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ZIP6-centered zinc regulatory and malignant characteristics of breast cancer cells

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Abstract

Zinc (Zn) is an essential trace element for numerous biological events in mammals. Zn functions as a signaling mediator, leading to the regulation of physiological cell actions and, therefore, has therapeutic potential. Recent breast cancer research has shown that Zn transporters contribute to malignancy processes; thus, elucidating the roles of Zn and Zn transporters in breast cancer may lead to the development of novel strategies for breast cancer diagnosis and therapy. The Zn transporter ZIP6 mediates the acquisition of malignant phenotypes such as hypoxic resistance and epithelial-mesenchymal transition (EMT), which determine breast tumor grade and prognosis. ZIP6 expression contributes to the efficacy of anticancer therapy through Zn-induced autophagy. The maintenance of breast cancer stem-like cells requires Zn modulation through the cooperative function of ZIP6 and ZIP7. These findings suggest that the ZIP6-mediated Zn network is a potent driving force toward malignancy. In this review, we summarize recent progress in understanding the emerging roles of Zn and ZIP6 in the regulation of malignant characteristics related to hypoxic adaptive response, drug therapy, and stemness. We also discuss the possibility and future challenges of innovative breast cancer therapies using ZIP6 and Zn-related molecules.

Key words: Zinc, zinc transporter, breast cancer, hypoxia, Bcl-2, breast cancer stem-like cell

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Introduction

Breast cancer is the most commonly occurring cancer in women, with both morbidity and mortality increasing on a yearly basis [1,2]. Recent breast cancer studies have elucidated the molecular mechanisms of its pathological conditions, and evidence-based theoretical treatment protocols including pharmacotherapy using molecular target drugs are selected according to the molecular features of breast cancer cells [3,4]. However, breast cancer cells acquire malignant phenotypes aggressively during treatment, even in the early stages of growth, causing metastasis, recurrence, and resistance to therapy [5,6]. Thus, the range of current therapies is limited, and little is known

about the regulatory machinery of breast cancer malignant transformation.

In recent years, a growing body of evidence has indicated that zinc (Zn) and Zn transporters are closely related to the malignant processes of breast cancer, presenting an attractive potential approach for novel therapeutic strategies [7-11]. As a trace element, Zn is essential for human survival; intracellular Zn^{2+} levels are spatiotemporally regulated by ZRT IRT-like proteins (ZIPs; SLC39A, 14 members) to facilitate the influx of Zn into the cytosol, and zinc transporters (ZnT; SLC30A, 9 members) mediate Zn efflux from the cytosol [12,13]. These transporters contribute to maintaining Zn homeostasis within cells and throughout the body by strictly managing the cellular Zn balance according to the distributions of their molecular species in a tissue-specific manner [8-13]. Zn has been shown to target molecules selectively as an intracellular and extracellular signaling mediator, such that the Zn signaling pathway spatiotemporally regulates cell functions and Zn transporter aberrations are linked to the onset and progression of diseases such as cancers [7-14], Alzheimer's disease [15], diabetes [16-18], and other pathological processes [19-24] (**Figure 1**). Interestingly, zinc transporters in cancers have been reported from various fields including clinical analysis as well as molecular and structural biology, and only 5 ZnTs and almost all ZIP transporters are involved in a number of cancers [25]. Patterns of ZIP dysregulation differ among cancers, and indicate the complicated roles of Zn in various cancer types including prostate cancer [26,43], pancreatic cancer [27-29,44,59], hepatocellular carcinoma [30,45], lung cancer [31], glioma [32], oral squamous [33], nasopharyngeal [34], ovarian cancer [35,60], colorectal cancer [46], esophageal cancer [36,47], breast cancer [37-42,49-52,54-57], gastric adenocarcinoma [48], neuroblastoma [53], and bladder cancer [58], as well as in phenotypes associated with tumorigenesis, metastasis, and therapeutic resistance (**Table 1**). In metastatic cancers, ZIP14 is upregulated in skeletal muscle, promoting cachexia [61].

Zn levels in the breast tissue and serum of patients with breast cancer are higher and lower, respectively, than those of healthy subjects [62-65]. Both clinical and *in vitro* studies have demonstrated the potential roles of ZIP6 in estrogen receptor (ER)-positive breast cancer in about 70% of breast cancer patients [37-42], of ZIP7 in ER antagonist tamoxifen-resistant breast cancer [49-52],

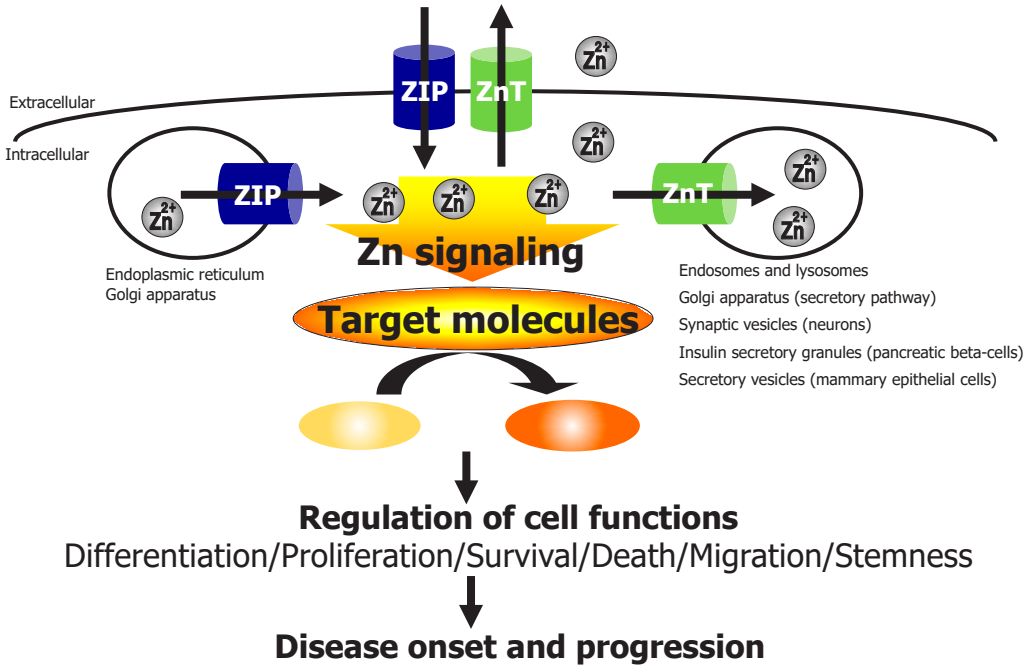

Figure 1. **Zn transporters contribute to cell functions and pathological processes.**
Zn modulates the intracellular signaling pathway, thereby determining the final outputs of various physiological reactions such as cell differentiation, proliferation, survival, and migration. Disorder of Zn transporters led to specific diseases.

Table 1. | ZIP transporters and cancers.

Gene name	Protein name	Type of cancer cells	Functional activity in cancer cells	References
SLA39a1	ZIP1	Prostate	Expression down-regulated	26
SLA39a2	ZIP2	Prostate	Expression down-regulated	26
SLA39a3	ZIP3	Prostate	Expression down-regulated	26
		Pancreatic	Expression down-regulated	27
SLA39a4	ZIP4	Pancreatic	Expression up-regulated	28
		Pancreatic	Expression up-regulated in cancer cell-derived exosomes	29
		Hepatocellular	Expression up-regulated	30
		Lung	Expression up-regulated	31
		Glioma	Expression up-regulated	32
		Oral squamous	Expression up-regulated	33
		Nasopharyngeal	Expression up-regulated	34
		Ovarian	Expression up-regulated	35
SLA39a5	ZIP5	Esophageal	Expression up-regulated	36
SLA39a6	ZIP6	Metastatic ER+breast	Expression up-regulated	37,67
		ER+breast	Expression down-regulated	38-42
		Prostate	Expression up-regulated	43
		Pancreatic	Expression up-regulated	44
		Hepatocellular	Expression up-regulated	45
		Colorectal	Expression up-regulated	46
		Esophageal squamous-cell	Expression up-regulated	47
		Gastric	Expression up-regulated	48
SLA39a7	ZIP7	Anti-hormone resistance in ER+breast	Expression up-regulated	49-52,92
SLA39a8	ZIP8	Neuroblastoma	Proliferation inhibited by ZIP8 knockdown	53
SLA39a9	ZIP9	Prostate, breast	Apoptosis induced by ZIP9 activation	54
SLA39a10	ZIP10	Metastatic breast	Expression up-regulated	55-57
SLA39a11	ZIP11	Renal cell	ZIP11 variant as risk factor	58
		Bladder	ZIP11 variant as risk factor	58
		Pancreatic	Expression up-regulated	59
SLA39a13	ZIP13	Ovarian	Expression up-regulated	60
SLA39a14	ZIP14	Cachexia in metastatic cancer	Expression up-regulated in skeletal muscle	61

and of ZIP10 in breast cancer invasion and metastasis [55-57]. In particular, ZIP6 was identified in human breast cancer MCF-7 cells expressing substantial levels of ER [66], and the ZIP6-centered Zn network was found to have important implications for ER-positive breast cancer [8,11,37-42,67]. Decreased expression of ZIP6 in MCF-7 in response to stimuli in the environment surrounding cancer cells such as high glucose concentration and hypoxia induces epithelial-mesenchymal transition (EMT), promoting stemness and resistance to cell death [8,11,39]. In the clinical setting, patients with low ZIP6 expression in primary breast cancer sites have worse prognoses than those with high ZIP6 expression, suggesting that ZIP6 is negatively associated with prognosis [40]. Therefore, the cell culture model of ZIP6-knockdown MCF-7 mimics highly malignant breast cancer and is a potential tool for the investigation of breast cancer progression [8,11,39].

In this review, we summarize current progress in our understanding of the role of the main ZIP6 and ZIP6-related Zn transporters, focusing on breast cancer cell behaviors in hypoxia as a crucial factor in the tumor microenvironment, as well as on hormone therapy and breast cancer stem-like cells, which directly impact malignant progression and prognosis. We also discuss Zn transporters and Zn-targeted molecules as candidate markers for the malignant phenotype of breast cancer, which may represent a promising target for novel treatment strategies.

ZIP6 and hypoxic adaptive response of breast cancer cells

Hypoxia occurs in internal solid tumor structures, including breast cancer, as a result of rapid tumor cell growth [68]. This hypoxic region has been reported to contribute to tumor plasticity and heterogeneity, and to promote more aggressive phenotypes such as angiogenesis, invasion, EMT, stemness, and resistance to chemotherapy and radiotherapy [69-71]. To clarify the hypoxic profile in breast cancer cells, we cultured MCF-7 in three dimensions using a soft agar colony formation assay [8,11]. MCF-7 formed colonies, and colony interior was confirmed to be hypoxic according to strong red fluorescence of the hypoxia-sensing probe LOX-1. The specific membrane-permeable Zn chelator *N,N,N′,N′*-tetrakis (2-pyridylmethyl) ethylenediamine (TPEN)

significantly inhibited colony formation, and this inhibition was rescued by increasing the level of intracellular free Zn using zinc ionophore pyrithion. These findings suggest that intracellular Zn is required for survival under hypoxia and tumorigenic potential. Hypoxia-inducible factor 1α (HIF-1α) is a pivotal regulator in the process of hypoxic adaptive response [72,73]. MCF-7 cultured under hypoxic conditions showed higher viability than normal cells, depending on the activity of HIF-1α, and HIF-1α activity was positively correlated with intracellular Zn levels under hypoxic conditions. These data suggest that Zn-mediated HIF-1α activity promotes MCF-7 cell survival. Although the mechanisms underlying Zn-mediated HIF-1α activity in MCF-7 remains unknown, HIF-1α protein requires Zn to maintain its structure [74]. The knockdown of ZIP6, which plays an important role in maintaining intracellular Zn homeostasis in MCF-7, indicated that the disruption of intracellular Zn homeostasis, implying the presence of other zinc transporters, leads to increased intracellular free Zn concentration and higher survival rates under hypoxic conditions through apoptosis inhibition and EMT induction [39]. A zebrafish embryo study showed that a downstream factor of ZIP6 regulates signal transducer and activator of transcription 3 (STAT3) expression, which is linked to EMT [37]. ZIP6 expression levels were found to be decreased in high-grade primary tumor sites among patients with breast cancer [8,11,41], and low ZIP6 expression levels at primary breast cancer sites are correlated with shorter relapse-free survival periods [40]. Both experimental findings and clinical observations indicate that ZIP6 downregulation is deeply involved in the malignancy phenotype, suggesting that ZIP6 levels in primary breast tumors are potential biomarkers of cancer grade and poor prognosis in patients with breast cancer (**Figure 2**) [8,11,40,41]. Further analysis of the ZIP6 downregulation-switched zinc network, including the involvement of other Zn transporters and the behavior of intracellular and extracellular Zn in malignant progression under hypoxia, is expected to indicate future directions for the development of breast cancer diagnosis and treatment.

ZIP6 and pharmacotherapy in breast cancer

At least 70% of breast cancers are female hormone ER-positive and thus benefit from endocrine treatments including ER antagonist tamoxifen and aromatase inhibitors, which block estrogen production [75]. However, more than 25 % of all breast cancer patients show endocrine resistance, and even after 5 years of tamoxifen use, one in three patients with endocrine treatments still recur within 15 years; thus, the elucidation of endocrine-resistant mechanisms is an urgent clinical challenge [75,76]. High expression of Bcl-2, an anti-apoptotic molecule that regulates programmed cell death, has been reported to cause endocrine

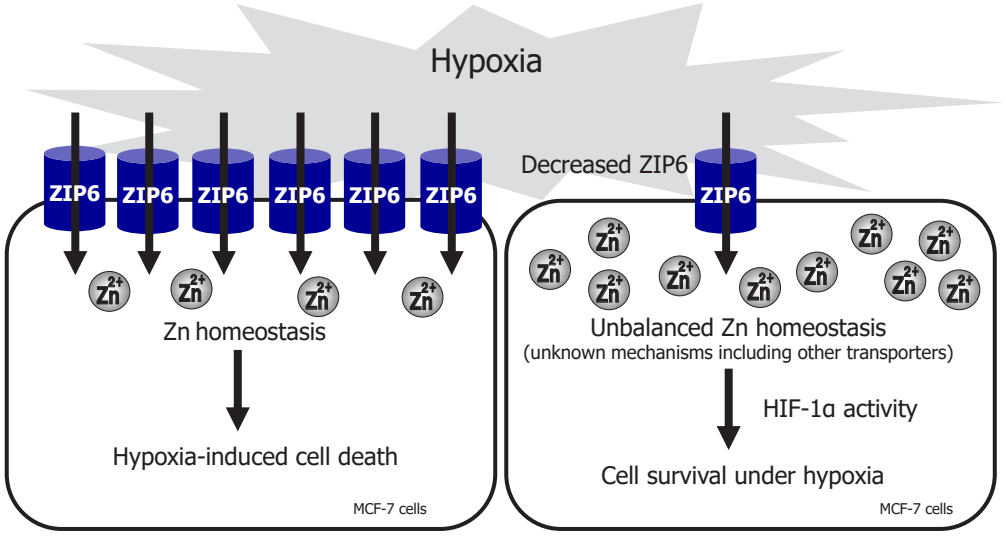

Figure 2. ZIP6 plays an important regulatory role under hypoxic stress.
ZIP6-downregulation disturbs intracellular Zn homeostasis, leading to increased cell survival against hypoxic stress in MCF-7 cells. ZIP6 is a key molecule for adaptation to hypoxic stress, which is implicated in malignant progression.

therapy resistance in breast cancer, and efficient inhibition of Bcl-2 function is expected to be a promising strategy to prevent endocrine resistance [76,77]. Great effort has been made to investigate the sensitivity of genetic or pharmacological inhibition of Bcl-2 in breast cancer [78]. YC137, a novel small molecule-specific inhibitor of Bcl-2, induces apoptosis in breast cancer cells that express high levels of Bcl-2, but does not attack normally functioning cells including hematopoietic progenitors, peripheral blood mononuclear cells, small intestine epithelial cells, and myoblasts [79]. Intriguingly, we found that the cytotoxicity of YC137 against estrogen-dependent human breast cancer cell, MCF-7, was markedly enhanced in combination with Zn chloride ($ZnCl_2$). Treatment with $ZnCl_2$ increased the concentration of labile Zn in MCF-7, and Zn supplementation triggered a switch from apoptotic cell death by YC137 (type I programmed cell death) to non-apoptotic cell death with autophagy (type II programmed cell death). Autophagy, in which autophagy-related protein-mediated autophagosomes form around misfolded proteins and damaged organelles to induce their degradation, is crucial for maintaining cell homeostasis and controlling cell death according to stress condition and breast cancer development stage [80,81]. Autophagy can be induced, and plays a cytoprotective or pro-survival role under most cancer therapies, whereas the collapse and excess of autophagy contributes to cytotoxicity in breast cancer cells [82]. During treatment with tamoxifen in MCF-7 cells, Zn accumulates in autophagosomes, resulting in autophagosome-mediated cell death [83]. Recent studies have demonstrated that Zn transporters ZIP4, ZIP8, ZIP14, ZnT2, ZnT4, and ZnT10, are located in endosomes, lysosomes, and autolysosomes, and have suggested that Zn contributes to autophagy [84,85]. The enhancement of YC137 cytotoxicity in combination with $ZnCl_2$ was abolished in ZIP6-knockdown MCF-7 cells, indicating that Zn supplied by ZIP6 is required for increased sensitivity of YC137. Studies on the roles of Zn in breast cancer therapy have recently begun, and will need to take into account the relationship between ZIP6 and autophagy. The combination of YC137 and $ZnCl_2$ does not induce damage to normal mammary gland cell model, human non-tumorigenic breast epithelial MCF-10A cells. As ZIP6 downregulation is involved in malignant progression in breast cancer [8,11,40,41], we propose that the combination of YC137 and $ZnCl_2$ may be an effective cancer-specific anticancer method for preventing the generation of therapeutic resistance, especially in early breast cancer, where ZIP6 expression is high. Future studies are required to elucidate the *in vivo* response to this treatment and to determine the appropriate dosing regimen with Zn supplement as adjuvant.

ZIP6/ZIP7 and breast cancer stem-like cells (BCSCs)

BCSCs are a distinct group of breast cancer-initiating cells with the capacity for self-renewal and differentiation; they hide within tumor tissue or throughout in the body [86,87]. BCSCs contribute to the cellular origin, tumor maintenance, and progression of breast cancer [88]. Clinically, BCSCs are considered to be responsible for the development of treatment resistance and cancer recurrence due to their relative resistance to radiation, cytotoxic chemotherapy, and molecular targeted therapy [86-88]. However, the molecular mechanisms that regulate BCSC maintenance remain poorly understood, and evaluation is required to improve the clinical outcomes of patients with breast cancer [86-88].

Among three-dimensional *in vitro* cell culture models, the spheroid culture method has been widely used as a powerful tool to maintain and grow cells selectively with cancer stem cell characteristics [88]. When MCF-7 cells were sphere-cultured in serum-free medium under non-adherent conditions, they formed spherical aggregates (spheres) and showed high expression of stem cell markers, self-renewal ability, and high tumorigenicity *in vivo*, all of which are characteristics of BCSCs [89]. In a spheroid culture assay using MCF-7 cells, treatment with TPEN revealed strong inhibition of sphere-forming capacity and nuclear expression of PR domain zinc finger protein 14 (PRDM14), a cancer stem cell transcription factor essential for the maintenance of BCSCs [90]. This inhibition was neutralized by the addition of Zn through zinc ionophores, suggesting that intracellular Zn-dependent PRDM14 expression in nuclear is essential for sphere-forming capacity. ZIP6 knockdown in MCF-7 cells resulted in significantly higher sphere formation efficiency compared to control cells. The high Zn-dependent PRDM14-mediated sphere-forming capacity of ZIP6-knockdown MCF-7 cells was significantly suppressed by functional inhibition of the zinc transporter ZIP7, which transports Zn from the endoplasmic reticulum to the cytoplasm. ZIP7, which directly drives pro-survival signaling pathways such as AKT, mTOR, and MAPK for tumorigenesis [91], is increased in endocrine-resistant breast cancer [50]. Phosphorylated ZIP7, which is the Zn-transporting form, may be a good candidate marker of aggressive cancer [92]. ZIP7 expression is also strongly associated with poor outcomes in clinical breast cancer samples [93]. BCSCs are increased in ZIP7 activity against ZIP6, suggesting that ZIP6 and ZIP7 cooperatively regulate BCSC maintenance via Zn-dependent regulation of PRDM14 expression (**Figure 3**). PRDM14 is not expressed in normal tissue stem cells, whereas PRDM14 is highly expressed in BCSCs

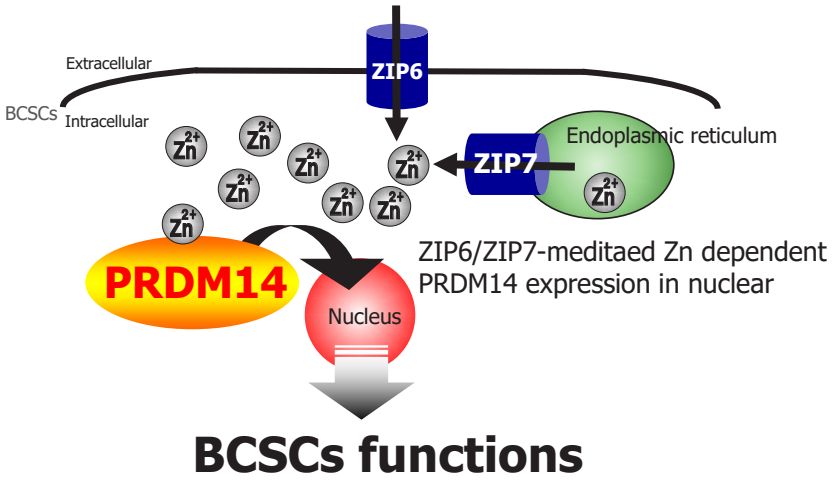

Figure 3. ZIP6/ZIP7 contribute to the maintenance of breast cancer stem-like cell (BCSC) functions.
ZIP6/ZIP7-mediated Zn is suggested to regulate BCSC maintenance through PRDM14 expression in nuclear. This is the first report of a biological role for Zn transporters in BCSCs.

as an essential transcription factor [90]. Survival analysis of breast cancer patients at stage II or III revealed that patients with high PRDM14 expression had worse prognoses than those with low or undetectable PRDM14 expression [90]. These findings suggest that PRDM14 is a promising target for the development of definitive therapeutic strategies. However, it is difficult to target the PRDM14 molecule using antibody and small-molecule therapeutics, because PRDM14 is expressed and activated in the nucleus [94]. The elucidation of Zn-mediated BCSCs through PRDM14 could dramatically expand the development of new molecularly targeted therapies for BCSCs.

Conclusion and perspective

ZIP6 is a key molecule determining the fate of ER-positive breast cancer cells, and its expression is controlled by the surrounding environment and malignant progression (**Figure 4**). A deeper understanding of the Zn regulatory network originating from ZIP6 will help to clarify the malignant mechanism of breast cancer and promote the development of novel strategies involving Zn-related molecules. The role of Zn biochemistry at the molecular level in therapeutic strategies, and the biology of the target molecules of Zn signaling and mechanisms regulating ZIP6 gene expression, require further study. Interestingly, the construction of ZIP6 includes a PrP-like amino acid sequence in the extracellular NH_2-terminal region, and two members of the LIV-1 subfamily (ZIP5 and 10) to which ZIP6 belongs have been reported to be involved in etiology of prion disease via processing [12,95-98]. The trafficking of ZIP6 to the plasma membrane is regulated by processing on the endoplasmic reticulum [12,37]; therefore, ZIP6 processing regulation may have important implications in breast cancer physiology, although the relationship between Zn status and processing must be considered [12]. The relationships between Zn transported via ZIP6 and Zn reservoirs (intracellular metallothionein or glutathione), the effects of other metals on Zn functions, and the roles of ZIPs other than ZIP6/ZIP7 and ZnTs in the cellular/extracellular Zn network of breast cancer also require further investigation. ZIP6 has been reported to function in conjunction with its close homolog ZIP10, which is located on the plasm membrane [55,56,99,100]. Zn transported via ZIP6 and ZIP10 was found to interact with NCAM1, which promotes cell detachment through the activation of glycogen synthase kinase 3 (GSK-3), which allows cells to migrate and become metastatic [100]. This finding is consistent with the high levels of ZIP6 found in patients with ER-positive breast cancer and lymph node metastasis [67]. A recent study also demonstrated that *ZIP10* mRNA expression was significantly higher in the breast cancer tissues of patients with lymph node metastasis than in

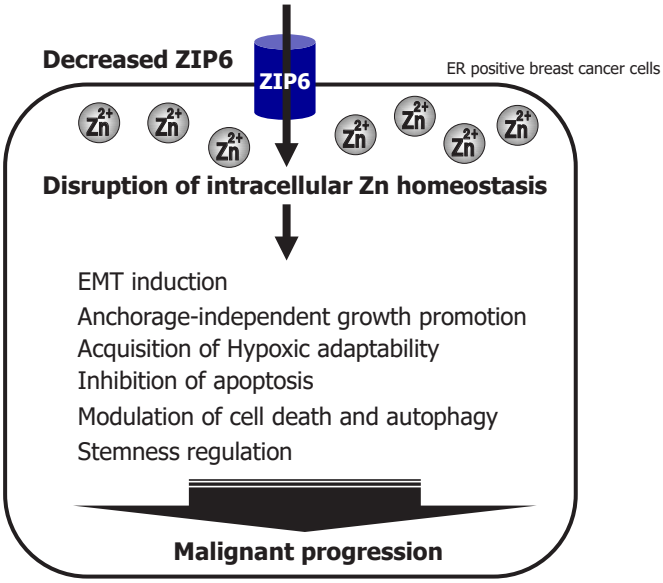

Figure 4. ZIP6 is a potent driving force of malignancy.
ZIP6 plays a key role in the fate of ER-positive breast cancer cells. An understanding of the Zn regulatory network originating from ZIP6 is anticipated to lead to promising therapeutic strategies, although the precise mechanisms remain unclear.

those without metastasis [57]. These data suggest that the role of ZIP6 differs between metastatic foci and primary tumors, and that ZIP6 and ZIP10 may cooperate with transporter functions during cell migration, although further studies are needed to clarify the involvement of a ZIP6 and ZIP10 heteromer [8,11,99,100]. For therapeutic applications, it is necessary to consider the regulation of ZIP6-mediated Zn signaling in a breast cancer phenotype-specific manner, in conjunction with drug delivery system research. The discovery and development of inhibitors and activators of ZIP6 and other Zn transporters may reveal promising anticancer therapies. A ZIP7 inhibitor (NVS-ZP7-4) was recently identified as the first reported ZIP-specific small molecule inhibitor using a phenotype-based high-throughput screening system that targeted the Notch pathway, although its function in breast cancer and *in vivo* remain poorly understood [101].

Finally, a further understanding of the role Zn in breast cancer is anticipated to reveal crucial molecular mechanisms that will facilitate the development of precise diagnostic and effective therapeutic strategies.

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