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Review

Zinc finger proteins and regulation of the hallmarks of cancer

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Summary. Zinc finger proteins (ZFPs) form one of the largest families of transcription factors in human genetics, via their conserved zinc finger motifs. ZFPs function in many biological processes including development, differentiation, metabolism and apoptosis. In addition, recent studies have demonstrated that ZFPs are closely associated with different stages of cancer development. One of the hallmarks of cancer is altered signal transduction cascades and an understanding of the changes in these pathways is essential for targeted cancer therapy. In this review, we discuss examples of ZFPs involved in development and progression of several types of cancer, which can provide new insights into cancer treatment

Key words: Zinc finger proteins, Transcription factors, Hallmarks of cancer, Cancer therapy

Introduction

DNA binding domains that can bind to specific DNA sequences have been found in many proteins, especially transcription factors. DNA binding domains contain amino acids that recognize certain DNA sequences through molecular interactions such as hydrogen bonding and charge coupling in the DNA major groove (Wolfe et al., 2000). A tri- or tetra-nucleotide sequence can be recognized by one zinc finger (Wolfe et al., 2000; Fedotova et al., 2017), and tandem zinc fingers can form very specific protein-DNA complexes (Ramirez et al., 2008; Lam et al., 2011). The most common DNA binding domain for ZFPs is the Cys2His2 (C2H2) type (Klug and Schwabe, 1995). The C2H2 zinc finger motif has two cysteine and two histidine residues with a zinc ion in a specific position to stabilize the structure (Razin et al., 2012), and it usually contains two or three β sheets and one α helix (Lupo et al., 2013). The C2H2 type ZFPs can be divided into distinct groups according to the number of zinc finger motifs (Razin et al., 2012). The groups may be composed of one cluster of three adjacent zinc fingers (Buck-Koehntop et al., 2012), one pair or more of zinc fingers (Nakamura et al., 1990), four or more zinc fingers (Filippova et al., 1996), or two paired zinc fingers and clusters of more than four zinc fingers (Lareu et al., 2005). Besides these zinc finger motifs, other domains mostly found at the NH2 terminus of ZFPs also play vital roles in functions of C2H2 ZFPs, including the BTB/POZ domain mediating a characterized protein-protein interaction (Albagli et al., 1995), the KRAB domain containing a highly homologous 42 amino-acid A element (Constantinou-Deltas et al., 1992) and the SCAN domain which is a conserved region regulating the interaction of proteins containing SCAN domains with noncovalent complexes (Stone et al., 2002; Sander et al., 2003; Razin et al., 2012; Lupo et al., 2013). A few ZFPs have a different

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zinc finger sequence from the classical C2H2-- Cys-X_2-Cys-X_{13}-Cys-X_2-Cys, called Cys2/Cys2 ZFPs (Culp et al., 1988).

ZFPs play key roles in several biological processes including development, differentiation, metabolism and apoptosis (Jen and Wang, 2016). Recent studies have also reported an intrinsic relationship between ZFPs and cancer progression.

The concept of cancer progression was postulated by Stephen Paget over a century ago, when he investigated the interaction of tumor cells with their microenvironment and showed that cancer progression involved a succession of cellular changes marked by increasing loss of normal controls (Paget, 1989). Components of the extracellular matrix, soluble factors, and infiltrating non-tumor cells, were all found to shape and regulate the malignant phenotype of tumor cells (Maman and Witz, 2018; Archetti and Pienta, 2019). The specific metabolic and genetic characteristics of cancer cells arise in part through their interaction with interstitial cells and parenchymal cells and involve the reprogramming of an elaborate integrated circuit within the cancer cells (Hanahan and Coussens, 2012).The hallmarks that distinguish cancer cells from healthy cells are legion, but current research focuses on nine major attributes: (1) sustained aberrant growth factor signaling (intrinsic or extrinsic), (2) evasion of growth suppressors and apoptotic signals leading to survival of cancer cells, (3) enabling of hyper-proliferation via replicative immortality, (4) induction of angiogenesis, (5) activation of invasiveness and metastatic potential (anoikis resistance), (6) genome instability through impaired DNA damage repair of mutations in cancer cell subclones, (7) reprogramming of energy production to promote neoplastic proliferation, (8) development of tumor-promoting inflammation involving specific cytokines and immune cells, and (9) reduced susceptibility to immune surveillance and destruction (Hanahan and Weinberg, 2000; Hornsveld and Dansen, 2016). In the present review, we intend to summarize the potential relevance between ZFPs and these common hallmarks of cancer, which may provide new clues for targeted cancer therapy.

ZFPs and sustained proliferative signaling in cancer

Normal tissues maintain a homeostatic state of cell numbers to ensure normal tissue architecture and function by carefully controlling the production and release of growth-promoting signals. However, cancer cells can produce signals through branched intracellular signaling pathways releasing the brakes on cell cycling and allowing unlimited cell growth (Hanahan and Weinberg, 2011).

Many studies have reported a relationship between ZFPs and cell proliferation. Jeon et al. (2012) showed that the Krüppel-like zinc finger transcription factor Kr-pok, which is encoded by the kidney cancer-related gene *KR-POK* (*ZBTB7C*), was overexpressed in more than 50% of the malignant human kidney cancer cases analyzed. The zinc finger domain of Kr-pok interacted directly with oligomerization domains of the growth suppressor, p53. The ZFP-p53 complex recognized and bound to the distal promoter region of the *CDKN1A* gene, an important p53 target encoding the cell cycle regulator, p21, thus repressing the expression of *CDKN1A* and promoting cell proliferation (Jeon et al., 2012). A recent study revealed that the ectopic expression of H-RAS, a member of the RAS superfamily, induced epithelial-to-mesenchymal transition (EMT) by activating a zinc finger E-box binding homeobox 1 (ZEB1), leading to increased sensitivity of tumor cells to the anti-proliferative activity of statins (Yu et al., 2018). Moreover, a conserved transcription factor ZNF521/ZFP521 has been reported to be enriched in hematopoietic stem cells (HSCs). Transcriptional analysis of human AML patient samples showed that ZNF521 was specifically and highly upregulated in acute myeloid leukemia (AML) with *MLL* translocations. ZNF521/ZFP521 was regarded as a critical regulator of HSC function to facilitate tumor cell proliferation (Garrison et al., 2017) and its knock-down could reduce the proliferation of AML cells with MLL translocations. A recent study performed by Ni et al. (2016) demonstrated that the zinc-finger transcription factor Snail1 could regulate the proliferation and activity of tumor-initiating cells in preneoplastic glands in breast tissue. It is thought that the mechanism behind Snail1's control of mammary tumor cell growth was that the transcription factor interacted with HDAC1 (histone deacetylase 1)/p53 to form a tri-molecular complex and the subsequent deacetylation led to the proteasomal degradation of p53. Thus, Snail1 was regarded as promoting the proliferation and anti-apoptotic effects of wild-type p53 in breast cancer (Ni et al., 2016). Costoya et al. (2008) showed that the promyelocytic leukemia ZFP, PLZF, which belongs to the family of transcriptional repressors of POK (POZ and Krüppel), induced cell cycle arrest at the G(1) to S transition and repressed the expression of key pro-proliferative genes such as *CCNA2* and *MYC*. However, the PEST domains of the hinge region of the cyclin-dependent kinase (CDK) recognized the two consensus sites of PLZF, allowing it to be phosphorylated, thereby triggering the ubiquitination and degradation of PLZF. This prevented PLZF from repressing transcription and inhibiting proliferation during the development and progression of human cancer (Costoya et al., 2008). Another zinc-finger transcription factor, Krüppel-like factor 4, (KLF4) was regarded as either a tumor suppressor or an oncogene in different types of cancers. KLF4, which is responsible for maintaining normal homeostasis in esophageal epithelia, was down-regulated in a number of human epithelial cancers, including esophageal, colorectal, gastric, and bladder carcinomas (Zhao et al., 2004; Tetreault et al., 2010). However, KLF4 was also markedly increased in some human osteosarcoma tissues and could increase the proliferation of osteosarcoma

cells by binding to the CRYAB promoter and upregulating its expression (Zhang et al., 2016b).

Taken together, the data on ZFPs demonstrate their close involvement in the regulation of cancer cell proliferation either by transactivation or suppression (Fig. 1).

The role of ZFPs in overcoming growth suppression and gaining replicative immortality

Telomere erosion and activation of p53 results in apoptosis and senescence in normal cells. However, in cancer cells, telomeres retain their normal length because of ectopic expression of telomerase, which can allow the cells to circumvent replicative senescence and acquire an immortal phenotype (Rufini et al., 2013).

Over the past decade, there have been a large number of reports linking ZFPs to both growth suppression and replicative immortality in cancer. For example, ZEB1 can decrease expression of the estrogen receptor α (ERα) and subsequently weaken cell growth inhibition in breast cancer cells. Mechanistically, ZEB1 suppresses ERα transcription via a ZEB1/DNMT3B/HDAC1 complex binding to the ERα promoter, and the subsequent DNA hypermethylation leads to the silencing of ERα (Zhang et al., 2017). Another factor, Yin Yang-1 (YY1), is a member of the GLI-Krüppel family and can act as either a tumor growth accelerator or a tumor suppressor depending on additional interacting proteins, the context of the promoter and the chromatin structure in various cancer types (Khachigian, 2018). For example, YY1 can act as a tumor promoter by downregulating p53 and activating epidermal growth factor receptor (EGFR), but may also suppress tumorigenesis by inhibiting Rb phosphorylation, increasing *Bax* transcription, and activating the tumor suppressor BRCA1 (breast cancer type 1 susceptibility protein) (Zhang et al., 2016a; Tseng et al., 2017). The *E1A* gene of adenovirus type 5 encodes a protein of 289 amino acid residues that contains a consensus zinc finger motif (Cys-X_2-Cys-X_{13}-Cys-X_2-Cys) which accounts for the ability of the E1A protein to stimulate transcription of E1A-inducible promoters (Culp et al., 1988). It has been shown that E1A acts as an anti-tumor protein by suppressing AXL, a member of the TAM (Tyro-3, Axl, Mer) receptor tyrosine kinase (RTK) subfamily (Feneyrolles et al., 2014). A combination cancer therapy employing *E1A* gene upregulation or AXL inhibitors with EGFR- tyrosine kinase inhibitors (TKI) was able to reverse EGFR-TKI resistance, resulting in significant suppression of tumor growth in certain breast cancer cells (Su et al., 2016).

In summary, ZFPs may play different roles in response to growth suppression of tumors (Fig. 2).

ZFPs and resistance to apoptosis in cancer cells

Programmed apoptotic cell death can be triggered through intrinsic (mitochondrial) pathways and/or extrinsic (death receptor-mediated) pathways that converge on caspases (cysteine-dependent, aspartate-targeted proteases). The survival of multicellular

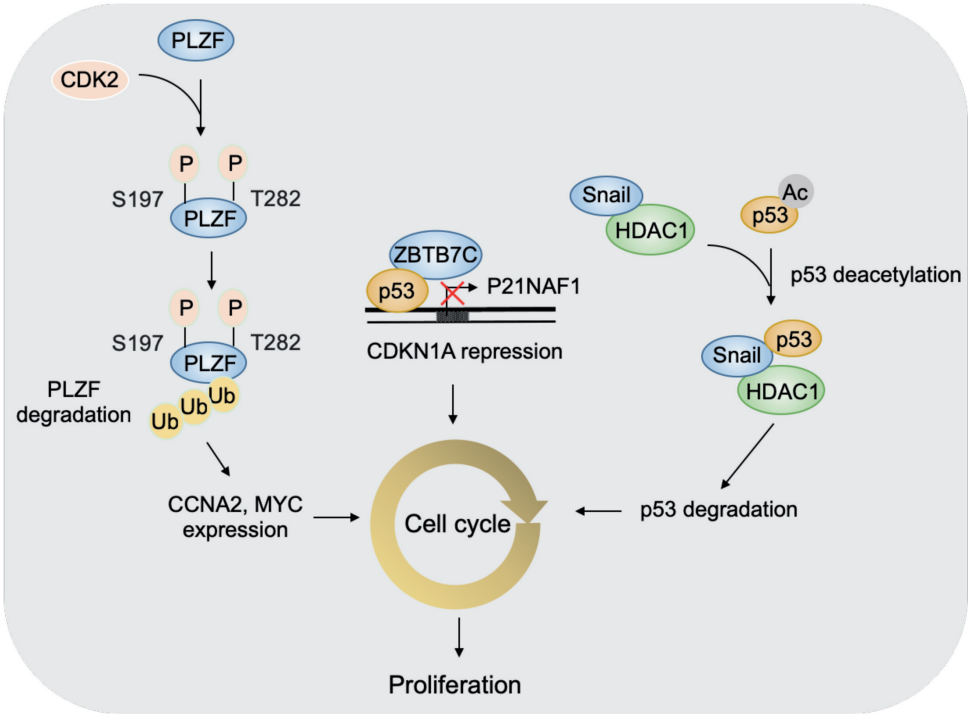

Fig. 1. ZFPs and sustained proliferative signaling in cancer. (left) PLZF induces cell cycle arrest at the G(1) to S transition and represses the expression of CCNA2 and MYC; however, the PEST domains of the hinge region of the cyclin-dependent kinase recognize the two consensus sites of PLZF and phosphorylate it, thereby triggering the ubiquitination and degradation of PLZF. (middle) The zinc finger domain of ZBTB7C interacts directly with the oligomerization domains of p53, and this binding complex recognizes and binds to the distal promoter region of the CDKN1A gene, an important p53 target gene encoding the cell cycle regulator p21, thus repressing the expression of CDKN1A gene and promoting cell proliferation. (right) Zinc-finger transcription factor Snail1 binds HDAC1/p53 to form a tri-molecular complex and the subsequent deacetylation of active p53 leads to proteasomal degradation of p53, thereby promoting proliferation and suppressing apoptosis in breast cancer. PLZF: promyelocytic leukemia zinc-finger; HDAC1: histone deacetylase 1; CDK2: cyclin-dependent kinase 2.

organisms depends on the proper regulation of apoptosis. Diminished apoptosis can contribute to autoimmune diseases and tumorigenesis (Vucic et al., 2011; Ouyang et al., 2012).

The Zfra (zinc finger-like protein that regulates apoptosis), a naturally occurring, 31 amino-acid protein, regulated cell death and inhibited the growth of many types of cancer cells by interacting with the receptor-adaptor protein TRADD (tumor necrosis factor receptor-associated death domain protein) and downstream JNK (c-Jun N-terminal kinase), NF-ϰB (nuclear factor kappa B) and WWOX/WOX1 (WW domain-containing oxidoreductase) which were regulated by tumor necrosis factor (TNF) (Dudekula et al., 2010; Lee et al., 2017). A recent study has revealed that the nuclear ZFP, LYAR, promotes the survival of neuroblastoma cells by downregulating the expression of *CHAC1* or some other oxidative stress genes, thereby increasing oxidative stress tolerance. However, knocking down LYAR expression can inhibit neuroblastoma cell growth via apoptosis induction (Sun et al., 2017). Another study has shown that the ZFP, TSHZ3, inhibits p53 activity; therefore, silencing TSHZ3 would stimulate p53 thereby inducing cell cycle arrest and cell death in non-small cell lung cancer (Siebring-van Olst et al., 2017). KLF4 is a ZFP transcription factor with several different biological functions and can act as either an oncogene or a tumor suppressor, in the case of embryonic development, development of stemness and carcinogenesis. Riverso et al. (2017) have shown that KLF4 promotes melanoma cell growth by reducing apoptosis. Deletion of KLF4 decreases melanoma cell proliferation and promotes cell death (Riverso et al., 2017). However, another study showed that exogenous expression of KLF4 significantly inhibited cell proliferation, decreased stemness, and suppressed migration and invasion of nasopharyngeal carcinoma (NPC) cells, suggesting that KLF4 can function as a tumor suppressor in NPC to prevent tumor progression (Li et al., 2017). The A20 protein is a Cys2/Cys2 ZFP (De Valck et al., 1999) that when overexpressed can induce the HSP70-mediated anti-apoptotic pathway in luminal breast cancer cell lines, thus protecting tumor cells from TNFα-induced cell death (Lee et al., 2019).

To sum up, ZFPs are able to mediate tumor cell death either by the apoptosis-induced stress response machinery or by cell-cycle arrest (Fig.3).

ZFPs and angiogenesis in cancer

Proliferating tumor cells need a constant supply of nutrients and oxygen to support growth as well as to remove metabolic wastes and carbon dioxide and thus exploit mutations that promote the process of angiogenesis (Hanahan and Weinberg, 2011). Vascular endothelial growth factors (VEGFs) are involved in the maintenance and development of the lymphatic vascular system and blood stream (Karaman et al., 2018). It has been reported that the ZFP, WT1, is a critical factor in angiogenesis that modifies the splicing of VEGF, thereby repressing the SRPK1 (serine/threonine-protein kinase) which contributes to angiogenesis in AML (Mohamed et al., 2014). A recent study showed that ZEB1 could promote angiogenesis in breast cancer cells (Langer et al., 2018). The secreted proteins, fibronectin 1 and SERPIN-E2 (serine protease inhibitor family E member 2), which are targets of ZEB1-repressed microRNAs, are essential for ZEB1-mediated angiogenesis (Langer et al., 2018). Additionally, overexpression of ZEB1 promoted *VEGFA* transcription and increased capillary formation in breast cancer tissues by increasing SP1 recruitment to its promoter, which was mediated by the activation of PI3K and p38 pathways (Liu et al., 2016a). The ZFP, BLU, also called

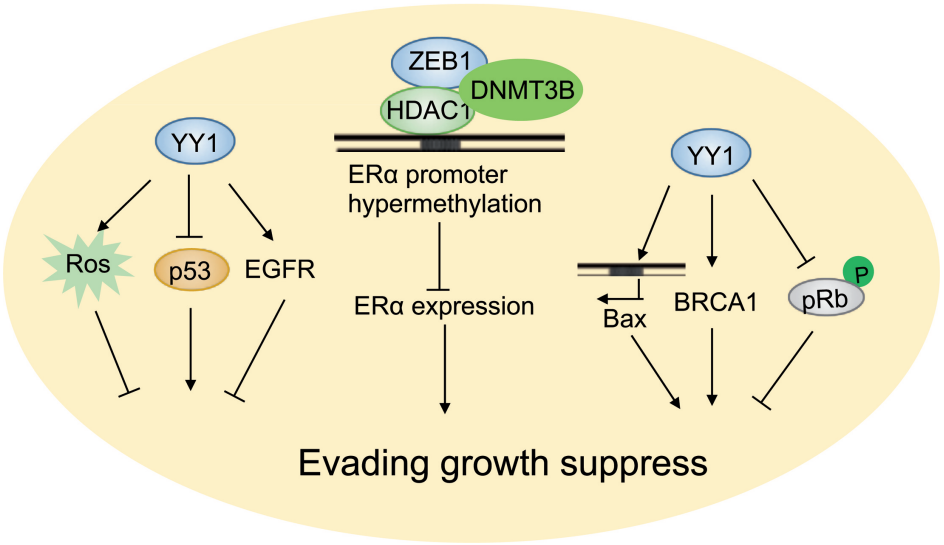

Fig. 2. Role of ZFPs in evading growth suppression and gaining replicative immortality. YY1 not only plays a tumor-promoting role by p53 inhibition and EGFR activation, but also functions as a tumor suppressor by inhibiting Rb phosphorylation, increasing Bax transcription, and stimulating the tumor suppressor BRCA1. ZEB1 can decrease the expression of ERα and subsequently weaken cell growth inhibition via a ZEB1/DNMT3B/HDAC1 complex binding to the ERα promoter, and subsequent DNA hypermethylation silences ERα. ZEB1: Zinc-finger E-box binding homeobox 1; DNMT: DNA methyltransferase; HDAC1: histone deacetylase 1; YY1: Yin Yang-1; BRCA1: breast cancer susceptibility gene.

MYND-type containing 10 (ZMYND10), was found to be downregulated in NPC. Overexpression of the *BLU* gene inhibited the VEGF expression that supports the angiogenesis network and is important for the development of NPC (Cheng et al., 2015). Another study has shown that the ZFP, KLF4, acts as a transcriptional repressor of *VEGF* and inhibits angiogenesis in breast cancer cells. The authors demonstrated that KLF4 suppressed *VEGF* expression via the occupancy by KLF4, HDAC2, and HDAC3 of the *VEGF* promoter (Ray et al., 2013). ZNF24, a C2H2-containing SCAN domain ZFP, acted as a negative regulator of *VEGF* in malignant breast cancer tissues. ZNF24 repressed *VEGF* transcription through directly occupying an 11-bp fragment of the *VEGF* proximal promoter (Jia et al., 2013).

Collectively, ZFPs are closely involved in the control of angiogenesis mainly by transcriptional regulation of expression of proteins of the VEGF family (Fig. 4).

ZFPs in cancer invasiveness and metastasis

Cancers develop in complex tissue environments that support sustained proliferation, and eventually can lead to metastasis (Quail and Joyce, 2013). EMT process switches static epithelial cells into motile mesenchymal cells that can contribute to the metastasis and invasiveness of tumor cells. This transition is induced by critical transcription factors, including Twist1, Snail, and ZEB (Lamouille et al., 2014; Wei et al., 2015).

Zhao et al. (2014) found that transcriptional upregulation of *ZEB2* by the transcription factor AP-1 in triple-negative breast cancer (TNBC) could repress the expression of E-cadherin and stimulate cell invasion (Zhao et al., 2014), Geng et al. (2014) revealed that *ZEB2* was downregulated by microRNA-192 which led to the increased expression of E-cadherin (Geng et al., 2014). Kaiso, a member of the BTB/POZ ZFP family, has been found overexpressed in breast, prostate, and colon cancers other than pancreatic ductal adenocarcinoma (PDCA) (Prokhortchouk et al., 2006; Jones et al., 2016; Wang et al., 2016; Bassey-Archibong et al., 2017). A recent study showed that this bi-modal transcription factor could increase the expression of ZEB1, leading to downregulation of E-cadherin and the subsequent progression of PDCAs (Jones et al., 2016). ZEB1 is regarded as an activator of the EMT in several cancer types, including breast, lung, pancreatic, prostate and bladder (Krebs et al., 2017; Peng et al., 2017; Zhang et al., 2018). ZEB1 has been reported to be regulated by hypoxia-inducible factor (HIF)-1α, and to induce EMT and subsequent metastasis in bladder cancer cells (Zhu et al., 2018). Moreover, a recent study revealed that MCRIP1 (an extracellular-regulated protein kinase, ERK, substrate) could bind to the transcriptional co-repressor, CtBP, and competitively inhibit the interaction between CtBP and ZEB1. However, the binding between MCRIP1 and CtBP could be reversed by MCRIP1 phosphorylation by ERK, thus demonstrating a molecular mechanism underlying ERK-mediated CtBP and ZEB1 interaction for the repression of E-cadherin during EMT (Ichikawa et al., 2015). Also, some authors reported that the expression of PLZF was decreased in

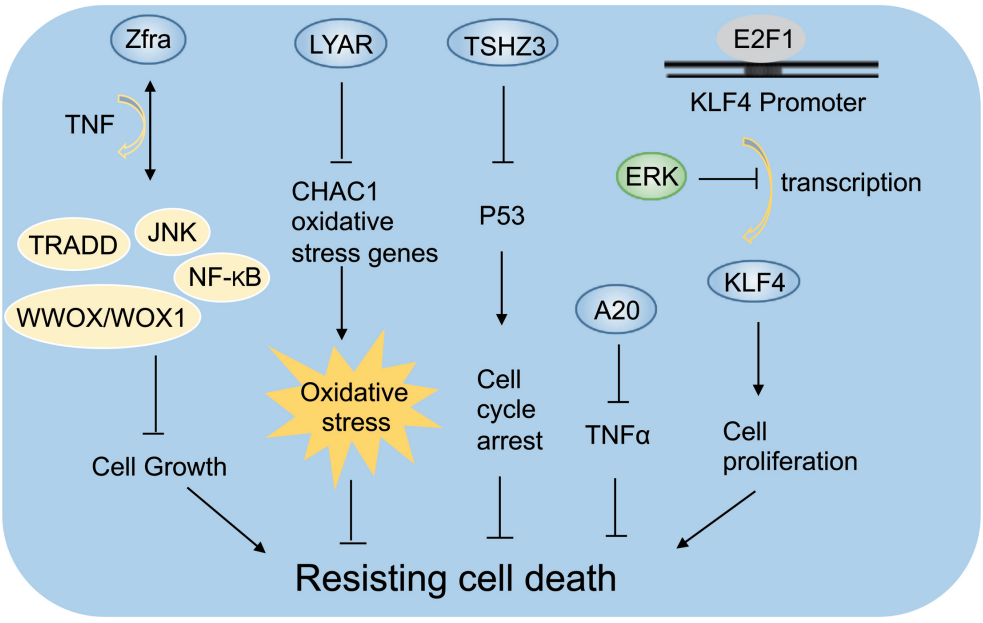

Fig. 3. ZFPs and cell death resistance in cancer. Zfra inhibits the growth of cancer cells via interacting with receptor adaptor protein TRADD and downstream JNK, NF-κB and WWOX/WOX1, which are regulated by TNF. LYAR promotes the survival of neuroblastoma cells by downregulating the expression of CHAC1 or other oxidative stress genes, thereby increasing oxidative stress tolerance. ZFP TSHZ3 acts as an inhibitor of p53 activity and silencing its gene would increase p53 levels, thereby inducing cell cycle arrest and cell death in non-small cell lung cancer. Overexpression of A20 (a Cys2/Cys2 ZFP) can induce the anti-apoptotic pathway in luminal breast cancer cell lines, thus protecting tumor cells from TNFα-induced cell death. The KLF4 promoter directly interacts with transcription factor E2F1 to regulate the expression of KLF4 which promotes cell proliferation and inhibits cell death. TRADD: TNF receptor associated death domain protein; JNK: c-Jun N-terminal kinase; NF-κB: nuclear factor kappa B; WWOX/WOX1: WW domain-containing oxidoreductase; TNF: tumor necrosis factor; CHAC1: the gene of glutathione-specific gamma-glutamylcyclotransferase 1.

many cancers including gallbladder cancer (GBC). Both *in vitro* and *in vivo* studies proved the decreased expression of PLZF in GBC cells, whose overexpression obviously reduced migration and invasion by regulating the expression of E-cadherin and N-cadherin. The transcription of interferon-induced protein with tetratricopeptide repeat 2 (IFIT2) is essential to maintain the tumor-suppressive function of PLZF (Shen et al., 2018). The A20 protein, which belongs to a class of Cys2/Cys2 ZFPs, has initially been identified as an inhibitor of both necrotic cell death and apoptosis (De Valck et al., 1996). A recent study revealed that A20 monoubiquitinates Snail1 at three lysine residues, thus decreasing Snail1 phosphorylation. Monoubiquitinated Snail1 could thus be stabilized in the nucleus and facilitate transforming growth factor-β (TGF-β1)-induced EMT and metastasis of basal-like breast cancers (Lee et al., 2017a). ERβ1 is a Cys2/Cys2 type ZFP that can downregulate ZEB1 and suppress the migration and tissue invasion of androgen receptor-positive, triple-negative breast cancer cells (TNBC) cells (Song et al., 2017).

Taken together, the data on regulation of EMT by ZFPs shows that these proteins are closely associated with tumor cell metastasis and tissue invasion (Fig. 5).

ZFPs, genome instability and DNA mutations

Cancer is a complex genetic disease involving the mutation of oncogenes or tumor suppressor genes (Ouyang et al., 2012). Accumulation of genetic alterations is one of the reiterative process by which cancer cells evolve, and sequential mutations in somatic cells with subclonal selection drives cancer progression (Greaves and Maley, 2012).

Interestingly, Nandan et al. (2008) have discovered a correlation between the regulation of cell proliferation by the zinc finger transcription factor, KLF5, and colorectal tumorigenesis. The study showed that KLF5 was an important mediator during colorectal tumorigenesis involving the mutated oncogene *KRAS* (Nandan et al., 2008). The ZFP, ZDHHC5, was closely associated with *p53* mutations which may result in the development of self-renewal and tumorigenicity of stem-like glioma cells. Mutations in *p53* changed the palmitoylation and phosphorylation status of the tumor suppressor EZH2, thereby upregulating the transcription of *ZDHHC5* and promoting the development of glioma (Chen et al., 2017). ZFP36 has two tandem zinc finger (TZF) regions belonging to CCCH-type ZFPs. The function of the ZFP is reversed as long as TZF is mutated, thereby promoting the ability of proliferation in tumor cells (Suk et al., 2018). U2AF35 is a ZFP that has two TZF regions and missense mutations in the two zinc-finger domains and the c.470A>G mutation within the second zinc-finger domain could lead to the Q157R substitution which is correlated with cancer progression (Herdt et al., 2017). The glucocorticoid receptor (GR) has two Cys2/Cys2 zinc finger domains. The substitution of arginine 493 by cysteine (R493C) in the second zinc finger of the DNA-binding domain could weaken the transcriptional activity of the GR, thus resulting in

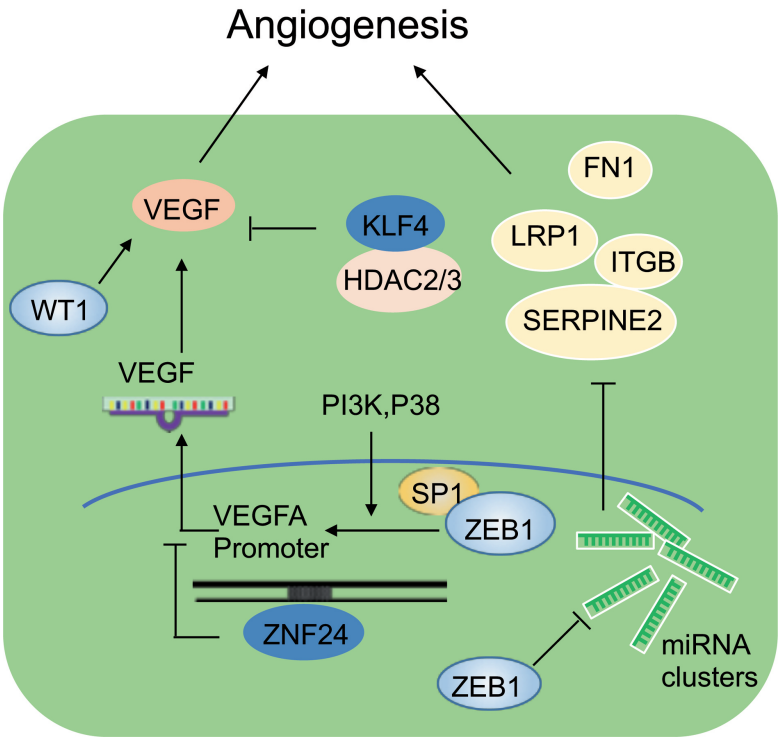

Fig. 4. ZFPs and angiogenesis in cancer. WT1 mediates angiogenesis by modifying the splicing of VEGF, thereby repressing the SRPK1 kinase which contributes to angiogenesis in acute myelogenous leukemia. The secreted proteins fibronectin 1 (FN1) and serine protease inhibitor (serpin) family E member 2 (SERPIN-E2), which are targets of ZEB1-repressed microRNAs, are essential for ZEB1-mediated angiogenesis. Overexpression of ZEB1 can also promote VEGFA transcription and increase capillary formation in breast cancer tissues by increasing SP1 recruitment to its promoter, which is mediated by the activation of PI3K and p38 pathways. KLF4 suppresses VEGF expression via the occupancy of KLF4, histone deacetylase 2 (HDAC2), and histone deacetylase3 (HDAC3) at the site of VEGF promoter. ZEB1: Zinc finger E-box binding homeobox 1; FN1: fibronectin 1; SERPINE2: serine protease inhibitor family E member 2; HDAC: histone deacetylase; VEGF: vascular endothelial growth factor.

glucocorticoid resistance in certain types of cancers (Banuelos et al., 2015).

ZFPs can promote tumorigenesis either by self-mutation or acting as a mediator of somatic genome instability and mutation.

ZFPs and metabolic reprogramming in cancer

Cancer cells commonly have high rates of proliferation and, in a process termed metabolic reprogramming, they change the metabolic pattern from oxidative phosphorylation to aerobic glycolysis in order to meet the challenges of macromolecular synthesis (Ward and Thompson, 2012).

In addition to the above-mentioned roles of ZEB1 in carcinogenesis, it also plays a key role in tumor energy metabolism. For example, the expression of phospholipid glutathione peroxidase (GPX4) was increased by high expression of ZEB1 in several cancer types. Increased levels of GPX4 prevented the iron-

Table 1. Summary of differential roles of ZFPs in cancer progression.

ZFPs	Gene name	Role	Cancer type	Roles in cancer progression	Reference
Kr-pok	*KR-POK (ZBTB7C)*	Oncogene	Kidney cancer	Promoting cancer cell proliferation	Jeon et al., 2012
ZEB1	*ZEB1*	Oncogene	Breast cancer	Evading growth suppression	Zhang et al., 2017
				Promoting angiogenesis	Liu et al., 2016a; Krebs et al., 2017; Langer et al., 2018
				Contributing to metastasis	
			Bladder cancer	Contributing to metastasis	Krebs et al., 2017; Peng et al., 2017; Zhang et al., 2018; Zhu et al., 2018
			Lung cancer		
			Pancreatic cancer		
			Prostate cancer		
			Ovarian cancer	Eliciting chronic glucose metabolism	Kanska et al., 2017
KLF4	*KLF4*	Oncogene	Osteosarcoma	Increasing cell proliferation	Zhang et al., 2016b
			Melanoma	Reducing apoptosis and promoting growth	Riverso et al., 2017
		TSG	Colorectal	Promoting the proliferation of alimentary tract epithelium	Zhao et al., 2004; Tetreault et al., 2010
			Gastric		
			Esophageal		
			Bladder carcinoma		
			Nasopharyngeal carcinoma	Cell death resistance	Li et al., 2017
			Breast cancer	Inhibiting angiogenesis	Ray et al., 2013
LYAR	*LYAR*	Oncogene	Neuroblastoma	Cell death resistance	Sun et al., 2017
TSHZ3	*TSHZ3*	TSG	Non-small cell lung cancer	Promoting cell cycle arrest and cell death	Siebring-van Olst et al., 2017
WT1	*WT1*	Oncogene	Acute myelogenous leukemia	Contributing to angiogenesis	Mohamed et al., 2014
E1A	*N/A*	TSG	Breast cancer	Suppression of tumor growth	Su et al., 2016
BLU/ZMYND10	*ZMYND10*	TSG	Nasopharyngeal carcinoma	Inhibiting angiogenesis	Cheng et al., 2015
ZNF24	*ZNF24*	TSG	Breast cancer	Inhibiting angiogenesis	Jia et al., 2013
ZEB2	*ZEB2*	Oncogene	Triple-negative breast cancer	Stimulating cell invasion	Zhao et al., 2014
Kaiso	*ZBTB33*	Oncogene	Pancreatic ductal adenocarcinoma	Promoting invasion and metastasis	Jones et al., 2016
A20	*TNFAIP3*	Oncogene	Basal-like breast cancer	Facilitating metastasis	Lee et al., 2017a
			Luminal breast cancer	Cell death resistance	Lee et al., 2019
ZFAND5/ZNF216	*ZFAND5*	Oncogene	Medulloblastomas	Facilitating metastasis	Mincione et al., 2016
			Nasopharyngeal carcinomas		
PLZF	*PLZF/ZBTB16*	TSG	Gallbladder cancer	Reducing migration and invasion	Shen et al., 2018
KLF5	*KLF5*	Oncogene	Colorectal tumor containing mutant KRAS	Promoting cell proliferation	Nandan et al., 2008
ZDHHC5	*ZDHHC5*	Oncogene	Glioma containing mutant p53	Driving cancer cell survival and malignant growth	Chen et al., 2017
Snail1	*SNAI1*	Oncogene	Breast cancer	Promoting cell proliferation	Ni et al., 2016
ZNF521	*ZNF521*	Oncogene	Acute myeloid leukemia	Facilitating tumor cell proliferation	Garrison et al., 2017
MZF-1	*MZF1*	TSG	Prostate cancer	Inhibiting DNA replication and iron-related energy metabolism	Chen et al., 2015
ZNF750	*ZNF750*	TSG	Oral squamous cell carcinoma	Inhibiting expression of inflammation gene	Pan et al., 2018
ERβ1	*erbeta1*	TSG	AR positive triple-negative breast cancer	Suppressing invasion and migration	Song et al., 2017

Tumor suppressor gene: TSG

mediated reactions of peroxides that induce ferroptotic cell death, leading to a therapy-resistant state of cancer cells (Viswanathan et al., 2017). Moreover, ZEB1 has a different role to play in glucose metabolism. ZEB1 elicits the plasticity of chronic glucose metabolism in ovarian cancer cells upon cell starvation by inducing the expression of NNMT (nicotinamide N-methyl-transferase) (Kanska et al., 2017). However, overexpressed ZEB1 or knocked down E-cadherin reduced glycolysis in SUM149 and 4T1 cells, the major mechanism of which was the lack of hypoxia-response genes (Chu et al., 2013). The ZFP, ZBTB7A, repressed glycolysis in cancer cells by inhibiting the transcription of key glycolytic genes such as *PKM* and *GLUT3* which were significantly upregulated in cancer cells when ZBTB7A was mutated, thus contributing to increased glycolysis and proliferation (Liu et al., 2016b). Myeloid zinc-finger 1 (MZF-1), a multifaceted transcription factor, was recently identified as regulating ferroportin expression. In prostate cancer, decreased expression of MZF-1 led to reduced ferroportin concentration, coupled with increased iron-related cellular activities and finally enhanced tumor cell growth via increased DNA replication and energy metabolism (Chen et al., 2015).

In summary, ZFPs function as key transcription factors in the regulation of metabolic reprogramming in cancer (Fig. 6).

ZFPs and immune surveillance for destruction of cancer cells

Tumors grow in a microenvironment containing epithelial cells, vascular and lymphatic vessels, cytokines and chemokines, and infiltrating immune cells. The progression of various types of tumors depends on the presence and activity of different types of immune cells (Fridman et al., 2012).

It has been reported that ZFPs are also involved in the regulation of inflammation and immune destruction in cancer. The ZFP, 750 (ZNF750), has been reported to act as a potential tumor suppressor in oral squamous cell carcinoma by regulating a number of the 39 genes associated with inflammation-related signaling pathways, including *TNF-alpha, TNF-SF10, CEBPD, CSF1*, and *ICAM1* (Pan et al., 2018). In addition, the PLZF transcription factor not only regulated the production of iNKT thereby modulating tumor surveillance and tumor metastasis (Wang et al., 2018), but also participated in the production of congenital $CD8^+$ T cells thus potentially controlling tumor progression (Barbarin et al., 2017). It has also been reported that in patients with cutaneous T-cell lymphoma, IL15 was tightly regulated by ZEB1. The authors found that hypermethylation of the ZEB1 binding region within the *IL15* promoter prevented ZEB1 binding and subsequently repressed transcription

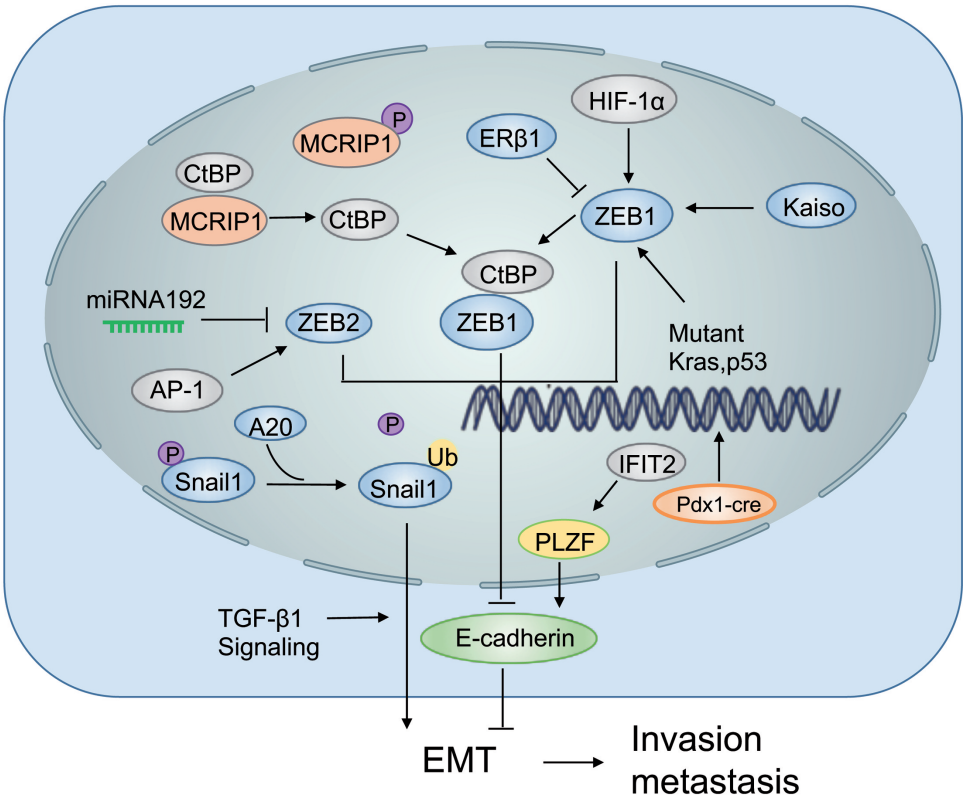

Fig. 5. ZFPs in cancer invasion and metastasis. ZEB2 participates in regulation of cancer invasiveness and metastasis either by transcriptional upregulation via transcription factor AP-1 or downregulation via microRNA-192 which leads to the abnormal expression of E-cadherin. Both Kaiso and HIF-1α are able to regulate ZEB1 to induce EMT and metastasis. MCRIP1 binds to the CtBP transcriptional co-repressor, and thereby competitively inhibits the interaction between CtBP and ZEB1. A20 monoubiquitinates Snail1 at three lysine residues, thus decreasing the phosphorylation of Snail1. Monoubiquitinated Snail1 could thus be stabilized in the nucleus and facilitate TGF-β1-induced EMT and metastasis of basal-like breast cancers. ZEB: Zinc finger E-box-binding homeobox; HIF: hypoxia-inducible factor.

(Mishra et al., 2016).

The above data collectively demonstrate that ZFPs are closely associated with the regulation of inflammation in cancer.

Conclusions

ZFPs including C2H2 and Cys2/Cys2 types belong to one of the largest families of pleiotropic transcription factors. The NH2-terminal domains of the ZFPs, including the BTB/POZ domain, the KRAB domain, and the SCAN domain also play vital roles in mediating the proper functioning of ZFPs. The transcriptional regulation of ZFPs depends on the successful recognition and binding between domains of ZFPs and DNA, RNA sequences or motifs of other proteins. ZFPs participate in the regulation of carcinogenesis, tumor progression, angiogenesis, metabolic reprogramming and metastasis. Different aspects of tumorigenesis can be regulated by different ZFPs. For example, ZEB1, ZEB2, Snail1, KLF4, and ZNF24 all participate in the regulation of the hallmarks of breast cancer, including the effects of proliferation, anti-proliferation, angiogenesis, anti-angiogenesis, growth suppression and energy metabolism. ZEB2, PLZF, and ZFP36 have close relationships with colorectal cancer in terms of tissue invasion and metastasis, genome instability and mutation, and inflammation/immune destruction. The same pathological characteristics may be regulated by different ZFPs in different types of cancer. For example, ZNF24, BLU, WT1, ZEB1, and KLF4 can all regulate angiogenesis in different cancer types, including AML, breast cancer, and nasopharyngeal carcinoma. A single ZFP can regulate two different hallmarks of cancer in a single tumor type, an example of which is ZEB1, a well-known transcriptional regulator of tumor invasion and metastasis, which can also function as a promoter of angiogenesis in breast cancer.

In summary, we have shown that ZFPs are intimately connected with cancer progression. As cancer is considered a major public health problem worldwide, a large amount of effort and money has been spent on tumor studies over the past several decades, but complete eradication and control of cancer remains elusive (Greaves and Maley, 2012). The rapid development and testing of targeted therapeutics will result in more effective and robust therapies for human cancer (Hanahan and Weinberg, 2011). A recent study discovered a chemical inhibitor of HDAC6 acting through its ZnF-UBD (zinc-finger ubiquitin binding domain), which will enable further optimization of chemical probes for combination therapy with proteasome inhibitors in multiple myeloma (Ferreira de Freitas et al., 2018). This review aimed to provide insight into the role of ZFPs in cancer progression from the perspective of the hallmarks of cancer, hopefully providing us with potential therapeutic targets, advancing the development of preclinical drugs and

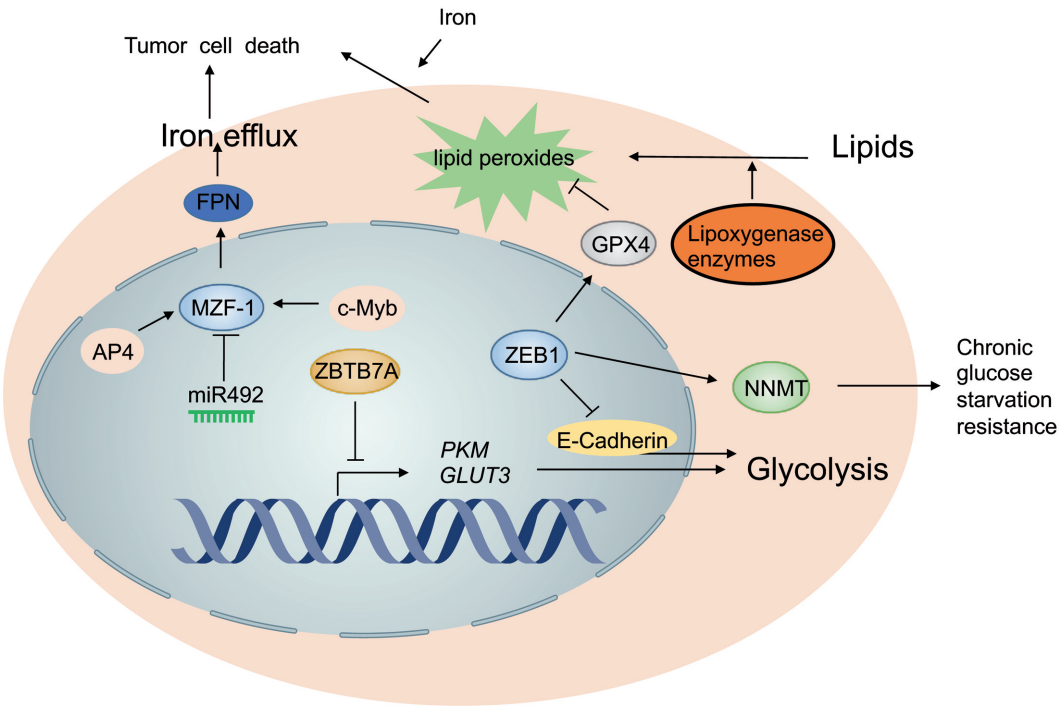

Fig. 6. ZFPs and metabolic reprogramming in cancer. MZF-1 is a multifaceted transcription factor that regulates FPN expression, and decreased expression of MZF-1 leads to reduced FPN concentration, coupled with increased iron-related cellular activities and finally enhances tumor cell growth via enhancing DNA replication and energy metabolism. ZFP ZBTB7A represses glycolysis in cancer cells by inhibiting transcription of the key glycolytic genes PKM and GLUT3 which are significantly upregulated in cancer cells when ZBTB7A is mutated, thus contributing to increased glycolysis and proliferation. The expression of GPX4 is upregulated by high expression of ZEB1, which prevents the iron-mediated reactions of peroxides that induce ferroptotic cell death, leading to a therapy-resistant state of cancer cells. ZEB1 elicits the plasticity of chronic glucose metabolism in ovarian cancer cells upon cell starvation by inducing the expression of NNMT. GPX4: phospholipid glutathione peroxidase; NNMT: nicotinamide N-methyltransferase; MZF-1: myeloid zinc-finger 1; FPN: ferroportin.

improving patient prognosis and overall survival.

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