

REVIEW

Open Access

Multifaced roles of PLAC8 in cancer



Misha Mao^{1,2†}, Yifan Cheng^{3†}, Jingjing Yang^{1,2}, Yongxia Chen^{1,2}, Ling Xu^{1,2}, Xun Zhang^{1,2}, Zhaoqing Li^{1,2}, Cong Chen^{1,2}, Siwei Ju^{1,2}, Jichun Zhou^{1,2*} and Linbo Wang^{1,2*}

Abstract

The role of *PLAC8* in tumorigenesis has been gradually elucidated with the development of research. Although there are common molecular mechanisms that enforce cell growth, the impact of *PLAC8* is varied and can, in some instances, have opposite effects on tumorigenesis. To systematically understand the role of *PLAC8* in tumors, the molecular functions of *PLAC8* in cancer will be discussed by focusing on how *PLAC8* impacts tumorigenesis when it arises within tumor cells and how these roles can change in different stages of cancer progression with the ultimate goal of suppressing *PLAC8*-relevant cancer behavior and related pathologies. In addition, we highlight the diversity of *PLAC8* in different tumors and its functional output beyond cancer cell growth. The comprehension of *PLAC8*'s molecular function might provide new target and lead to the development of novel anticancer therapies.

Keywords: *PLAC8*, Tumorigenesis, cancer stemness, Programmed cancer death

Introduction

Placenta specific 8 (*PLAC8*), also known as *Onzin*, *C15*, *DGIC* and *PNAS-144*, was first identified in genome-wide expression profiling of mid-gestation placentas and embryos using a 15,000 mouse-developmental cDNA microarray [1, 2]. *PLAC8* expression is dynamic during pregnancy and placental development and accumulates in an implantation-dependent manner [1, 3]. *PLAC8* has also been found to be involved in embryo development [4–8]. And *PLAC8* is found to be highly expressed in the endometrium of pregnant cows compared to nonpregnant cows, and it is upregulated in blastocysts, resulting in calf delivery [9–12]. Subsequent research on *PLAC8* was not limited to animals but also involved humans and many plants [13–16]. During the differentiation process of cytotrophoblast cells into interstitial extravillous trophoblast cells, *PLAC8* is greatly induced [17]. To date, *PLAC8* has been determined to be involved in organ development and tumorigenesis [18–21]. In addition, *PLAC8* is a molecular marker to predict

prognosis and distinguish between different cell subpopulations [17, 22]. *PLAC8* also plays different roles in a cell- or tissue-type specific manner. Throughout this review, we discuss the structure of *PLAC8* and how *PLAC8* evokes widely different responses in tumorigenesis.

PLAC8 protein

The *PLAC8* gene is located in human chromosome 4 and *Mus musculus* chromosome 5, which is one of the placenta-regulatory genes and belongs to the cornifelin family.

The *PLAC8* protein contains five exons, coding for a mRNA species of 829 bp and an open reading frame of 115 amino acids [1], which shows a high degree of conservation (83%) between humans and mice [1, 23]. In addition, *FW2.2-like (FWL)* genes which are identified in plant species and *PLAC8* genes, which both contain highly conserved cysteine-rich motifs, share a common ancestor before the divergence between plants and animals [24]. The first 11 amino acids of this cysteine-rich domain are reported to be required for binding of *PLAC8* with Akt1 and MDM-2 protein, and then regulate the activity of Akt1 and MDM-2 [25]. This same

* Correspondence: jichun-zhou@zju.edu.cn; linbowang@zju.edu.cn

†Misha Mao and Yifan Cheng contributed equally to this work.

¹Department of Surgical Oncology, Sir Run Run Shaw Hospital, Zhejiang University, Zhejiang 310000, Hangzhou, China

Full list of author information is available at the end of the article



© The Author(s). 2021 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

region is also found to be required for *PLAC8* transiently binds to the *C/EBP β* promoter and induce its transcription [26]. In addition, this cysteine-rich domain is called the *PLAC8* motif which does not conform to consensus zinc- or RING-finger domains [27, 28]. The *PLAC8* motif-containing proteins form a large family and members which can be found in *fungi, algae, higher plants and animals* [29, 30]. In *plants*, *AtPCR1* and *AtPCR2* which contain *PLAC8* motif play an important role in transport of heavy metals such as cadmium or zinc [29]. However, our knowledge about the function of *PLAC8* motif-containing proteins is very limited. To some extent, although *PLAC8* protein has only 115 amino acids (Fig. 1), investigation of its intact domain will help to provide a full understanding of its function and *PLAC8* motif-containing proteins.

PLAC8 protein does not have an N-terminal signal peptide, indicating that this protein is not a secretory protein and functions within the cytoplasm or the nucleus [31]. And the precise cellular location of *PLAC8* varies greatly depending on its specific context. For instance, the intracellular distribution of the *PLAC8* protein is dynamic and regulated in an implantation-dependent manner [32]. *PLAC8* is specifically expressed in the interstitial extravillous trophoblast cells on the fetomaternal interface, while its expression is hardly detectable in the endovascular trophoblast cells [17]. *PLAC8* is found exclusively at the apical domain of fully differentiated normal colonic epithelium in both colonocytes and goblet cells [33], and it localizes at the trophoblast cell periphery [17]. In addition, *PLAC8* has been found in nasopharyngeal carcinoma and breast cancer cell cytoplasm and membrane [34, 35]. After breast cancer cells acquired drug resistance, *PLAC8* accumulated both in nucleus and cytoplasm [36]. In pancreatic cancer cells, *PLAC8* is located in the inner plasma membrane [37]. However, in pancreatic ductal adenocarcinoma, *PLAC8* is mainly located in lysosomes [38]. The lysosomes contain transporters and participates in the export of molecules [39]. The location of *PLAC8* in

lysosomes might cause the different location of *PLAC8* because of lysosomes interact with other organelles thus leading fusion or non-fusogenic contacts. And these varying localizations may result in its functional differences.

Since *PLAC8* was identified 20 years ago, many studies have been performed to identify the characteristics and molecular functions of *PLAC8* in cancer (Fig. 2) [40]. *PLAC8* promotes the growth of tumor cells in prostate cancer cells [41] but significantly inhibits the growth of tumor cells in hepatocellular carcinoma [42]. This interesting phenomenon prompts us to explore the underlying mechanisms and regulatory network of *PLAC8*. Therefore, research on *PLAC8* will help us to further understand the biological characteristics of tumors.

Connections with cancer

As a key regulator of growth in different species, including *fungi* [43], *plants* [24, 44] and *mammals* [3, 30, 45, 46], *PLAC8* participates in many important physiological activities in different contexts [31, 47–49]. Such as, the ratio of *FAIM3:PLAC8* might be a diagnostic biomarker in sepsis [47]. And *PLAC8* is related with septic shock [49]. To date, researchers have also found that *PLAC8* acts as a tumor associated gene that is involved in many cancer processes (Fig. 3) [50–55]. We further discuss the various molecular functions of *PLAC8* in cancer in our review.

Programmed cell death

Programmed cell death, referring to apoptosis, autophagy, programmed necrosis and ferroptosis, may jointly decide the fate of malignant neoplasm cells [56–58]. These forms of programmed cell death balance cell death with cell survival, thus regulating cancer cell fate. Many oncogenes or tumor suppressor genes are linked with tumorigenesis through programmed cell death [59–61]. *PLAC8*, as an oncogene, promotes colorectal and prostate cancer cell growth [62–64]. Cancer growth is always accompanied by programmed cell death. As

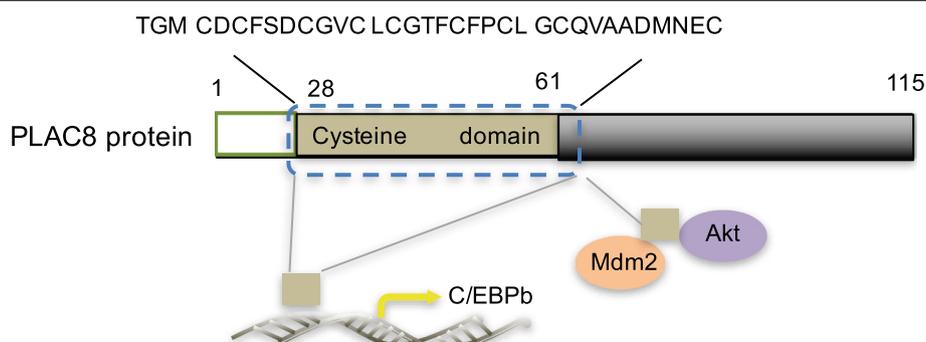
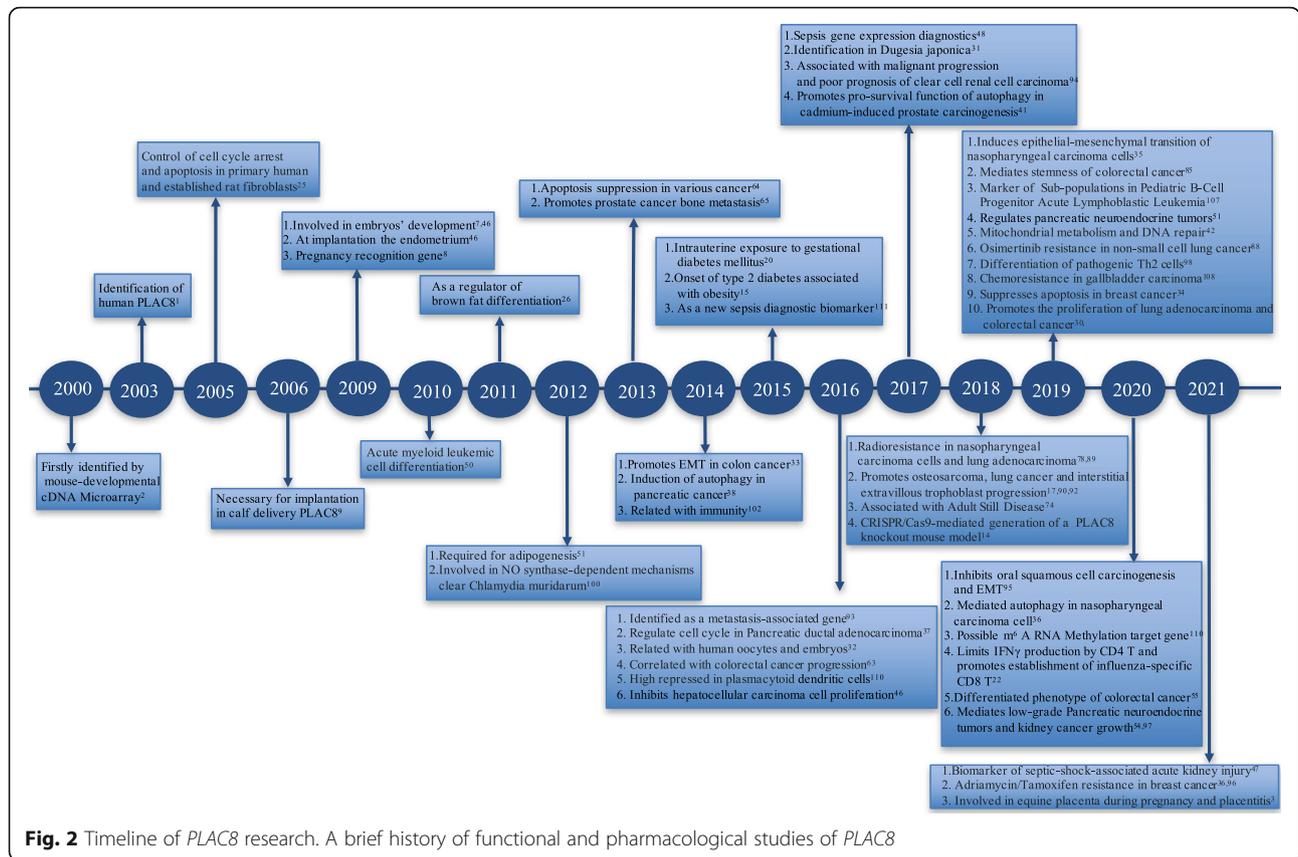
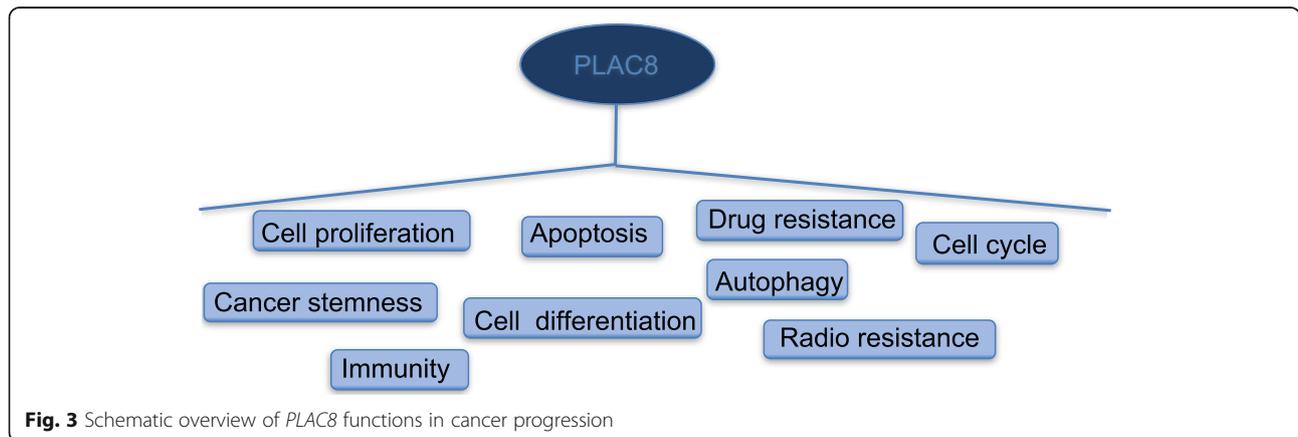


Fig. 1 *PLAC8* structure. The cysteine-rich domain of the human *PLAC8* protein is located between amino acids 28 and 61



expected, *PLAC8* regulates cell apoptosis in various cancers [65]. We found that *PLAC8* inhibits breast cancer cell apoptosis, thus promoting cell proliferation [34]. *PLAC8* decreases the sensitivity of lung adenocarcinoma cells to gefitinib-induced apoptosis by reducing the expression of cleaved caspase 3 and cleaved PARP [45]. The mRNA levels of *PLAC8* are increased in stool, and that its increased expression correlates with colorectal cells relapse [63, 66]. *PLAC8* is also upregulated in late-stage colorectal patient's tissues and butyrate which produces microorganisms downregulated *PLAC8*

expression. And butyrate increased cleaved PARP fragment and then induced apoptosis in colorectal cells [62]. Exception of cancer cells, *PLAC8* can also inhibits cell apoptosis of primary human and established rat fibroblasts via promoting the activation of *MDM-2* and *AKT1* and then inhibiting *p53* [25]. Akt/*MDM-2*/*p53* pathway serves an important role in the regulation of cell apoptosis [67]. And autophagy, is a process that delivers cytoplasmic components to the lysosomes which *PLAC8* locates in [38], has opposing and context-dependent roles in cancer [68]. Autophagy induces



pancreatic ductal adenocarcinoma cells growth [69]. Pancreatic ductal adenocarcinoma has signature oncogenic mutations of *KRAS* and the inactivation of *p53* [70]. Additionally, in pancreatic ductal adenocarcinoma cell lines, *PLAC8* is cooperatively induced in response to mutations in *KRAS* [71] and *p53* [72] which are the two of the most commonly occurring mutations in cancer. And then *PLAC8* promote pancreatic ductal adenocarcinoma cell lines autophagy thus promoting tumor formation [38]. The oncogenic role of *PLAC8* in inducing the prosurvival function of autophagy protects cells from environmental stress and aids in the transformation of prostate epithelial cells during chronic exposure to cadmium [41]. We previously shown that *PLAC8* collaborates with p62 to suppress autophagy in doxorubicin resistant breast cancer cells [36]. *PLAC8* inhibits autophagy via the AKT/mTOR pathway in nasopharyngeal carcinoma cells [73]. In addition to cancer, *PLAC8* also enhances autophagy in adult-onset Still's disease [74] and promotes trophoblast cells autophagy through regulating autophagy-related markers, including LC3B I/II, ATG12 and Beclin-1 [75]. However, the relationship of *PLAC8* with programmed necrosis and ferroptosis, which is a new form of cell death, is still unknown. We previously discussed that an interaction exists between ferroptosis and autophagy [76]. The crosstalk between autophagy and apoptosis regulates testicular injury induced by cadmium via PI3K and a mTOR-independent pathway [77]. Interestingly, *PLAC8* regulates the PI3K pathway and interacts with AKT, which is an important kinase of the PI3K pathway [34, 42, 78]. These results strongly indicate that *PLAC8* may be a core regulator in programmed cell death, affect different forms of cell death and decide cancer cell fate. This intriguing contrast in the effects of *PLAC8* on cell fate in different cellular contexts presents attractive possibilities for the development of novel therapies for cancers.

Cancer stemness

Stem cells are a population of undifferentiated cells characterized by the ability of self-renewal, such as embryonic stem cells. Studies have shown that the expression of *PLAC8* and several recognized stem cell markers (*NANOG* [79], *SOX2* [80] and *POU5F1* [81]) are commonly highly expressed in embryo development [82]. In *POU5F1*-null embryonic stem cells, *PLAC8* is downregulated [83]. *PLAC8* also may be upstream of *KLF4* which is a stem cell marker [84] in triggering adipogenesis [51]. These studies suggest that *PLAC8* may involve in stem cell progression via interacting with stem cell markers. Consistent with stem cells, cancer stem cells (CSCs) have the potential to self-renew, and they often appear dormant and resist cancer treatments, such as radiation and chemotherapy, leading to cancer recurrence. Higher

PLAC8 expression is found in the sphere-forming colorectal cancer cells than in colorectal cancer cells. And *Id1* gene which can activate the Wnt/ β -catenin and Shh signaling pathways promote *PLAC8* expression and then maintains cell stemness in colorectal cancer [85]. In non-small cell lung cancer, *PLAC8* promotes the levels of *ALDH1A1* which is a putative marker for CSCs in numerous types of tumors [86–88]. Additionally, *PLAC8* regulates the expression of *POU5F1*, thus increasing stemness during lung adenocarcinoma cell resistance to radiotherapy [89]. And our previous study showed that *KLF4* regulates *PLAC8* transcription in lung cancer cells [90]. These studies strongly indicates that the regulation loop between stem cell markers (*POU5F1* and *KLF4*) and *PLAC8* and the various roles of *PLAC8* in cancer stemness. The precise association of *PLAC8* with recognized stem cell markers still need further explored. Based on emerging evidence, *PLAC8* may be a promising stemness related marker in tumor initiation and development.

Epithelial-mesenchymal transition

Epithelial–mesenchymal transition (EMT) is a cellular process in which cells lose their epithelial characteristics and acquire mesenchymal features that have been associated with metastasis [91]. Studies have shown that *PLAC8* overexpression contributes to MAPK pathway activation and metastatic phenotypes [92] and that *PLAC8* plays a role in the epithelial-mesenchymal transition [93] in different types of cancer. *PLAC8* promotes trophoblast cell, non-small cell lung cancer cell, and clear cell renal cell carcinoma invasion and migration [17, 88, 94, 95]. However, *PLAC8* inhibits oral squamous cell invasion [95]. *PLAC8* reflects the expression of epithelial-mesenchymal related markers including *E-cadherin*, *N-cadherin* and *vimentin* thus involving epithelial-mesenchymal transition process. In breast cancer cells, embryonic kidney 293 T cells, colorectal cancer cells and nasopharyngeal carcinoma cells, *PLAC8* downregulates the level of *E-cadherin* thus regulating cell migration and invasion [34, 35, 96, 97]. On the other hand, *PLAC8* upregulates *N-cadherin* and *vimentin* levels in breast cancer and nasopharyngeal carcinoma cells [34, 73]. Interestingly, *PLAC8* decreases *E-cadherin* expression but increases *P-cadherin* and *vimentin* expression; however, the level of *N-cadherin* is stable in colorectal cancer cells [33]. These studies demonstrate that the molecular function of *PLAC8* varies in different contexts. The difference in cellular position may not be sufficient to explain this phenomenon, and in-depth research is needed in the future. In addition to cadherin family proteins, the abundant expression of *PLAC8* in interstitial extravillous trophoblast cells promotes cell invasion and migration partially by upregulating the activation of

RAC1 and *CDC42* without change their expression [17]. *PLAC8* not only promotes EMT progression but is also involved in cancer metastasis, such as bone metastasis in prostate cancer cells and lung metastasis in colorectal cancer cells *in vivo* [62, 64]. Taken together, *PLAC8* may reflect epithelial-mesenchymal related genes thus involving EMT progression and cancer metastasis. Additionally, the expression of *PLAC8* can predict of changes in EMT markers, including *E-cadherin*, *N-cadherin* and *vimentin* and be the hallmark of EMT progression.

Cancer immunity

PLAC8 exists in a variety of immune cells and the level of *PLAC8* varies in different immune cells. *PLAC8* is higher expressed by Th1 CD4 T-cells compared to Th2, Th17 and iTreg CD4 T-cells [22]. In addition, *PLAC8* is relatively highly expressed in airway T helper 2 (Th2) cells which play a pathogenic role in allergies [98]. *PLAC8* is robustly downregulated in CD39⁺ human regulatory T-cells [99]. In addition to being expressed in immune cells, *PLAC8* also interacts with immune factors and regulates inflammation. For example, *PLAC8* suppresses the production of the pro-inflammatory cytokines, IL-1b and IL-18, via enhancement of autophagy in adult-onset Still's disease [74]. *PLAC8* is important for suppressing IFN γ production by IL-12 stimulation in CD4 T-cell [22]. And CD4 T-cell expression of *PLAC8* correlates with potent termination of Chlamydia replication and relative independence from IFN γ pretreatment of epithelial monolayers [100, 101]. And Chlamydia-specific CD8 T-cell clones do not express *PLAC8* [102], but *PLAC8* also promotes effector CD8 T-cell establishment through a T cell-intrinsic mechanism. In addition, *PLAC8* is identified in placental functions, and *PLAC8* is relatively higher in placentitis cells [103]. *PLAC8* mRNA is also increased in the myometrium of adenomyosis patients, indicating the role of the immune response in the myometrium of women with adenomyosis [104]. These evidences suggest that *PLAC8* may play an important role in immune system [31, 105, 106]. Determining factors that regulate *PLAC8* expression in T cells may help to identify how it can be utilized therapeutically during T cell-driven inflammation, and the functions of *PLAC8* in the immune system, especially in the regulation of different populations of immune cells, need to be explored further.

When referred to cancer immunity, *PLAC8* is found to be most intensively expressed in the FXIII-A dim subgroup and helps to define three novel subpopulations in pediatric B-cell progenitor acute lymphoblastic leukemia [107]. And RNA sequencing data of clear cell renal cell carcinoma has shown that *PLAC8* is mainly involved in immunity-related pathways [94]. With unbiased RNA sequence analysis, *CXCL5*, which is an inflammatory

mediator, has been identified as one of the downstream targets of *PLAC8* overexpression in osteosarcoma [92]. Gong et al. found that *PLAC8* is abnormally overexpressed in gallbladder carcinoma cells and that its expression positively correlates with *PD-L1* expression, which is the main checkpoint of the immune system [108]. However, time and more research will begin to address questions that how *PLAC8* involves cancer immunity. While these findings were initially unexpected, *PLAC8* is an immune-related gene and may be a targeting gene for immune reactions in cancer.

Drug resistance

In the *ericoid mycorrhizal fungus*, *Oidiodendron maius*, *PLAC8*-containing proteins have been reported to be involved in cadmium tolerance [28]. Additionally, specifically targeting *PLAC8* may affect prostate carcinogenesis in humans, and *PLAC8* activation may be used as a biomarker for the early detection of prostate cancer in cadmium-exposed populations [41]. These findings indicate that the expression of *PLAC8* might be altered upon exposure to certain drugs. Drug resistance is one of the main reasons for the failure of tumor therapy, which greatly limits the choice and use of cancer drugs. Researchers have demonstrated that *PLAC8* is related to multidrug resistance in various cancers. In nasopharyngeal carcinoma cells, knockout of *PLAC8* radiosensitizes nasopharyngeal carcinoma cells by activating the PI3K/AKT/GSK3 β pathway [78]. Our study found that overexpression of *PLAC8* can promote tamoxifen resistance in breast cancer and that the expression of *PLAC8* can be reduced by curcumin [96]. In addition to endocrine resistance, *PLAC8* regulates *RAC1* levels, and another study has reported that *RAC1* promotes breast cancer chemoresistance by influencing DNA damage repair [17, 109]. These findings indicate that *PLAC8* may predict multidrug resistance in breast cancer. In non-small cell lung cancer, overexpression of *PLAC8* in parental cells markedly decreases osimertinib sensitivity [88]. Enhanced sensitivity to cisplatin treatment following silencing of *PLAC8* in clear cell renal cell carcinoma cells suggests a potential therapeutic target of *PLAC8* [94]. *PLAC8* overexpression decreases sensitivity to gemcitabine and oxaliplatin in gallbladder carcinoma cells [108]. Overexpression of *PLAC8* significantly decreases the sensitivity of lung adenocarcinoma to gefitinib [45]. Taken together, these results suggest that *PLAC8* may predict drug resistance in various cancer cells and be a promising therapeutic target.

Other diseases

In addition to its important role in tumors, *PLAC8* also participates in other disease processes, such as respiratory diseases and some infectious diseases [98, 102, 110].

For example, *PLAC8* is upregulated in activated monocytes and in monocytes isolated from active ASD patients [74]. In addition, many studies have shown that *PLAC8* is related to glucose metabolism [26]. However, animal models have shown that *PLAC8* is expressed at different levels in F344-fa and F344-fa-nidd2 rats and is closely related to obesity and glucose loading [15]. The AIM3:*PLAC8* ratio is a candidate biomarker that can be used to assist in the rapid diagnosis of CAP on ICU admission [111]. The study of *PLAC8* in different systemic diseases in humans may help to further understand the function of this gene.

Overview of the *PLAC8*-regulated network

There is mounting evidence of the potential role of *PLAC8*-regulated network in cancer (Fig. 4) [104, 111, 112]. *PLAC8* can be regulated at the transcriptional level. For example, *PLAC8* is involved in pro-mesonephros regulation, and *PAX2* regulates the transcription of *PLAC8* [113]. *PLAC8* is upregulated by IFNT [114], and the expression of *PLAC8* is upregulated under hypoxia [17]. *PLAC8* acts as a

transcription factor involved in the expression of different genes. In CD4 T cells, *PLAC8* suppresses IL-12-induced IFN γ production at the transcriptional level [22]. *PLAC8* binds to the *C/EBP β* promoter to induce its transcription [26]. *PLAC8* activates the Akt/MDM-2 pathway, ultimately leading to an inability to upregulate *p53*. In addition, *PLAC8* directly interacts with MDM-2 and Akt, thereby influencing the localization of both proteins [25]. In functional extravillous trophoblasts, *PLAC8* colocalizes with *p53* and regulates *p53* expression at the posttranslational level [75]. In addition, the expression of *PLAC8* can be reduced by curcumin in tamoxifen resistant breast cancer [96]. And butyrate reduced the expression of *PLAC8* in colorectal cancer cells [62]. In acute myeloid leukemic cell lines, all-trans retinoic acid (ATRA) and phorbol 12-myristate 13-acetate (PMA) downregulate *PLAC8* expression though PKC ϵ -ERK2 signaling pathway [50]. As shown in Fig. 3, *PLAC8* interacts with tumor-related genes both at the transcriptional and posttranscriptional levels, thereby playing a functional role in cancer progression.

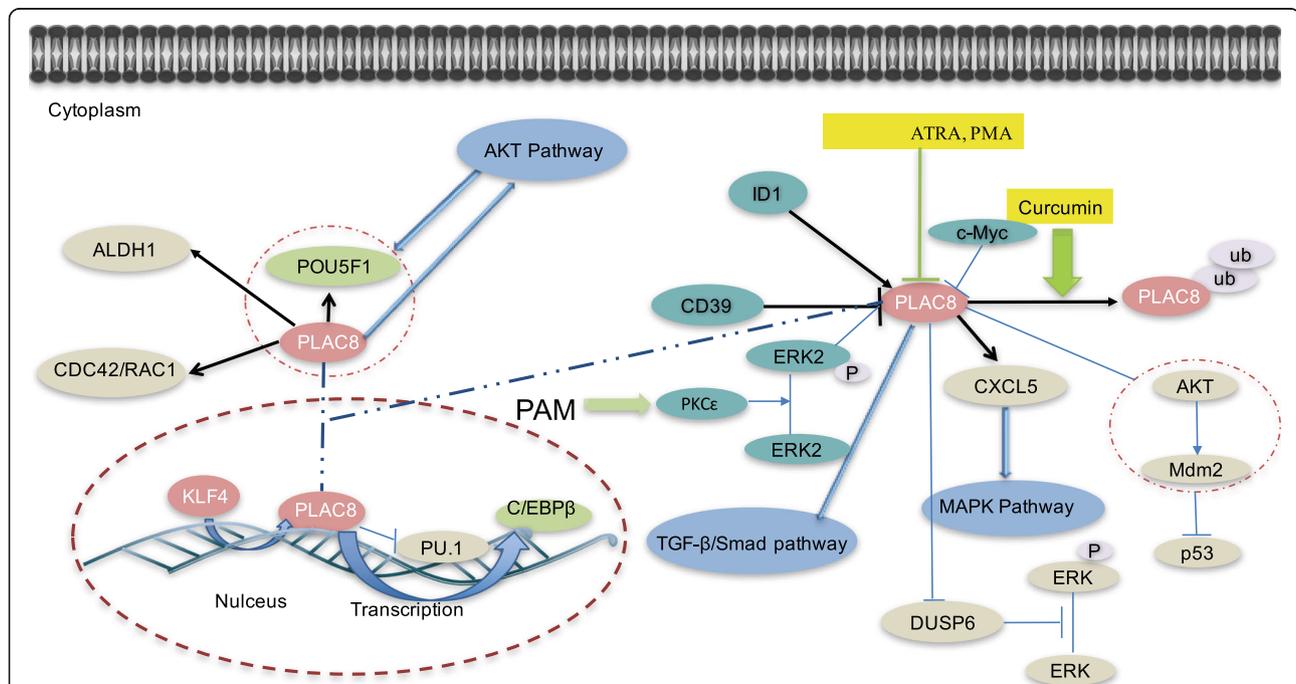
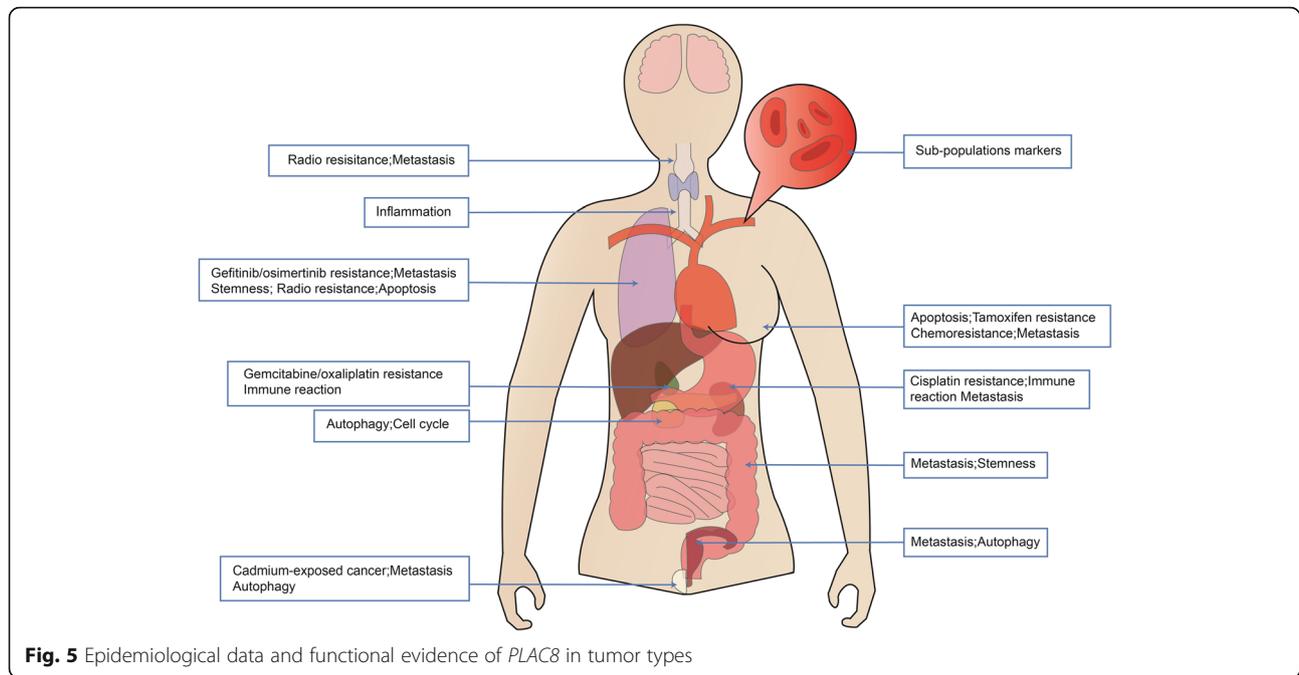


Fig. 4 Signaling pathways and genes controlling *PLAC8* expression and its regulatory system. *PLAC8* regulation is driven by different factors in both the nucleus and cytoplasm. It is important to point out that published mechanisms of *PLAC8* regulation are not yet completely understood. Studies have shown that growth-related signaling pathways, such as the AKT, MAPK and TGF- β /Smad pathways, interact with *PLAC8*. Some drugs, such as curcumin and PAM, directly and indirectly affect *PLAC8* levels. In addition, *PLAC8*, as a transcription factor, promotes *C/EBP β* transcription and inhibits *PU.1* transcription. The dashed lines depict mechanisms that are not completely understood. *C/EBP β* , enhancer-binding protein β ; *ALDH1A1*, aldehyde dehydrogenase 1 family member A1; *CDC42*, cell division control protein 42; *POU5F1*, POU Class 5 homeobox 1; *RAC1*, ras-related C3 botulinum toxin substrate 1; *KLF4*, Kruppel-like factor-4; *PLAC8*, placenta-specific gene 8; *PU.1*, Spi-1 proto-oncogene; *CD98*, ectonucleoside triphosphate diphosphohydrolase 1; *ID1*, inhibitor of differentiation1d-1; *PKC ϵ* , protein kinase C ϵ ; *ERK2*, extracellular regulated protein kinases 2; *c-Myc*, cellular myelocytomatosis viral oncogene; *CXCL5*, C-X-C motif chemokine 5; *DUSP6*, dual specificity phosphatase 6; *MDM-2*, murine double minute 2; *p53*, tumor protein 53



Conclusion and perspectives

Our understanding of the molecular mechanisms of *PLAC8* has expanded over the last decade, and this knowledge has been used to build better models that allow us to unravel the complicated role of the *PLAC8* gene in human diseases. Furthermore, these studies have led to the identification of putative therapeutics to target *PLAC8*. While *PLAC8* accumulates in most tumor cells, it tends to contribute to tumor progression by inducing tumorigenesis, immune reactions, chemoresistance and metastasis. As discussed above, *PLAC8* has been identified in breast cancer, prostate cancer, lung cancer, gallbladder cancer and nasopharyngeal cancer (Fig. 5). The molecular functions of *PLAC8* in the brain, gastric carcinoma and osteocarcinoma remain unknown and need to be explored. Based on these studies, we suggest that *PLAC8* may be a promising marker and predictor for clinical drug selection, immunotherapy response and tumor prognosis. The precise roles of *PLAC8* in different cancers vary, and its underlying mechanisms should be determined in the future. In addition, the relative network related to *PLAC8* is still not clear. Therefore, the mechanisms by which *PLAC8* selects its downstream partners and is reflected by other genes may reveal new players and mechanisms by which *PLAC8* orchestrates cancer cell behavior, thereby suggesting new targets for therapy. Another aspect that deserves attention is to understand the functional structure of each region of the *PLAC8* protein, which will help to comprehend the related molecular mechanism of the protein. Further characterization of the *PLAC8* protein in different cell

types is paramount not only to enrich our understanding of this gene in normal physiology but also to enhance our ability to target it to reduce cancer progression. Thus, the precise roles of *PLAC8* in different forms of programmed cancer death need to be discovered in the future.

Acknowledgements

Not applicable.

Authors' contributions

MMS, CYF, JZC and WLB designed the review. MMS and CYF researched the literature and drafted the manuscript. YJJ, XL, CYX, JSW, LZQ, CC, and XZ edited the manuscript. All authors approved the final version of the manuscript.

Funding

The work was supported by the National Natural Science Foundation of China (No. 81972453 and No. 81972597), Zhejiang Provincial Natural Science Foundation of China (under Grant Nos. LY19H160055, LY19H160059, LY18H160005, and LY20H160026), and Zhejiang Provincial Medical and Health Science and Technology (Youth Talent Program) Project No. 2021RC016.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Surgical Oncology, Sir Run Run Shaw Hospital, Zhejiang University, Zhejiang 310000, Hangzhou, China. ²Biomedical Research Center and Key Laboratory of Biotherapy of Zhejiang Province, Zhejiang 310000, Hangzhou, China. ³Department of Gastrointestinal Surgery, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University, Taizhou, Zhejiang 318000, People's Republic of China.

Received: 26 July 2021 Accepted: 20 September 2021

Published online: 09 October 2021

References

- Galaviz-Hernandez C, Stagg C, de Ridder G, Tanaka TS, Ko MSH, Schlessinger D, et al. Plac8 and Plac9, novel placental-enriched genes identified through microarray analysis. *Gene*. 2003;309(2):81–9. [https://doi.org/10.1016/S0378-1119\(03\)00508-0](https://doi.org/10.1016/S0378-1119(03)00508-0).
- Tanaka TS, Jaradat SA, Lim MK, et al. Genome-wide expression profiling of mid-gestation placenta and embryo using a 15,000 mouse developmental cDNA microarray. *Proc Natl Acad Sci U S A*. 2000;97(16):9127–32.
- El-Sheikh Ali H, Scoggin K, Linhares Boakari Y, et al. Kinetics of placenta-specific 8 (PLAC8) in equine placenta during pregnancy and placentitis. *Theriogenology*. 2021;160:81–9. <https://doi.org/10.1016/j.theriogenology.2020.10.041>.
- Lopera-Vasquez R, Hamdi M, Fernandez-Fuertes B, et al. Extracellular vesicles from BOEC in in vitro embryo development and quality. *PLoS One*. 2016;11(2):e0148083. <https://doi.org/10.1371/journal.pone.0148083>.
- Machado GM, Caixeta ES, Lucci CM, Rumpf R, Franco MM, Dode MA. Post-hatching development of bovine embryos in vitro: the effects of tunnel preparation and gender. *Zygote*. 2012;20(2):123–34. <https://doi.org/10.1017/S0967199411000086>.
- Machado GM, Ferreira AR, Guardieiro MM, Bastos MR, Carvalho JO, Lucci CM, et al. Morphology, sex ratio and gene expression of day 14 in vivo and in vitro bovine embryos. *Reprod Fertil Dev*. 2013;25(4):600–8. <https://doi.org/10.1071/RD11282>.
- Hoelker M, Rings F, Lund Q, Ghanem N, Phatsara C, Griese J, et al. Effect of the microenvironment and embryo density on developmental characteristics and gene expression profile of bovine preimplantative embryos cultured in vitro. *Reproduction*. 2009;137(3):415–25. <https://doi.org/10.1530/REP-08-0370>.
- Gomez E, Caamano JN, Bermejo-Alvarez P, et al. Gene expression in early expanded parthenogenetic and in vitro fertilized bovine blastocysts. *J Reprod Dev*. 2009;55(6):607–14.
- El-Sayed A, Hoelker M, Rings F, et al. Large-scale transcriptional analysis of bovine embryo biopsies in relation to pregnancy success after transfer to recipients. *Physiol Genomics*. 2006;28(1):84–96. <https://doi.org/10.1152/physiolgenomics.00111.2006>.
- Gomez E, Gutierrez-Adan A, Diez C, et al. Biological differences between in vitro produced bovine embryos and parthenotes. *Reproduction*. 2009;137(2):285–95. <https://doi.org/10.1530/REP-08-0220>.
- Lazzari G, Colleoni S, Duchi R, Galli A, Houghton FD, Galli C. Embryonic genotype and inbreeding affect preimplantation development in cattle. *Reproduction*. 2011;141(5):625–32. <https://doi.org/10.1530/REP-10-0282>.
- Bermejo-Alvarez P, Lonergan P, Rath D, Gutierrez-Adan A, Rizos D. Developmental kinetics and gene expression in male and female bovine embryos produced in vitro with sex-sorted spermatozoa. *Reprod Fertil Dev*. 2010;22(2):426–36. <https://doi.org/10.1071/RD09142>.
- Sultana N, Islam S, Juhasz A, Yang R, She M, Alhabbar Z, et al. Transcriptomic study for identification of major nitrogen stress responsive genes in Australian bread wheat cultivars. *Front Genet*. 2020;11:583785. <https://doi.org/10.3389/fgene.2020.583785>.
- Lee H, Kim JI, Park JS, Roh JI, Lee J, Kang BC, et al. CRISPR/Cas9-mediated generation of a Plac8 knockout mouse model. *Lab Anim Res*. 2018;34(4):279–87. <https://doi.org/10.5625/lar.2018.34.4.279>.
- Sasaki D, Kotoh J, Watadani R, Matsumoto K. New animal models reveal that coenzyme Q2 (Coq2) and placenta-specific 8 (Plac8) are candidate genes for the onset of type 2 diabetes associated with obesity in rats. *Mamm Genome*. 2015;26(11–12):619–29. <https://doi.org/10.1007/s00335-015-9597-4>.
- Cebrian-Serrano A, Salvador I, García-Roselló E, Pericuesta E, Pérez-Cerezales S, Gutierrez-Adán A, et al. Effect of the bovine Oviductal fluid on In Vitro Fertilization, development and gene expression of in vitro-produced bovine blastocysts. *Reprod Domest Anim*. 2013;48(2):331–8. <https://doi.org/10.1111/j.1439-0531.2012.02157.x>.
- Chang WL, Liu YW, Dang YL, et al. PLAC8, a new marker for human interstitial extravillous trophoblast cells, promotes their invasion and migration. *Development*. 2018;145(2):dev148932. <https://doi.org/10.1242/dev.148932>.
- Suwik K, Sinderewicz E, Boruszewska D, et al. mRNA expression and role of PPARgamma and PPARdelta in bovine preimplantation embryos depending on the quality and developmental stage. *Animals (Basel)*. 2020;10(12):2358. <https://doi.org/10.3390/ani10122358>.
- Korzekwa AJ, Kotlarczyk AM, Szczepanska AA, Grzyb M, Siergiej A, Woclawek-Potocka I. Antioxidative potential of red deer embryos depends on reproductive stage of hind as a oocyte donor. *Animals (Basel)*. 2020;10(7):1190. <https://doi.org/10.3390/ani10071190>.
- Blue EK, Sheehan BM, Nuss ZV, et al. Epigenetic regulation of placenta-specific 8 contributes to altered function of endothelial Colony-forming cells exposed to intrauterine gestational diabetes mellitus. *Diabetes*. 2015;64(7):2664–75. <https://doi.org/10.2337/db14-1709>.
- Machado GM, Ferreira AR, Pivato I, Fidelis A, Sprigico JF, Paulini F, et al. Post-hatching development of in vitro bovine embryos from day 7 to 14 in vivo versus in vitro. *Mol Reprod Dev*. 2013;80(11):936–47. <https://doi.org/10.1002/mrd.22230>.
- Slade CD, Reagin KL, Lakshmanan HG, Klonowski KD, Watford WT. Placenta-specific 8 limits IFNgamma production by CD4 T cells in vitro and promotes establishment of influenza-specific CD8 T cells in vivo. *PLoS One*. 2020;15(7):e0235706. <https://doi.org/10.1371/journal.pone.0235706>.
- Tanaka TS, Jaradat SA, Lim MK, Kargul GJ, Wang X, Grahovac MJ, et al. Genome-wide expression profiling of mid-gestation placenta and embryo using a 15,000 mouse developmental cDNA microarray. *Proc Natl Acad Sci U S A*. 2000;97(16):9127–32. <https://doi.org/10.1073/pnas.97.16.9127>.
- Libault M, Stacey G. Evolution of FW2.2-like (FWL) and PLAC8 genes in eukaryotes. *Plant Signal Behav*. 2010;5(10):1226–8. <https://doi.org/10.4161/psb.5.10.12808>.
- Rogulski K, Li Y, Rothermund K, Pu L, Watkins S, Yi F, et al. Onzin, a c-Myc-repressed target, promotes survival and transformation by modulating the Akt-Mdm2-p53 pathway. *Oncogene*. 2005;24(51):7524–41. <https://doi.org/10.1038/sj.onc.1208897>.
- Jimenez-Preitner M, Berney X, Uldry M, Vitali A, Cinti S, Ledford JG, et al. Plac8 is an inducer of C/EBPbeta required for brown fat differentiation, thermoregulation, and control of body weight. *Cell Metab*. 2011;14(5):658–70. <https://doi.org/10.1016/j.cmet.2011.08.008>.
- Nakano M, Iida K, Nyunoya H, Iida H. Determination of structural regions important for Ca²⁺ uptake activity in Arabidopsis MCA1 and MCA2 expressed in yeast. *Plant Cell Physiol*. 2011;52(11):1915–30. <https://doi.org/10.1093/pcp/pcr131>.
- Di Vietro L, Daghino S, Abbà S, Perotto S. Gene expression and role in cadmium tolerance of two PLAC8-containing proteins identified in the ericoid mycorrhizal fungus *Oidiodendron maius*. *Fungal Biol*. 2014;118(8):695–703. <https://doi.org/10.1016/j.funbio.2014.04.011>.
- Song WY, Hortensteiner S, Tomioka R, Lee Y, Martinioia E. Common functions or only phylogenetically related? The large family of PLAC8 motif-containing/PCR genes. *Mol Cells*. 2011;31(1):1–7. <https://doi.org/10.1007/s10059-011-0024-8>.
- Cabreira-Cagliari C, Dias NdC, Bohn B, et al. revising the PLAC8 gene family: from a central role in differentiation, proliferation, and apoptosis in mammals to a multifunctional role in plants. *Genome*. 2018;61(12):857–65. <https://doi.org/10.1139/gen-2018-0035>.
- Pang Q, Gao L, Bai Y, Deng H, Han Y, Hu W, et al. Identification and characterization of a novel multifunctional placenta specific protein 8 in *Dugesia japonica*. *Gene*. 2017;613:1–9. <https://doi.org/10.1016/j.gene.2017.02.024>.
- Li M, Liu D, Wang L, Wang W, Wang A, Yao Y. Expression of placenta-specific 8 in human oocytes, embryos, and models of in vitro implantation. *Fertil Steril*. 2016;106(3):781–9 e782. <https://doi.org/10.1016/j.fertnstert.2016.05.018>.
- Li C, Ma H, Wang Y, Cao Z, Graves-Deal R, Powell AE, et al. Excess PLAC8 promotes an unconventional ERK2-dependent EMT in colon cancer. *J Clin Invest*. 2014;124(5):2172–87. <https://doi.org/10.1172/JCI71103>.
- Mao M, Chen Y, Jia Y, Yang J, Wei Q, Li Z, et al. PLCA8 suppresses breast cancer apoptosis by activating the PI3k/AKT/NF-kappaB pathway. *J Cell Mol Med*. 2019;23(10):6930–41. <https://doi.org/10.1111/jcmm.14578>.

35. Huang M-L, Zou Y, Yang R, Jiang Y, Sheng JF, Han JB, et al. Placenta specific 8 gene induces epithelial-mesenchymal transition of nasopharyngeal carcinoma cells via the TGF- β /Smad pathway. *Exp Cell Res*. 2019;374(1):172–80. <https://doi.org/10.1016/j.yexcr.2018.11.021>.
36. Chen Y, Jia Y, Mao M, et al. PLAC8 promotes adriamycin resistance via blocking autophagy in breast cancer. *J Cell Mol Med*. 2021.
37. Kaistha BP, Lorenz H, Schmidt H, Sipos B, Pawlak M, Gierke B, et al. PLAC8 localizes to the inner plasma membrane of pancreatic Cancer cells and regulates cell growth and disease progression through critical cell-cycle regulatory pathways. *Cancer Res*. 2016;76(1):96–107. <https://doi.org/10.1158/0008-5472.CAN-15-0216>.
38. Kinsey C, Balakrishnan V, O'Dell MR, et al. Plac8 links oncogenic mutations to regulation of autophagy and is critical to pancreatic cancer progression. *Cell Rep*. 2014;7(4):1143–55. <https://doi.org/10.1016/j.celrep.2014.03.061>.
39. Ballabio A, Bonifacino JS. Lysosomes as dynamic regulators of cell and organismal homeostasis. *Nat Rev Mol Cell Biol*. 2020;21(2):101–18. <https://doi.org/10.1038/s41580-019-0185-4>.
40. Grate LR. Many accurate small-discriminatory feature subsets exist in microarray transcript data: biomarker discovery. *BMC Bioinformatics*. 2005; 6(1):97. <https://doi.org/10.1186/1471-2105-6-97>.
41. Kolluru V, Pal D, Papu John AMS, Ankem MK, Freedman JH, Damodaran C. Induction of Plac8 promotes pro-survival function of autophagy in cadmium-induced prostate carcinogenesis. *Cancer Lett*. 2017;408:121–9. <https://doi.org/10.1016/j.canlet.2017.08.023>.
42. Zou L, Chai J, Gao Y, Guan J, Liu Q, Du JJ. Down-regulated PLAC8 promotes hepatocellular carcinoma cell proliferation by enhancing PI3K/Akt/GSK3 β /Wnt/ β -catenin signaling. *Biomed Pharmacother*. 2016;84:139–46. <https://doi.org/10.1016/j.biopha.2016.09.015>.
43. Daghino S, Di Vietro L, Pettiti L, et al. Yeast expression of mammalian Onzin and fungal FCR1 suggests ancestral functions of PLAC8 proteins in mitochondrial metabolism and DNA repair. *Sci Rep*. 2019;9(1):6629. <https://doi.org/10.1038/s41598-019-43136-3>.
44. Guo M, Rupe MA, Dieter JA, Zou J, Spielbauer D, Duncan KE, et al. Cell number Regulator1 affects plant and organ size in maize: implications for crop yield enhancement and heterosis. *Plant Cell*. 2010;22(4):1057–73. <https://doi.org/10.1105/tpc.109.073676>.
45. Zeng X, Liu Q, Yang Y, Jia W, Li S, He D, et al. Placenta-specific protein 8 promotes the proliferation of lung adenocarcinoma PC-9 cells and their tolerance to an epidermal growth factor receptor tyrosine kinase inhibitor by activating the ERK signaling pathway. *Oncol Lett*. 2019;18(5):5621–7. <https://doi.org/10.3892/ol.2019.10911>.
46. Mansouri-Attia N, Aubert J, Reinaud P, Giraud-Delville C, Taghouti G, Galio L, et al. Gene expression profiles of bovine caruncular and intercaruncular endometrium at implantation. *Physiol Genomics*. 2009;39(1):14–27. <https://doi.org/10.1152/physiolgenomics.90404.2008>.
47. Sweeney TE, Khatri P. Comprehensive validation of the FAIM3:PLAC8 ratio in time-matched public gene expression data. *Am J Respir Crit Care Med*. 2015;192(10):1260–1.
48. Sweeney TE, Khatri P. Benchmarking Sepsis gene expression diagnostics using public data. *Crit Care Med*. 2017;45(1):1–10. <https://doi.org/10.1097/CCM.0000000000002021>.
49. Tang Y, Yang X, Shu H, Yu Y, Pan S, Xu J, et al. Bioinformatic analysis identifies potential biomarkers and therapeutic targets of septic-shock-associated acute kidney injury. *Hereditas*. 2021;158(1):13. <https://doi.org/10.1111/his.14065>.
50. Wu SF, Huang Y, Hou JK, Yuan TT, Zhou CX, Zhang J, et al. The downregulation of onzin expression by PKCepsilon-ERK2 signaling and its potential role in AML cell differentiation. *Leukemia*. 2010;24(3):544–51. <https://doi.org/10.1038/leu.2009.280>.
51. Jimenez-Preitner M, Berney X, Thorens B. Plac8 is required for white adipocyte differentiation in vitro and cell number control in vivo. *PLoS One*. 2012;7(11):e48767. <https://doi.org/10.1371/journal.pone.0048767>.
52. Reddy RB, Bhat AR, James BL, Govindan SV, Mathew R, DR R, et al. Meta-analyses of microarray datasets identifies ANO1 and FADD as prognostic markers of head and neck Cancer. *PLoS One*. 2016;11(1):e0147409. <https://doi.org/10.1371/journal.pone.0147409>.
53. Li H, Wang X, Fang Y, Huo Z, Lu X, Zhan X, et al. Integrated expression profiles analysis reveals novel predictive biomarker in pancreatic ductal adenocarcinoma. *Oncotarget*. 2017;8(32):52571–83. <https://doi.org/10.18632/oncotarget.16732>.
54. Tatura M, Schmidt H, Hajjat M, Stark M, Rinke A, Diels R, et al. Placenta-specific 8 is overexpressed and regulates cell proliferation in low-grade human pancreatic neuroendocrine tumors. *Neuroendocrinology*. 2020; 110(1–2):23–34. <https://doi.org/10.1159/000500541>.
55. Hung CS, Wang YC, Guo JW, Yang RN, Lee CL, Shen MH, et al. Expression pattern of placenta specific 8 and keratin 20 in different types of gastrointestinal cancer. *Mol Med Rep*. 2020;21(2):659–66. <https://doi.org/10.3892/mmr.2019.10871>.
56. Dixon Scott J, Lemberg Kathryn M, Lamprecht Michael R, et al. Ferroptosis: an Iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149(5):1060–72. <https://doi.org/10.1016/j.cell.2012.03.042>.
57. Kroemer G, Galluzzi L, Vandenabeele P, Abrams J, Alnemri ES, Baehrecke EH, et al. Classification of cell death: recommendations of the nomenclature committee on cell death 2009. *Cell Death Differ*. 2009;16(1):3–11. <https://doi.org/10.1038/cdd.2008.150>.
58. D'Arcy MS. Cell death: a review of the major forms of apoptosis, necrosis and autophagy. *Cell Biol Int*. 2019;43(6):582–92. <https://doi.org/10.1002/cbin.11137>.
59. Tang D, Kang R, Berghe TV, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. *Cell Res*. 2019;29(5):347–64. <https://doi.org/10.1038/s41422-019-0164-5>.
60. Van Opendenbosch N, Lamkanfi M. Caspases in cell death, inflammation, and disease. *Immunity*. 2019;50(6):1352–64. <https://doi.org/10.1016/j.immuni.2019.05.020>.
61. Newton K, Wickliffe KE, Maltzman A, Dugger DL, Reja R, Zhang Y, et al. Activity of caspase-8 determines plasticity between cell death pathways. *Nature*. 2019;575(7784):679–82. <https://doi.org/10.1038/s41586-019-1752-8>.
62. Huang CC, Shen MH, Chen SK, Yang SH, Liu CY, Guo JW, et al. Gut butyrate-producing organisms correlate to placenta specific 8 protein: importance to colorectal cancer progression. *J Adv Res*. 2020;22:7–20. <https://doi.org/10.1016/j.jare.2019.11.005>.
63. Lee CL, Huang CJ, Yang SH, Chang CC, Huang CC, Chien CC, et al. Discovery of genes from feces correlated with colorectal cancer progression. *Oncol Lett*. 2016;12(5):3378–84. <https://doi.org/10.3892/ol.2016.5069>.
64. Uehara H, Takahashi T, Izumi K. Induction of retinol-binding protein 4 and placenta-specific 8 expression in human prostate cancer cells remaining in bone following osteolytic tumor growth inhibition by osteoprotegerin. *Int J Oncol*. 2013;43(2):365–74. <https://doi.org/10.3892/ijo.2013.1954>.
65. Mourtada-Maarabouni M, Watson D, Munir M, Farzaneh F, T. Williams G. Apoptosis suppression by candidate oncogene PLAC8 is reversed in other cell types. *Curr Cancer Drug Targets*. 2013;13(1):80–91. <https://doi.org/10.2174/156800913804486584>.
66. Chang CC, Huang CC, Yang SH, Chien CC, Lee CL, Huang CJ. Data on clinical significance of GAS2 in colorectal cancer cells. *Data Brief*. 2016;8:82–6. <https://doi.org/10.1016/j.dib.2016.05.010>.
67. Xu W, Gao L, Li T, Zheng J, Shao A, Zhang J. Mesencephalic astrocyte-derived neurotrophic factor (MANF) protects against neuronal apoptosis via activation of Akt/MDM2/p53 signaling pathway in a rat model of intracerebral hemorrhage. *Front Mol Neurosci*. 2018;11:176. <https://doi.org/10.3389/fnmol.2018.00176>.
68. Levy JMM, Towers CG, Thorburn A. Targeting autophagy in cancer. *Nat Rev Cancer*. 2017;17(9):528–42. <https://doi.org/10.1038/nrc.2017.53>.
69. Yang S, Wang X, Contino G, Liesa M, Sahin E, Ying H, et al. Pancreatic cancers require autophagy for tumor growth. *Genes Dev*. 2011;25(7):717–29. <https://doi.org/10.1101/gad.2016111>.
70. Ying H, Dey P, Yao W, Kimmelman AC, Draetta GF, Maitra A, et al. Genetics and biology of pancreatic ductal adenocarcinoma. *Genes Dev*. 2016;30(4): 355–85. <https://doi.org/10.1101/gad.275776.115>.
71. Prior IA, Hood FE, Hartley JL. The frequency of Ras mutations in Cancer. *Cancer Res*. 2020;80(14):2969–74. <https://doi.org/10.1158/0008-5472.CAN-19-3682>.
72. Levine AJ. p53: 800 million years of evolution and 40 years of discovery. *Nat Rev Cancer*. 2020;20(8):471–80. <https://doi.org/10.1038/s41568-020-0262-1>.
73. Huang ML, Qi CL, Zou Y, et al. Plac8-mediated autophagy regulates nasopharyngeal carcinoma cell function via AKT/mTOR pathway. *J Cell Mol Med*. 2020;24(14):7778–88.
74. Segawa S, Kondo Y, Nakai Y, Iizuka A, Kaneko S, Yokosawa M, et al. Placenta specific 8 suppresses IL-18 production through regulation of autophagy and is associated with adult still disease. *J Immunol*. 2018;201(12):3534–45. <https://doi.org/10.4049/jimmunol.1800667>.
75. Feng X, Wei Z, Tao X, et al. PLAC8 promotes the autophagic activity and improves the growth priority of human trophoblast cells. *FASEB J*. 2021; 35(3):e21351. <https://doi.org/10.1096/fj.202002075RR>.
76. Zhou Y, Shen Y, Chen C, Sui X, Yang J, Wang L, et al. The crosstalk between autophagy and ferroptosis: what can we learn to target drug resistance in

- cancer? *Cancer Biol Med.* 2019;16(4):630–46. <https://doi.org/10.20892/jissn.2095-3941.2019.0158>.
77. Wang M, Wang XF, Li YM, Chen N, Fan Y, Huang WK, et al. Cross-talk between autophagy and apoptosis regulates testicular injury/recovery induced by cadmium via PI3K with mTOR-independent pathway. *Cell Death Dis.* 2020;11(1):46. <https://doi.org/10.1038/s41419-020-2246-1>.
78. Yang R, Tao ZZ, Huang ML, Zheng YF, Dai MY, Zou Y, et al. Knockout of the placenta specific 8 gene radiosensitizes nasopharyngeal carcinoma cells by activating the PI3K/AKT/GSK3beta pathway. *Am J Transl Res.* 2018;10(2):455–64.
79. Pan G, Thomson JA. Nanog and transcriptional networks in embryonic stem cell pluripotency. *Cell Res.* 2007;17(1):42–9. <https://doi.org/10.1038/sj.cr.7310125>.
80. Schaefer T, Lengerke C. SOX2 protein biochemistry in stemness, reprogramming, and cancer: the PI3K/AKT/SOX2 axis and beyond. *Oncogene.* 2020;39(2):278–92. <https://doi.org/10.1038/s41388-019-0997-x>.
81. Boyer LA, Lee TI, Cole MF, Johnstone SE, Levine SS, Zucker JP, et al. Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell.* 2005;122(6):947–56. <https://doi.org/10.1016/j.cell.2005.08.020>.
82. Sugimura S, Kobayashi S, Hashiyada Y, Ohtake M, Kaneda M, Yamanouchi T, et al. Follicular growth-stimulated cows provide favorable oocytes for producing cloned embryos. *Cell Reprogram.* 2012;14(1):29–37. <https://doi.org/10.1089/cell.2011.0060>.
83. Fogarty NME, McCarthy A, Snijders KE, Powell BE, Kubikova N, Blakeley P, et al. Genome editing reveals a role for OCT4 in human embryogenesis. *Nature.* 2017;550(7674):67–73. <https://doi.org/10.1038/nature24033>.
84. Yin M, Zhou HJ, Lin C, et al. CD34+KLF4+ stromal stem cells contribute to endometrial regeneration and repair. *Cell Rep.* 2019;27(9):2709–2724.e2703.
85. Sun Y, Lai X, Yu Y, Li J, Cao L, Lin W, et al. Inhibitor of DNA binding 1 (Id1) mediates stemness of colorectal cancer cells through the Id1-c-Myc-PLAC8 axis via the Wnt/ β -catenin and Shh signaling pathways<p>. *Cancer Manag Res.* 2019;11:6855–69. <https://doi.org/10.2147/CMAR.S207167>.
86. Wang Q, Jiang J, Ying G, et al. Tamoxifen enhances stemness and promotes metastasis of ERalpha36(+) breast cancer by upregulating ALDH1A1 in cancer cells. *Cell Res.* 2018;28(3):336–58.
87. Mori Y, Yamawaki K, Ishiguro T, Yoshihara K, Ueda H, Sato A, et al. ALDH-dependent glycolytic activation mediates Stemness and paclitaxel resistance in patient-derived spheroid models of uterine endometrial Cancer. *Stem Cell Rep.* 2019;13(4):730–46. <https://doi.org/10.1016/j.stemcr.2019.08.015>.
88. Fei X, Wang G, Shen H, Gu X. Placenta-specific 8 is a potential novel target for osimertinib resistance in non-small cell lung cancer. *Oncol Lett.* 2019; 18(1):955–61. <https://doi.org/10.3892/ol.2019.10344>.
89. Jin Z, Guan L, Xiang GM, Gao BA. Radiation resistance of the lung adenocarcinoma is related to the AKT-Onzin-POU5F1 axis. *Biochem Biophys Res Commun.* 2018;499(3):538–43. <https://doi.org/10.1016/j.bbrc.2018.03.185>.
90. Jia Y, Ying X, Zhou J, Chen Y, Luo X, Xie S, et al. The novel KLF4/PLAC8 signaling pathway regulates lung cancer growth. *Cell Death Dis.* 2018;9(6): 603. <https://doi.org/10.1038/s41419-018-0580-3>.
91. Pastushenko I, Blanpain C. EMT transition states during tumor progression and metastasis. *Trends Cell Biol.* 2019;29(3):212–26. <https://doi.org/10.1016/j.tcb.2018.12.001>.
92. Zhang Y, Hu Q, Li G, Li L, Liang S, Zhang Y, et al. ONZIN upregulation by mutant p53 contributes to osteosarcoma metastasis through the CXCL5-MAPK signaling pathway. *Cell Physiol Biochem.* 2018;48(3):1099–111. <https://doi.org/10.1159/000491976>.
93. Qi C, Hong L, Cheng Z, Yin Q. Identification of metastasis-associated genes in colorectal cancer using metaDE and survival analysis. *Oncol Lett.* 2016; 11(1):568–74. <https://doi.org/10.3892/ol.2015.3956>.
94. Shi L, Xiao L, Heng B, Mo S, Chen W, Su Z. Overexpression of placenta specific 8 is associated with malignant progression and poor prognosis of clear cell renal cell carcinoma. *Int Urol Nephrol.* 2017;49(7):1165–76. <https://doi.org/10.1007/s11255-017-1578-y>.
95. Wu J, Wang X, Shang A, Vella G, Sun Z, Ji P, et al. PLAC8 inhibits oral squamous cell carcinogenesis and epithelial-mesenchymal transition via the Wnt/ β -catenin and PI3K/Akt/GSK3beta signaling pathways. *Oncol Lett.* 2020;20(5):128. <https://doi.org/10.3892/ol.2020.11989>.
96. Mao M, Hu D, Yang J, Chen Y, Zhang X, Shen J, et al. Regulation of tamoxifen sensitivity by the PLAC8/MAPK pathway axis is antagonized by curcumin-induced protein stability change. *J Mol Med.* 2021;99(6):845–58. <https://doi.org/10.1007/s00109-021-02047-5>.
97. Qin X-H, Wang H-X, Ma L, Shen J, Liu Q-H, Xue L. Knockout of the placenta specific 8 gene affects the proliferation and migration of human embryonic kidney 293T cell. *Cell Biochem Biophys.* 2019;78(1):55–64. <https://doi.org/10.1007/s12013-019-00893-2>.
98. Tibbitt CA, Stark JM, Martens L, Ma J, Mold JE, Deswarte K, et al. Single-cell RNA sequencing of the T helper cell response to house dust mites defines a distinct gene expression signature in airway Th2 cells. *Immunity.* 2019; 51(1):169–184.e5. <https://doi.org/10.1016/j.immuni.2019.05.014>.
99. Gerner MC, Ziegler LS, Schmidt RLJ, Krenn M, Zimprich F, Uyanik-Uenal K, et al. The TGF- β /SOX4 axis and ROS-driven autophagy co-mediate CD39 expression in regulatory T-cells. *FASEB J.* 2020;34(6):8367–84. <https://doi.org/10.1096/fj.201902664>.
100. Johnson RM, Kerr MS, Slaven JE. Plac8-dependent and inducible NO synthase-dependent mechanisms clear Chlamydia muridarum infections from the genital tract. *J Immunol.* 2012;188(4):1896–904. <https://doi.org/10.4049/jimmunol.1102764>.
101. Johnson RM, Kerr MS, Slaven JE. Perforin is detrimental to controlling [corrected] *C. muridarum* replication in vitro, but not in vivo. *PLoS One.* 2013;8(5):e63340.
102. Johnson RM, Kerr MS, Slaven JE. An atypical CD8 T-cell response to Chlamydia muridarum genital tract infections includes T cells that produce interleukin-13. *Immunology.* 2014;142(2):248–57. <https://doi.org/10.1111/imm.12248>.
103. El-Sheikh Ali H, Dini P, Scoggin K, et al. Transcriptomic analysis of equine placenta reveals key regulators and pathways involved in ascending placentitis. *Biol Reprod.* 2021;104(3):638–56. <https://doi.org/10.1093/biolre/iaaa209>.
104. Zhai J, Li S, Sen S, et al. m (6) A RNA methylation regulators contribute to eutopic endometrium and myometrium dysfunction in adenomyosis. *Front Genet.* 2020;11:716.
105. McHugh L, Seldon TA, Brandon RA, Kirk JT, Rapisarda A, Sutherland AJ, et al. A molecular host response assay to discriminate between Sepsis and infection-negative systemic inflammation in critically ill patients: discovery and validation in independent cohorts. *PLoS Med.* 2015;12(12):e1001916. <https://doi.org/10.1371/journal.pmed.1001916>.
106. Verboom DM, Koster-Brouwer ME, Varkila MRJ, Bonten MJM, Cremer OL. Profile of the SeptiCyt[™] LAB gene expression assay to diagnose infection in critically ill patients. *Expert Rev Mol Diagn.* 2019;19(2):95–108. <https://doi.org/10.1080/14737159.2019.1567333>.
107. Gyurina K, Karai B, Ujfalusi A, et al. Coagulation FXIII-A protein expression defines three novel sub-populations in pediatric B-cell progenitor acute lymphoblastic leukemia characterized by distinct gene expression signatures. *Front Oncol.* 2019;9:1063. <https://doi.org/10.3389/fonc.2019.01063>.
108. Gong K, Gong Z-J, Lu P-X, Ni XL, Shen S, Liu H, et al. PLAC8 overexpression correlates with PD-L1 upregulation and acquired resistance to chemotherapies in gallbladder carcinoma. *Biochem Biophys Res Commun.* 2019;516(3):983–90. <https://doi.org/10.1016/j.bbrc.2019.06.121>.
109. Li Q, Qin T, Bi Z, Hong H, Ding L, Chen J, et al. Rac1 activates non-oxidative pentose phosphate pathway to induce chemoresistance of breast cancer. *Nat Commun.* 2020;11(1):1456. <https://doi.org/10.1038/s41467-020-15308-7>.
110. Ziegler A, Marti E, Summerfield A, Baumann A. Identification and characterization of equine blood plasmacytoid dendritic cells. *Dev Comp Immunol.* 2016;65:352–7. <https://doi.org/10.1016/j.dci.2016.08.005>.
111. Scicluna BP, Klein Klouwenberg PM, van Vught LA, et al. A molecular biomarker to diagnose community-acquired pneumonia on intensive care unit admission. *Am J Respir Crit Care Med.* 2015;192(7):826–35. <https://doi.org/10.1164/rccm.201502-0355OC>.
112. Y-y M, Liu J, Zhu J, et al. The effect of botulinum toxin type a on expression profiling of long noncoding RNAs in human dermal fibroblasts. *BioMed Res Int.* 2017;2017:1–13.
113. Boualia SK, Gaitan Y, Tremblay M, Sharma R, Cardin J, Kania A, et al. A core transcriptional network composed of Pax2/8, Gata3 and Lim1 regulates key players of pro/mesonephros morphogenesis. *Dev Biol.* 2013;382(2):555–66. <https://doi.org/10.1016/j.jydbio.2013.07.028>.
114. Cheng Z, Chauhan L, Barry AT, Abudureyimu A, Oguejiofor CF, Chen X, et al. Acute bovine viral diarrhoea virus infection inhibits expression of interferon tau-stimulated genes in bovine endometrium. *Biol Reprod.* 2017;96(6):1142–53. <https://doi.org/10.1093/biolre/iox056>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.