Yang, et al. 2013).

Pituitary adenoma

Desiderio and Zhan (Desiderio, et al. 2003), using proteomics approaches, found CALR to be a differently expressed protein in pituitary adenoma compared to control tissue.

To be noted

The discovery of the recurrent exon 9 indel CALR mutations in myeloproliferative neoplasms combined with the fact that these mutations are mutually exclusive with JAK2 and MPL mutations (except in very rare cases) was a marked advance in the elucidation of the molecular basis of these neoplasms. Recently, studies using cellular and animal models have provided important information regarding the mechanisms of action of the mutated-CALR protein. Results from several independent research groups converge to the same point: mutated CALR activates the thrombopoietin receptor (MPL) and leads to the activation of MPL downstream targets, including JAK2/STAT and MAPK signaling pathways.

Furthermore, MPL inhibition in cellular models (MPL-expressing Ba/F3 or UT-7 cell lines) and MPL knockout in mice prevent the transformation caused by the CALR mutation, providing new therapeutic possibilities for myeloproliferative neoplasm patients (Araki, et al. 2016; Balligand, et al. 2016; Chachoua, et al. 2016; Elf, et al. 2016; Marty, et al. 2016; Nivarthi, et al. 2016). Other notable cancer-related findings are that aberrant CALR exposure at cell surface caused by reticulum stress in hyperploid cancer cells represents an important mechanism to avoid cancer development

and progression by immunosurveillance (Senovilla, et al. 2012).

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