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*Review Article*

# ZNF217: the cerberus who fails to guard the gateway to lethal malignancy

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**Abstract:** The aberrant expression of the zinc finger protein 217 (ZNF217) promotes multiple malignant phenotypes, such as replicative immortality, maintenance of proliferation, malignant heterogeneity, metastasis, and cell death resistance, via diverse mechanisms, including transcriptional activation, mRNA $N^6$-methyladenosine ($m^6A$) regulation, and protein interactions. The induction of these cellular processes by ZNF217 leads to therapeutic resistance and patients' poor outcomes. However, few ZNF217 related clinical applications or trials, have been reported. Moreover, looming observations about ZNF217 roles in $m^6A$ regulation and cancer immune response triggered significant attention while lacking critical evidence. Thus, in this review, we revisit the literature about ZNF217 and emphasize its importance as a prognostic biomarker for early prevention and as a therapeutic target.

**Keywords:** ZNF217, Zfp217, drug resistance, cancer, $m^6A$, triciribine, adipogenesis, embryonic stem cell

## Introduction

Cancer remains a major cause of death worldwide [1]. The discovery of specific biomarkers of various types of neoplasms will improve early diagnosis and individualized therapies for better prevention and therapeutic outcomes. However, anti-neoplastic treatments are not always satisfactory due to the activation of other signaling pathways that weaken the therapeutic effects [2]. Moreover, the increase in cancer mortality demands accurate biomarkers to perfect the detection of lesions with high cancer risks through an early diagnosis of premalignant tissues [3]. In this review we focus our attention on ZNF217, a member of a large family of zinc finger transcription factors, which plays a key role in eukaryotic gene regulation, and which dysregulation, is often observed in cancer [4, 5]. Recent observations suggest that ZNF217 regulates gene expression in various cancers, where it promotes tumorigenesis through increasing proliferation, invasion and metastasis, and inhibition of apoptosis. These hallmarks correlate with therapeutic resistance and poor outcomes. However, there are no reviews that summarize and discuss the relationship between ZNF217 and therapeutic resistance. Here, we review the literature on the role of ZNF217 in cancer and other diseases and explore the complex regulatory network that is triggered by ZNF217. We also emphasize its clinical application value in prognostic prediction and therapeutic design.

## Expression of ZNF217: battles within transcriptional or post-transcriptional layer

*ZNF217* aberrant gene amplification, located in chromosome 20q13.2 region, was frequently detected in various precancerous lesions and cancers, including breast [6-12], ovarian [13-16], gastric [17, 18], prostate [19], esophagus [18, 20], pancreatic [21], and colorectal carcinomas [22-25], glioblastoma [26, 27], hepatoma [28], lung cancer [29], lymphoma [30], Barrett's esophagus [31-33], head and neck squamous cell carcinoma [34] and melanoma [35]. *ZNF217* aberrant gene amplification and mRNA levels are associated with high cancer risk and poor therapeutic sensitivity [36-43]. However, ZNF217 expression level does not

consistently correlate with its gene amplification status [10, 44]. Indeed, there exists a sophisticated regulatory mechanism that involves the triggering of *ZNF217* uncontrollable expression to stimulate downstream signaling pathways and cause pathological alterations.

At the transcriptional level, a negative correlation between *ZNF217* promoter methylation and its expression, was demonstrated by a whole-genome integrative analysis in glioblastoma that indicated that DNA methylation reduces its expression level [26]. In cytotrophoblasts, *ZNF217* DNA methylation inversely correlated with oxygen concentration in most tumor tissues that were exposed to hypoxia due to their unlimited cell proliferation [45, 46]. Under hypoxic conditions, *ZNF217* mRNA and ZNF217 protein expression levels are upregulated by hypoxia-inducible factor-1α (HIF-1α) and HIF2α in glioblastoma [27]. Another transcriptional factor, the signal transducer and activator of transcription 3 (STAT3), directly binds on the *Zfp217* promoter, and upregulates its expression following melatonin treatment of mouse ESCs, suggesting a STAT3 potential regulatory role of *ZNF217* expression [47].

At the post-transcriptional level, noncoding RNAs, such as microRNAs (miRNAs) and long-noncoding RNAs (lncRNA), possess vital regulatory functions of ZNF217 expression. For instance, the 3'UTR region of the *ZNF217* mRNA could be targeted and repressed by microRNAs, even when their expression levels are decreased in diseases. In breast cancer, ZNF217 expression is negatively correlated with miR-503, which is upregulated by estrogen ($E_2$) stimulation, whereas estrogen receptor (ER) antagonists, such as ICI 182,780 (fulvestrant), upregulates ZNF217 expression that may be associated with the inhibition of the ER signaling pathway [48, 49]. Additionally, a recent study demonstrated that a stiffer periductal stroma downregulates miR-203 level, which increases ZNF217 expression and triggers early-stage tumorigenesis in high mammographic density breast tissues [50]. Contrarily to microRNAs, long-noncoding RNAs appear to promote ZNF217 expression. LncATB, which shows aberrant expression and promotes carcinogenesis in various cancers [51], upregulates ZNF217 expression via suppressing miR-200c to induce carcinogenic phenotype in breast and prostatic cancers [52, 53]. Other noncoding RNAs, which expression correlated with ZNF217 expression have been reported in other diseases (**Table 1**). Significantly, clustered rearrangements that were detected in breast cancer, may lead to ZNF217 gene amplification, while these rearrangements usually cause aberrant transcriptional activation or decreased affinity to microRNAs [54]. Therefore, microRNA based anti-ZNF217 treatment should be verified in tumor masses. In summary, both transcriptional and post-transcriptional mechanisms contribute to aberrant ZNF217 expression, while no evidence on ZNF217 protein modification has been reported to date.

### Epigenetic regulator ZNF217: a social butterfly meets chromatin, protein and RNA

ZNF217 contains eight zinc fingers and unlike traditional C2H2-type zinc finger proteins, it directly binds to DNA sequences by its 6th and 7th zinc fingers, and two methyl-π interactions that strengthen its DNA affinity [55, 56]. After binding, ZNF217 acts as a bridge that recruits cofactors and orchestrates a transcriptional repressor complex that regulates the transcriptional functions of target genes. These interacting cofactors are mostly gene suppressors, such as REST transcriptional co-repressor (CoREST) [57-59], C-terminal binding protein 1/2 (CtBP1/2) [57-61], lysine specific demethylase 1 (LSD1) [57-59], histone deacetylase (HDAC) [57, 58], lysine-specific demethylase 5B (Jarid1b) [59], lysine methyltransferase G9a [59, 62], lysine methylase enhancer of zeste homolog 2 (EZH2) [59, 63, 64] and DNA methyltransferase 3 alpha (DNMT3A) [65]. For instance, ZNF217 is usually contained within canonical repressor complexes, such as CoREST and CtBP. ZNF217 contains several binding regions with CoREST and consistently co-bind independently of CtBPs [58, 65, 66]. For CtBPs, ZNF217 contains two different types of motifs (PXDLS and RRT) that bind with CtBPs [60, 67]. The CoREST or CtBPs complex then induces histone methylation, histone deacetylation and/or DNA methylation to suppress gene transcription [68, 69]. Thus, adenovirus type 5 E1A (AdE1A) interaction with the CtBP1/ZNF217 complex to reverse transcriptional repressors activity, may contribute to the design of an anti-ZNF217 treatment [70].

**Table 1.** Upstream factors regulating ZNF217/Zfp217 function in tissues and diseases

| Tissues or diseases | Tissues from patients or cells lines | Special treatment | Factors upstream to ZNF217/Zfp217 | Changes of ZNF217/Zfp217 expression | Changes in cells or tissues | references |
|---|---|---|---|---|---|---|
| Glioblastoma | GSCs cultured from glioblastoma patients, U87, A172 | Hypoxia | HIF-1α (+)<br>HIF-2α (+) | Upregulated | GSC maintenance (+) | [27] |
| Breast cancer | MCF-7, MVLN | E2 stimulation | miR-503 (+) | Downregulated | Proliferation (-)<br>(miR-503 overexpression) | [48, 49] |
| | MVLN | Fulvestrant (ICI 182780) | Unknown | Upregulated | | [48] |
| | SKBr-3 (Trastuzumab resistant) | | miR-200c (-) | Upregulated | Trastuzumab resistance (+)<br>Metastasis (+) | [101] |
| | SKBr-3 (Trastuzumab resistant) | | Lnc-ATB (+)/miR200c (-) | Upregulated | Trastuzumab resistance (+)<br>Invasion (+) | [52] |
| Hepatoma | HepG2, PLC-PRF-5, SK-Hep1, Huh7, MHCC97H, Immortalized human liver cell line | | miR-101 (-) | Upregulated | Proliferation (+)<br>Invasion (+) | [43] |
| Prostate cancer | 26 tumor tissues, LNCaP, DU145 | | miR-24 (-)<br>miR-22 (-) | Upregulated | Proliferation (+) | [179] |
| | 58 tumor tissues, PC-3, DU-145 | | Lnc-ATB (+) | Upregulated | Proliferation (+)<br>EMT process (+) | [53] |
| | 82 tumor tissues, PC-3, DU-145, LNCaP, HEK293T | | GATA-3/miR-503 (-) | Upregulated | Proliferation (+)<br>Colony formation (+)<br>Invasion (+)<br>Migration (+) | [180] |
| Non-small cell lung cancer | 24 tumor tissues, A549, H358 | | Lnc-SNHG15 (+)/miR-211-3p (-) | Upregulated | Proliferation (+)<br>Migration (+) | [181] |
| Cervical cancer | 72 tumor tissues, HeLa, SiHa | | Lnc-CTBP1-AS2 (+)/miR-3163 (-) | Upregulated | Proliferation (+)<br>Invasion (+)<br>Migration (+)<br>Anti-apoptosis (+) | [182] |
| Epithelial ovarian cancer | 40 tumor tissues, HEY, A2780, SKOV3, OVCAR3 | | Lnc-OIP5-AS1 (+)/miR-137 (-) | Upregulated | Proliferation (+)<br>Invasion (+)<br>Migration (+)<br>Metastasis (+) | [183] |
| Osteosarcoma | Genetically engineered mouse model (Expression of ZNF217), SJSA-1 | PI3K inhibitor (LY294002), Triciribine | PI3K/Akt pathway (-) | Downregulated | Proliferation (-)<br>Invasion (-)<br>Migration (-)<br>Apoptosis (+) | [76] |
| Keloid fibroblasts | 57 keloid tissues, Keloid fibroblasts | | Lnc-ATB (+)/miR-200c (-) | Upregulated | Not mentioned | [73] |
| Alzheimer's disease | 18 cerebrospinal fluid samples, PC12 | Amyloid β-protein treatment | Lnc-ATB (+)/miR-200 (-) | Upregulated | Viability (-)<br>Apoptosis (-)<br>Inflammatory response (+)<br>Oxidative stress (+) | [172] |
| | SK-N-SH, CHP212 | Amyloid β-protein treatment | SNHG1 (+)/miR-361-3p (-) | Upregulated | Viability (-)<br>Apoptosis (-)<br>Inflammatory response (+)<br>Oxidative stress (+) | [173] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Intervertebral disc degeneration (IDD) | 48 IDD rats | Ilizarov-type apparatus | Unknown | Upregulated | Unknown | [184] |
| Breast tissue | 22 normal human breast tissues, MCF10A MECs | Stiff collagen matrix | miR-203 (-) | Upregulated | Akt activity (+)<br>Tumor progression (+) | [50] |
| ESCs | Mouse V6.5 ESCs, OG2-ESCs, MEFs | Melatonin | MT1-JAK2 (+)/STAT3 (+) | Upregulated | Proliferation (+)<br>Pluripotency factors stability (+)<br>Pluripotency (+) | [47] |
| Adipocytes | 3T3-L1, C3H10T1/2 | microRNA-mimics | miR-503-5p (+)<br>miR-135a-5p (+)<br>miR-19a-3p (+) | Downregulated | Adipogenesis (-)<br>Lipid droplet accumulation (-) | [154] |

Phenotypes or factors that are enhanced or upregulated are labeled by "+", while "-" means the opposite.

Besides forming a transcriptional repression complex, ZNF217 also stimulates gene transcription to promote disease progression. For instance, ZNF217 directly binds to the *ErbB3* promoter and upregulates its expression in MCF-7 and mouse embryonic fibroblasts (MEFs) [71]. Other promoters are also activated by ZNF217, such as mesenchymal genes that include *SNAIL1*, *SNAIL2*, and *Vimentin* [72], as well as critical genes involved in the transforming growth factor beta (TGF-β) autocrine pathway, and which include *TGF-β2*, *TGF-β3* [40, 73]. It is odd that all ZNF217 recruited factors are gene suppressors. Co-factors interacting with ZNF217 to stimulate gene transcription are yet to be identified.

Moreover, ZNF217 localization is not limited to the nucleus, as more studies have shown that ZNF217/Zfp217 functionally interacts with proteins both in nucleus and cytoplasm to regulate different phenotypes [74-76]. Thus, signaling receptors, such as ERα and mRNA $m^6A$ mediators, including methyltransferase-like 3 (METTL3), are under the control of ZNF217 or Zfp217. $m^6A$ is the most prevalent internal modification on eukaryotic mRNA, that alters mRNA activity to regulate target gene expression and plays a significant role in carcinogenesis, which also suggests its potential use as a therapeutic target [77]. Therefore, new evidence, at the post-transcriptional and post-translational level, expand the regulatory network of ZNF217. Whereas reports on ZNF217 induced $m^6A$ variation in cancer, remain limited.

Besides interacting with ERα, ZNF217 also regulates epigenetics via other mechanisms at the post-translational level, including phosphorylation, acetylation, ubiquitination. ZNF217 upregulates Akt phosphorylation via the activation of the PI3K-Akt signaling pathway which promotes breast cancer progression [71, 72, 78]. Moreover, the ZNF217/mouse double minute 2 (MDM2) complex significantly reduces p53 acetylation [79]. Though there is no report about ZNF217 in ubiquitination, the relationship between ubiquitination and CtBP1, one of the cofactors of ZNF217, has been reported. CtBP1 could serve as a platform for SUMOylation of CtBP-interacting protein (CtIP) such as ZEB1 [66]. Deubiquitination of CtBP-interacting protein would promote DNA end resection and homologous recombination [80]. Thus, ZNF217 may participate in ubiquitination through CtBP1 and other cofactors.

## ZNF217 role in carcinogenesis and tumor progression

An advanced understanding of the regulatory mechanisms of carcinogenesis would result in novel and more effective therapeutic strategies. However, a successful antineoplastic therapy is usually limited by the advanced cancer stage and drug resistance; therefore, it is urgent to overcome these challenges [2]. In various cancer patients, ZNF217 aberrant overexpression is associated with poor prognosis [27, 38, 40, 72, 74, 78, 81]. Previously, we have discussed the causes of ZNF217 aberrant expression and the model of regulatory mechanisms, which is triggered by ZNF217. In the subsequent context, we explore in detail the function of ZNF217 in carcinogenesis, including overcoming agonescence, accelerating cell-cycle, triggering EMT, promoting heterogeneity, facilitating metastasis, and inhibiting apoptosis. These processes induced by ZNF217 also preserve cancer cells' survival from stresses, such as anti-neoplastic therapy and others. Therefore, in-depth understanding of ZNF217 functions, is necessary for the latent therapeutic options that are based on ZNF217 (**Figure 1**).

### *ZNF217 and immortality: overcoming agonescence*

During the development of organisms, cells have a limited proliferation via a periodic cell-cycle. Normal somatic cells meet their destination by entering the apoptotic process when telomeres become shorter enough. However, aberrant ZNF217 expression results in unlimited growth and uncontrolled proliferation, even bypassing senescence to achieve immortality, which features among the basic hallmark of tumorigenesis (**Figure 2**).

After selection in serum-free medium, part of the human mammary epithelial cells (HMECs) acquires $p16^{ink4a}$ inactivity and keep proliferating until telomeres are shorter, which results in a mitotic failure [82]. Agonescence, a crisis during this process, is a barrier to immortality whereas ectopic ZNF217 expression could overcome this dilemma. A concomitant phenomenon with ZNF217 overexpression in

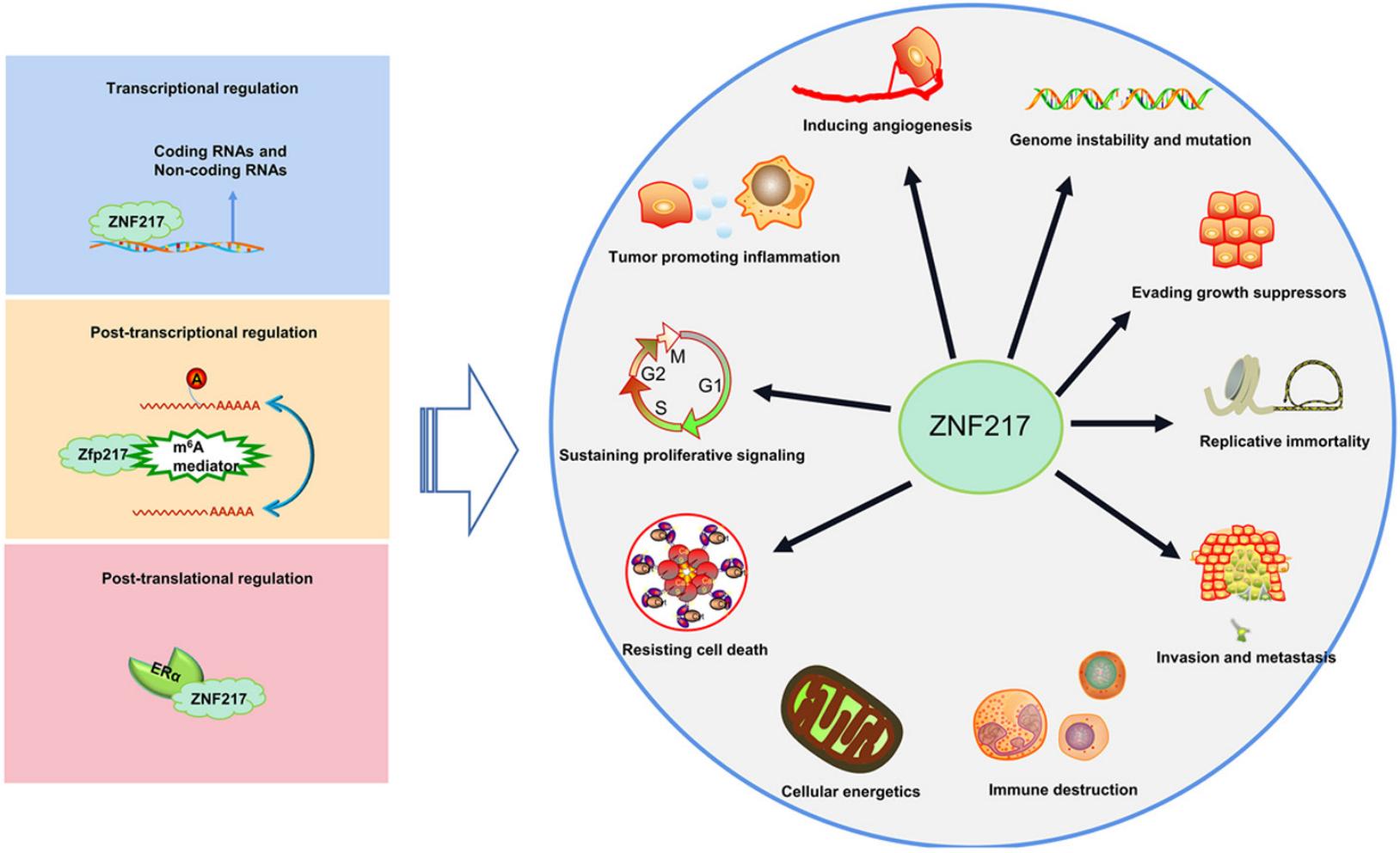


**Figure 1.** ZNF217/Zfp217 mediates cancer hallmarks at different expression levels. ZNF217/Zfp217 induces carcinogenesis (Right circle) by stimulating or suppressing gene transcription (Upper corner of left rectangle), interacting with factors (Middle corner of left rectangle) and regulating m$^6$A (bottom of left rectangle).

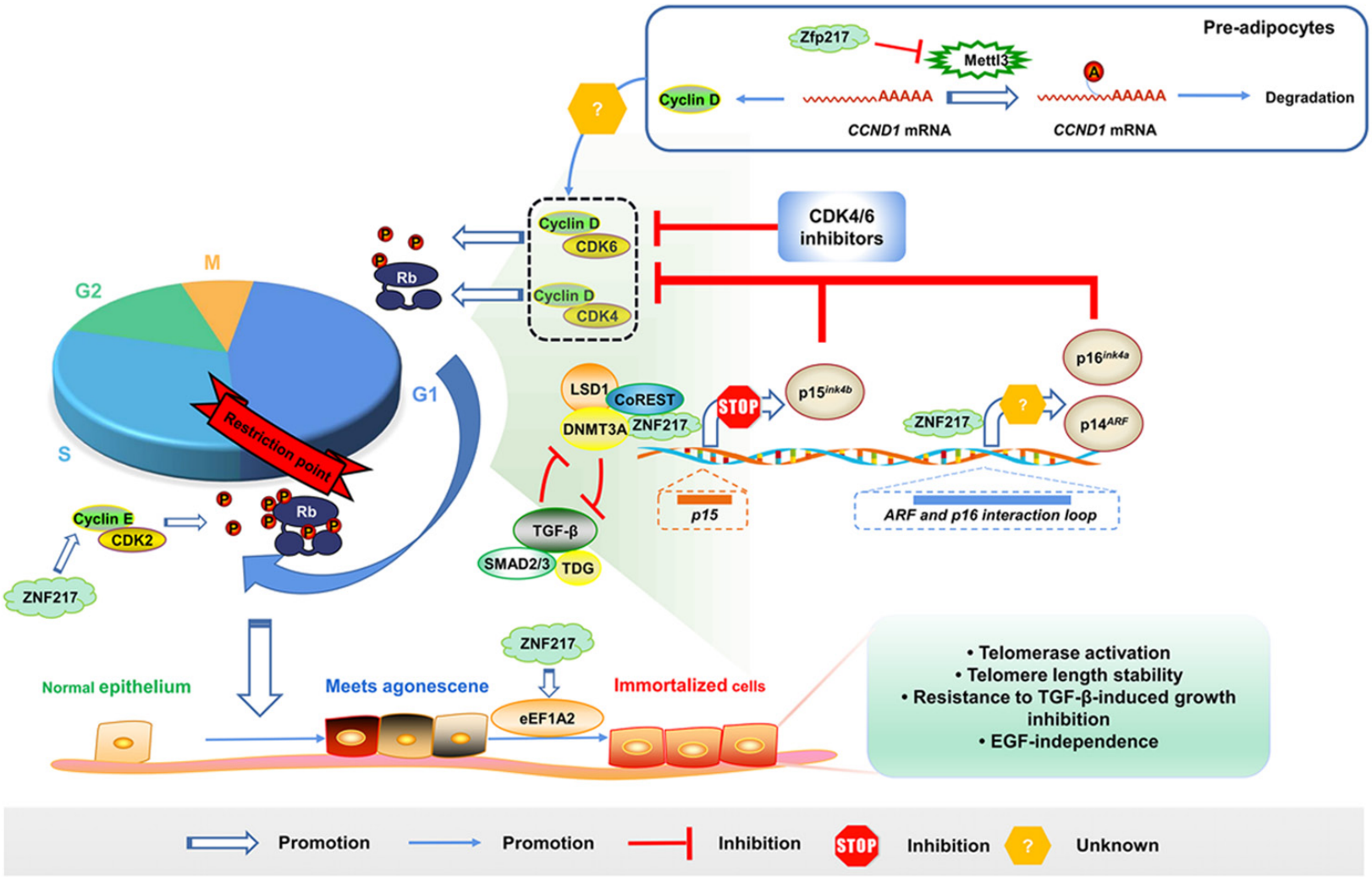


**Figure 2.** ZNF217 induces immortality and evades growth suppressors. CDK4 and CDK6 are directly inhibited by $p16^{ink4a}$ and $p15^{ink4b}$ and antineoplastic treatment such as CDK4/6 inhibitor. Deficiency of $p16^{ink4a}$ and $p15^{ink4b}$ could be detected in numerous human cancers and are sensitive to CDK4/6 inhibitors. The balance between ZNF217 and TGF-β in proliferation is disrupted by aberrant ZNF217 expression and results in decreased $p15^{ink4b}$ and upregulated cyclin D1 (possible via $m^6A$ regulation). $p16^{ink4a}$ is another potential target for ZNF217, which mechanism is unknown. Moreover, ZNF217 also targets *CCNE* (encoding Cyclin E) and stimulates its expression [61]. These mechanisms, together with the upregulation of the expression of eEF1A2, induced by ZNF217, contribute to agonescene escape in normal epithelium, which finally transformed into immortalized cells. It is worth noting that the upregulation of CyclinE1, Cyclin E2 and Cyclin A2 is concomitantly observed following ZNF217-overexpression (not be mentioned in the figure) [92]. Thus, ZNF217 may also participate in other phases of cell-cycle to sustain proliferative signaling.

HMECs is associated with telomerase activation, telomere length stability and resistance to TGF-β-induced growth inhibition [83]. The telomeric repeat-binding factor 2 (TRF2) is a telomerase which expression is increased in immortalized HMECs where it protects telomeres, may contribute to ZNF217-induced telomeres stability [84]. Moreover, lethal treatments, such as the combination of doxorubicin and negative TRF2 mutant (inducing ATM/p53 dependent apoptosis) or TRF1 (inducing ATM/p53 independent apoptosis), are ineffective following ZNF217 overexpression in both normal and malignant cell lines [78]. Obviously, the relationship between ZNF217 and TRFs is vital to cellular immortality, whereas the precise regulatory networks have yet to be elucidated.

The timing to start a biological behavior in cells is under the control of the organism requirements. However, overexpressed ZNF217 acts differently in this process. Short-term epithelial growth factor (EGF) treatment is required for ZNF217-induced immortality, near the time of agonescence, in p53/phosphorylated Retinoblastoma (pRb)-activated human immortalized ovarian surface epithelial cells (IOSEs), while the maintenance of eternal cells is EGF-independent [85]. It is worth noting that ZNF217 successfully induces immortality alone in p53/pRb-deficient IOSEs, whereas it fails to achieve it in p53/pRb-activated IOSEs [85]. However, alterations in p53 and/or pRb are not a prerequisite to ZNF217-induced immortalization [78]. Additionally, elongation factor 1-α 2 (eEF1A2), which co-exists with ZNF217 at the 20q13 locus, is upregulated by ZNF217 during immortalization, whereas its absence reverses ZNF217-transduced immortalization in IOSEs [86]. Other studies demonstrated that eEF1A2 stimulates the phospholipid signaling and activates the PI3K/Akt signaling pathway to promote metastasis and actin remodeling that ultimately favor tumorigenesis [87]. Therefore, the eEF1A2-induced anti-apoptotic effect may also play a significant role in ZNF217-induced immortalization. Attentionally, ZNF217 combines and enhances lysine-specific demethylase 5B (Jarid1b) suppressive function on breast cancer susceptibility genes (*BRCA1*), which plays a significant role in several DNA repair pathways [59]. Therefore, immortalization features as a basic event in ZNF217-induced carcinogenesis, which provides tumor cells an eternal lifespan and increases the possibility of DNA mutation. Thus, these results spark great interest in monitoring the aberrant expression of ZNF217 for early cancer risk prevention.

*ZNF217 and cell cycle regulation: the beacon for CDK4/6 inhibitor?*

CDK4/6 inhibitors have been approved by the Food and Drug Administration (FDA) for the treatment of breast cancer. Cyclin-dependent kinase inhibitors 2A/B (*CDKN2A/B*) play a significant role in epigenetic regulation by encoding cell cycle inhibitors [88]. The epigenetic silencing or mutational inactivation of *CDKN2A* (encoding $p16^{ink4a}$ and $p14^{ARF}$) and *CDKN2B* (encoding $p15^{ink4b}$) could be detected in numerous human cancers and are sensitive to CDK4/6 inhibitors [89, 90]. Herein, the relationship between ZNF217 and *CDKN2A/B* provides a potential reference value for the application of CDK4/6 inhibitors in malignant tumors (**Figure 2**).

In MCF-7, the $p15^{ink4b}$ promoter is occupied and suppressed by ZNF217 and its cofactors, such as LSD1 and CoREST, in CtBP1-independent manner [58]. Histone modifications of the $p15^{ink4b}$ promoter by H3K4me2 is increased, whereas its modification by H3K9/14ac is decreased in the absence of ZNF217 [58, 91]. Additionally, ZNF217 recruited DNMT3A to methylate the $p15^{ink4b}$ promoter and prevent thymine DNA glycosylase (TDG)-dependent DNA demethylation that was induced by TGF-β in ZNF217-transfected HaCaT cells [65]. Thus, histone modification and DNA methylation, induced by ZNF217, impair *CDKN2B* transcription and resist TGF-β-dependent DNA methylation. Besides, the expression of Cyclin D1, a member of the D-type cyclins, which pairs with CDK4/6 to overcome restriction point, significantly correlated with ZNF217 expression and maybe a hallmark for the sensitivity to CKD4/6 inhibitors [92, 93]. In summary, ZNF217 counteracts TGF-β activity by repressing $p15^{ink4b}$ and upregulating Cyclin-D1 expression to promote proliferation. In contrast, the absence of ZNF217 causes a significant decrease in pRb and an elevated percentage of cells that curbed the G1 phase [58, 65].

Moreover, another region in *CDKN2A/B* has been recently recognized as a target of

ZNF217. The combination between ZNF217 and *ARF/p16* interaction loop was confirmed by Genetic CRISPR screening in SEM cells [90]. It is worth noting that ZNF217 could directly bind with *ARF/p16$^{ink4a}$* interaction loop in the long-distance chromatin interaction model, suggesting that the binding pattern of ZNF217 on *ARF/p16$^{ink4a}$*, depends on the chromatin spatial structure [90]. Similar to p15$^{ink4b}$, p16$^{ink4a}$ also plays a significant role in cell-cycle regulation, while another factor, p14$^{ARF}$, is a canonical regulator of p53 that prevents DNA damage and induces apoptosis [94]. Hence, it is important to verify whether p14$^{ARF}$ and p16$^{ink4a}$ are under the control of ZNF217. Ac-cording to the abovementioned findings, ZNF217 interaction with *CDKN2A/B* plays a significant role in the anti-neoplastic effect of CDK4/6 inhibitors. Thus, it is reasonable to unveil the role of ZNF217 in CDK4/6 treatment.

*ZNF217 and invasion: welcome to the "EMT" express*

Epithelial-mesenchymal transition (EMT) is a process in which cells lose their epithelial characteristics and acquire mesenchymal features, which promotes the emergence of heterogeneous populations of invasive and metastatic tumor cells. This intra-tumoral heterogeneity is also a major driver of drug resistance [95, 96]. It is worth noting that ZNF217 gene amplification is higher in primary and distant metastatic lesions compared to non-metastatic lesions in colorectal cancer and ovarian clear cell carcinoma [28, 97]. *In vitro* and *in vivo* experiments also demonstrated that ZNF217 enhances invasion and metastasis via promoting EMT of cancer cells [40, 71, 72, 98] (**Figure 3**).

During EMT, the expression of the epithelial marker E-cadherin (encoded by *CDH1*) is decreased, and the expression of mesenchymal markers is increased. ZNF217 directly targets the *CDH1* promoter to repress E-cadherin expression via recruiting CtBPs in MCF-7 and NTERA-2 cells [58, 61]. Meanwhile, LSD1 is also recruited by ZNF217 to increase the level of H3K4me2 at the *CDH1* promoter and inhibits E-cadherin expression in HCC cells [43]. On the contrary, ZNF217 enriched at and upregulated mesenchymal genes such as *SNAIL1*, *SNAIL2* and *TWIST* promoters [72]. Additionally, E-cadherin could be suppressed by several mesenchymal factors, such as SNAIL (encoded by *SNAIL1*), SLUG (encoded by *SNAIL2*), and TWIST [99]. Moreover, an upregulation of the expression of other mesenchymal genes, such as N-cadherin and vimentin, was also observed following ZNF217 overexpression [43]. Intriguingly, unlike the competitive relationship in p15$^{ink4b}$ regulation, ZNF217 positively regulates TGF-β expression, which is a canonical regulator of EMT [100]. ZNF217 promotes the TGF-β autocrine pathway by transcriptionally activating *TGF-β2* and *TGF-β3*, while TGF-β pathway inhibitors reverse ZNF217-induced EMT [40, 101]. To restrain the process, miR-200c could curb the ZNF217-induced TGF-β autocrine pathway and alleviate trastuzumab resistance and metastasis, whereas ZNF217 overexpression decreases miR-200c via suppressing TGF-β2 in HER2-positive breast cancer cells [101]. Indeed, the functional differences within TGF-β isoforms are vital in immune regulation, suggesting that ZNF217 may transform immune response by stimulating the expression of TGF-β isoforms [102]. In summary, ZNF217 is a critical promoter of EMT that leads to metastasis.

*ZNF217 and metastasis: breaking the new world*

Though cancer cells acquire the ability of intravasation via EMT which leads to metastasis, anoikis that is enhanced by endovascular and lymphatic environments undermines the survival of cancer cells [103]. Therefore, circulating tumor cells must develop an anchorage-independent ability to overcome this challenge. Moreover, extravasating and colonizing cancer cells end up in unfamiliar environment that is also an additional challenge [104]. Thus, elucidating the mechanism of metastasis and inhibiting pivotal signaling pathways that are associated with EMT, are significant to improve patient outcomes. For this reason, ZNF217, which promotes the formation of an anchorage-independent growth and metastatic microenvironment, attracts increasing attention (**Figure 3**).

Cells with high ZNF217 expression acquire the ability to survive anoikis. ZNF217 overexpression in primary MECs increased their self-renewal capacity in a serum-free nonadherent culture environment, while in NIH3T3 cells, its overexpression stimulated anchorage-independent growth in soft agar [72]. In ZNF217-trans-

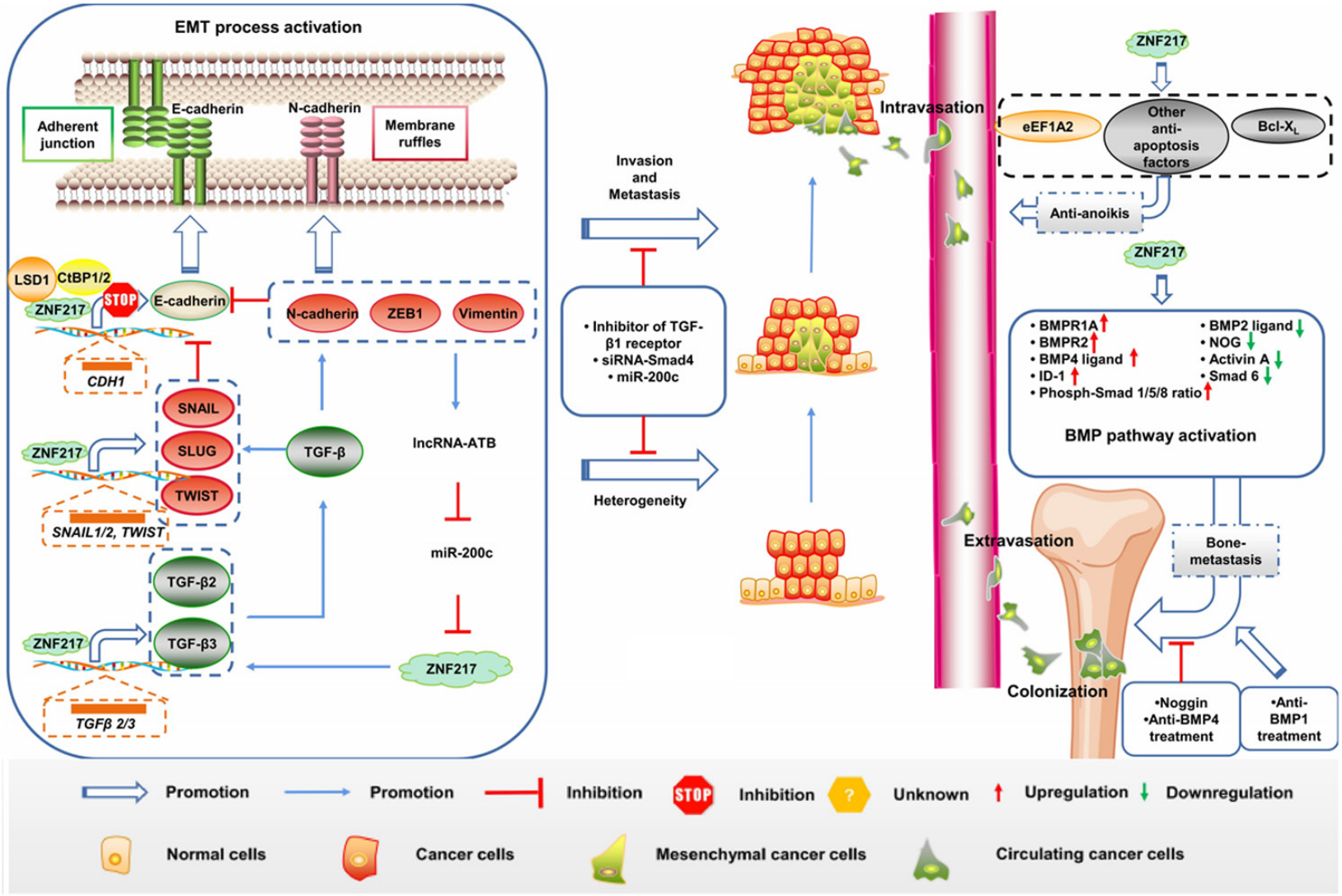


**Figure 3.** ZNF217 triggers EMT process, anti-apoptosis ability and BMP pathway activation to promote heterogeneity, anti-anoikis and metastasis. E-cadherin maintains the adhesive junctions between epithelia cells and preserves the epithelial phenotype, while the absence of E-cadherin promotes the loss of cellular contact leading to malignant metastasis [185, 186]. ZNF217 directly inactivates E-cadherin transcription or indirectly stimulates mesenchymal genes, such as *TGF-β2/3, SNAIL1/2 and TWIST*. It also increases N-cadherin expression resulting in membrane ruffles. Thus, tumor cells become heterogeneous and more aggressive, while anti-TGF-β treatment would suspend the process. ZNF217 also upregulates eEF1A2, Bcl-$X_L$ and stimulates other anti-apoptosis factors to promote anti-anoikis in tumor cells, which help CTCs to survive in the circulatory system. With EMT enhancement and anoikis inhibition that induced by ZNF217, circulating tumor cells are inclined to finish intravasation and extravasation to colonize distant organs, such as bone (BMP pathway activation).

fected IOSEs, cells exhibited anchorage independence and a reduced serum dependence [85]. Several factors regulated by ZNF217 participate in the progression of metastasis. ZNF217 upregulates eEF1A2 to promote the metastatic phenotype, while eEf1A2 knockdown reverses this effect impact in IOSEs [86]. The expression of *BCL2L1* (encoding Bcl-$X_L$), which plays an essential role as an anti-anoikis factor in various cancers, is associated with the *ZNF217* increased mRNA levels of and contributes to the anchorage-independent growth of colorectal cancer cells [105-107]. Attentionally, other anti-apoptosis signaling pathways (discussed later) activated by ZNF217, may also contribute to anchorage-independent growth. Thus, circulating cells with high ZNF217 expression have an advantage in finalizing their colonization journey.

The formation of a cancer microenvironment is crucial for the colonization process of metastatic cancer cells. Interestingly, ZNF217 promotes colonization by playing a pivotal role in the formation of the bone metastatic microenvironment [108-110]. In primary tumors, *ZNF217* mRNA expression level correlates with a high risk of bone metastasis in breast cancer patients [111]. *In vitro* experiments showed that ZNF217 overexpression enhances the BMP pathway in MDA-MB-231 cells (MDA-MB-231-ZNF217), while soluble factors that are released by differentiated osteoblasts and MDA-MB-231-ZNF217, contribute to the chemotaxis of metastatic cells [111]. Further explorations distinguished the precise factor within the BMP pathway that was influenced by ZNF217 in bone metastasis. Noggin (inhibitor of BMP type I and II receptors), anti-BMP4 antibody or LDN-193189 (inhibitor of BMP type I receptor) reversed ZNF217-induced invasion and metastasis *in vitro* and *in vivo* [111]. Whereas according to the *in vivo* experiments, LDN-193189 increased both the number and size of metastases in MDA-MB-231-ZNF217 xenograft mice [112]. Though the conclusions are paradoxical, these findings contribute to a better understanding of ZNF217-induced bone metastasis and suggest the possibility to use BMP-inhibitor in anti-ZNF217 based treatments. Additionally, *in vivo* experiments demonstrated that ZNF217- or Zfp217 overexpression in breast cancer cells, leads to increased lung micrometastases in mice, however, the precise mechanisms have yet to be elucidated [40, 113].

*ZNF217 and stemness: the initiator of evil*

Without early detection, cancer cells with unlimited growth and EMT progression, get enough time to generate tumor heterogeneity. The emergence of CSCs, a process of establishing stem-like malignant cells during cancer progression, leads to increased self-renewal, heterogeneity, treatment resistance and cancer relapse [114]. Suppressing pathways related to CSCs emergence, would be an efficient therapeutic strategy to treat cancer and to prevent its relapse [115]. Thus, ZNF217, the EMT mediator that stimulates CSCs emergence and differentiation, could be a good target to improve patients' therapeutic outcomes. Moreover, studies on the role of Zfp217 in induced pluripotent stem cells (iPSCs), would extremely help understand ZNF217 functions in CSCs emergence.

Reprogramming is a multi-step process that comprises enhanced proliferation, followed by mesenchymal-to-epithelial transition (MET) and is completed by the activation of pluripotency genes that transform somatic cells into induced pluripotent stem cells (iPSCs) [116]. This process is a good reference in understanding the mechanism of CSC emergence due to the similarity with cancer cells' dedifferentiation. *Zfp217* depletion mostly causes decreased expression of pluripotency genes, indicating that Zfp217 is mainly required for later stages of reprogramming [117]. However, there exists a complex relationship between Zfp217 and these stemness genes (**Figure 4A**). At the transcriptional level, Zfp217 and/or Zfp516 recruits CtBP2 to directly co-occupy and repress promoter regions of stemness genes in embryonic stem cells (ESCs) [63]. These regions exhibit a decreased H3K27ac that is induced by the nucleosome remodeling deacetylase (NuRD) complex, and an increased H3K27me3 which is induced by the polycomb repressive complex 2 (PRC2) [63]. Another research showed that Zfp217, Lsd1 and Oct4 (encoded by POU class 5 homeobox 1, Pou5F1) also co-occupy ESCs genomic sites, including those of nanog homeobox (Nanog), SRY-box transcription factor 2 (Sox2), Krüppel-like factor 4 (Klf4), and cellular Myelocytomatosis (c-Myc) [117]. Based on these reports, Zfp217 appears to be a stemness repressor, as its function as a post-transcriptional regulator of stemness is more significant, especially in an $m^6A$ manner.

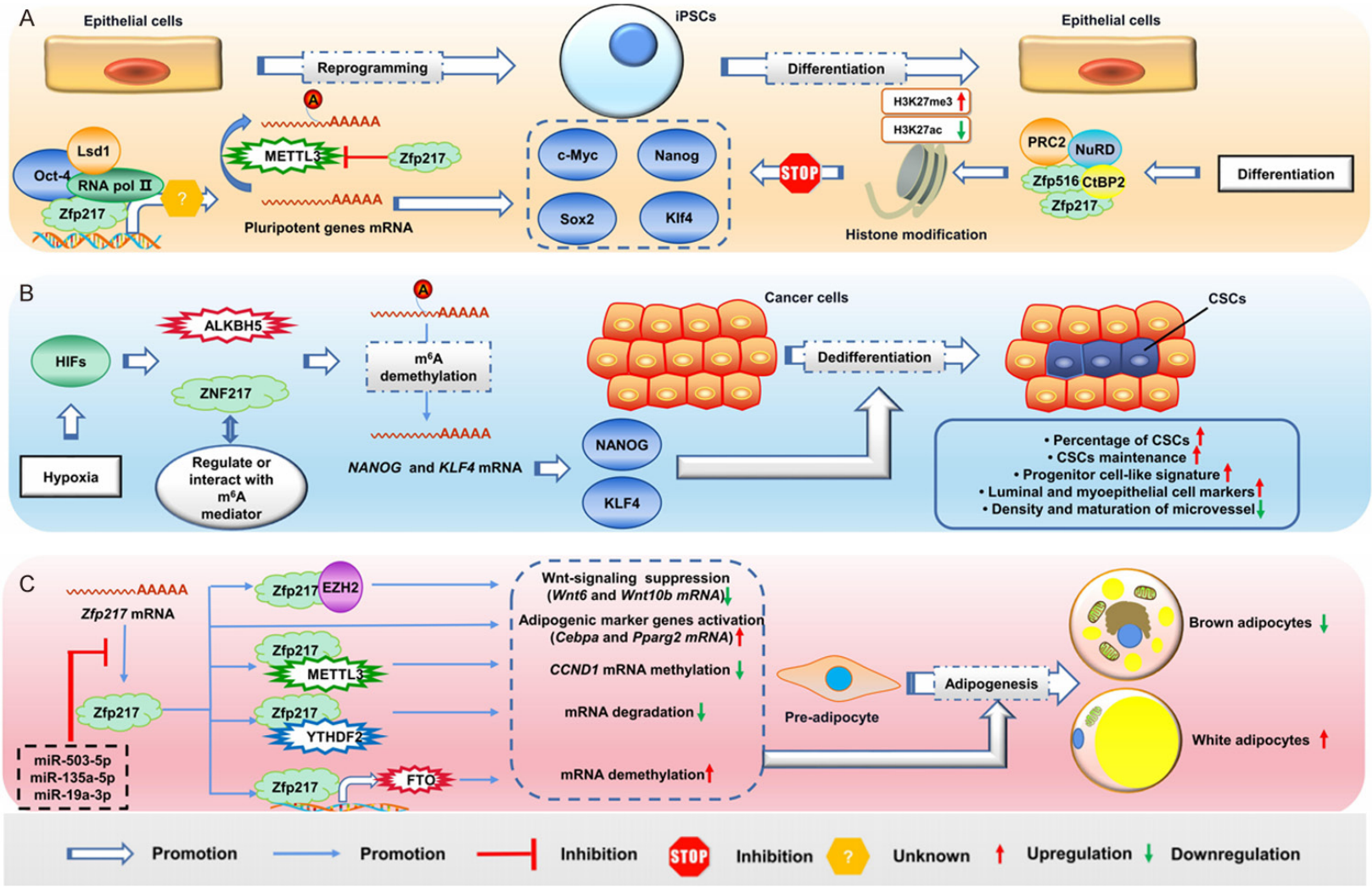


**Figure 4.** ZNF217 regulates differentiation or dedifferentiation of CSCs, ESCs and MECs. A. In ESCs, Zfp217 post-transcriptionally stimulates mRNA expression of pluripotency genes, such as *c-Myc, Nanog, Sox2* and *Klf4*, to regulate reprogramming. While the function of the transcriptional complex (including Zfp217, Oct4, Lsd1 and RNA pol II) which targets pluripotency genes is still unclear. Otherwise, after differentiation treatment, Zfp217 transcriptionally suppresses pluripotency genes by regulating histone modification, and triggering differentiation. Thus, the dual function of Zfp217 has a vital role in stem cell engineering. B. In tumor cells, HIFs transcriptionally stimulate *ZNF217* gene expression (the binding may be indirect due to the core hypoxia response element motif that is not comprised in the binding region) and ALKBH5 to trigger dedifferentiation from cancer cells to CSCs by stimulating the m$^6$A demethylation of NANOG and KLF4 mRNA. C. In pre-adipocytes, Zfp217 determines the direction of adipogenesis to white adipocytes rather than brown adipocytes by interacting with EZH2, METTL3, YTHDF2 and stimulating the expression of FTO. These studies emphasized the significant role of ZNF217/Zfp217 in m$^6$A regulation.

Zfp217 regulates stemness hallmarks via its interaction with m$^6$A mediators, while the depletion of *Zfp217* globally increased m$^6$A levels and impaired MEFs reprogramming into iPSCs [63, 117]. For instance, METTL3 is a major methyltransferase that globally promotes mRNA methylation and is associated with carcinogenesis [118-120]. Zfp217 alleviates stemness mRNAs degradation by combining with METTL3 and impeding METTL3 to bind RNAs, while the depletion of *Zfp217* does not change the mRNA and protein expression levels of METTL3 in iPSCs [117]. A gradual decrease of ZFP217 was detected in retinoic acid (RA)-induced and leukemia inhibitory factor (LIF)-induced iPSCs, which coincided with the downregulation of pluripotency factors, such as Nanog, Oct4, and Sox2 [63, 117]. Moreover, Zfp217 absence abortively inhibits the expression of pluripotency genes, resulting in a failure of differentiation and an increased percentage of undifferentiated cells that succumbed to growth arrest and senescence [63, 117]. Noteworthy, melatonin treatment could restore the pluripotency of long-term cultured ESCs by stimulating the MT1-JAK2/STAT3-Zfp217 axis, resulting in a significant decrease in global m$^6$A modification and an elevated Oct4 expression [47]. Intriguingly, the paradoxical function of Zfp217 that varies between the transcriptional and post-transcriptional levels, maybe due to the expression levels of some genes that could be upregulated when their promoters are enriched by the repressive factor ZNF217. It is worth noting that the functional parallels between CSCs and non-neoplastic stem cells (such as ESCs) are considered to be extensive [121]. Therefore, the abovementioned findings shed light on the significant role of Zfp217 in ESC reprogramming and differentiation and the possible regulatory mechanism of ZNF217 in CSCs emergence (**Figure 4B**).

Similar to Zfp217 expression in ESCs, ZNF217 expression level is much higher in glioma stem cells (GSCs) compared with non-GSCs, and *ZNF217* mRNA levels decreased after GSCs differentiation [27]. Furthermore, under hypoxia, HIFs increase ZNF217 and AlkB homologue 5 (ALKBH5) expression to upregulate *NANOG* and *KLF4* mRNA levels in an m$^6$A manner, however, the study did not investigate the interaction between ZNF217 and METTL3 in cancer cells [122]. In both experiments, HIF1α and HIF1β target the *ZNF217* promoter and upregulate its expression (possibly through indirect binding), while ZNF217 deficiency harms CSCs emergence, suggesting that ZNF217 plays a significant role in HIFs-dependent CSC emergence [27, 122, 123]. Additionally, ZNF217 overexpression downregulates adult stem cell gene expression signature, while also causing an increased progenitor cell-like gene expression signature ($CD44^{high}/CD24^{low}$) in HMECs. This effect was also observed with the expression of luminal and myoepithelial cell markers ($K8^+K14^+$) in tumor cells [72, 124]. Moreover, Ntera2, a tumor stem cell line that can differentiate into neurons and other cell types under RA treatment, efficiently realized its pluripotent embryonal ability with the depletion of ZNF217 [61]. Apparently, these studies extended the role of ZNF217 in the regulation of stemness and suggest a possible application of ZNF217 in regenerative medicine and anti-neoplastic treatments. Nevertheless, ZNF217 role in carcinogenesis highlights the urgency in developing targeting strategies of this oncogene. Drug resistance, a lethal malignant progression that is responsible for treatment failures and patient deaths, emphasizes the importance of clinical applications that target ZNF217.

### Role of ZNF217 in drug resistance

For anti-neoplastic treatments, the usage of cytotoxic drugs, mainly causes global apoptosis, while targeted therapy antagonizes specific receptors. Both treatment methods result in a significant improvement to the outcomes of cancer patients. However, both therapies have limitations due to treatment invalidation, or drug resistance. To resolve this issue, it is essential to select patients who are more sensitive to the treatments or identify new targets that can be used for the inhibition of tumorigenesis and cancer progression. Based on the prementioned studies, ZNF217 promotes carcinogenesis in tumor tissues by triggering the activation or suppression of multiple signaling pathways. The variation usually results in an enhanced proliferation, an inhibited apoptosis, and an increased cancer heterogeneity. Thus, these cancer cells resist stresses, such as anti-neoplastic treatments. In the next section, we focus on the role of ZNF217 in drug-resistance and suggest a potential use of ZNF217 as a biomarker that predicts drug resistance and its

clinical application for the Akt-inhibitor, triciribine.

*ZNF217 and anti-apoptosis: all roads do lead to chemoresistance*

Chemotherapy is the usage of cytotoxic agents to induce apoptosis in tumor cells [125]. Cancer cells' resistance to chemotherapy is usually featured by an accelerated drug metabolism or a deficit in apoptotic signaling pathways. Besides, pre-mentioned factors, such as eEF1A2 and Bcl-$X_L$, contribute to the anti-apoptotic effect, together with other factors induced by ZNF217 and that also contribute to a decreased sensitivity to chemotherapy. The tumor suppressor gene *p53* plays a pivotal role in apoptosis, whereas its mutation or enhanced expression of the p53 inhibitor, MDM2, causes cellular defects in responding to various stresses, including chemotherapy [126]. ZNF217 overexpression forms a ZNF217/MDM2 complex which significantly reduces p53 acetylation state of p53, and directly binds to and suppresses the *CDKN1A* (encoding CDK2 and CDC2 inhibitor, $p21^{CIP1}$) promoter in H1299 cell line [79]. Furthermore, ZNF217 overexpression causes an upregulation of anti-apoptotic proteins, such as Bcl-2 and Bcl-$X_L$, and a downregulation of pro-apoptotic proteins, such as Bad, Bak and Bax, while the expression levels of these p53 downstream factors could be less varied compared with control cells when facing paclitaxel stimulation in MDA-MB-231 cells [92, 127, 128]. Thus, ZNF217 contains a comprehensive regulatory relationship with the canonical p53 signaling pathway (**Figure 5**). However, mutant p53 prevalently exists in multiple tumor masses, and whether p53 plays a significant role in ZNF217-induced drug resistance needs further study.

Distinct from the p53 signaling pathway, other factors induced by ZNF217 also contribute to chemoresistance. ZNF217 suppresses EPB41L4A-AS2, a lncRNA that inhibits tumorigenesis and induces apoptosis in breast cancer, by recruiting EZH2 to the *EPB41L4A-AS2* locus with increased H3K27me3 enrichment [64]. Aurora-A, a serine threonine kinase that regulates cell division and cell cycle progression, is co-amplified with ZNF217 in IOSEs [129, 130]. Aurora-A positively regulated by ZNF217 in MCF-7 and results in paclitaxel resistance, while Aurora-A kinase inhibitor reverses ZNF217-induced drug resistance [92]. In ovarian clear cell carcinoma (OCCC), *ZNF217* gene amplification is an independent prognostic factor for progression-free and overall survival after standard platinum agent-based chemotherapy [38]. AT-rich interaction domain 1A (ARID1A) is an epigenetic tumor suppressor, whereas its gene mutation is detected in approximately 50% of OCCC [131]. Loss of ARID1A expression is significantly related to younger patients, ZNF217 amplification and PI3K/Akt pathway activation in OCCC [132]. *ZNF217* gene amplification correlated with a decreased E-cadherin expression and an activated PI3K/Akt pathway in OCCCs [44]. Thus, a correlation between ZNF217 amplification and ARID1A mutant may contribute to OCCC progression and platinum resistance, while the abovementioned studies require evolving evidence. However, a precise relationship between the PI3K/Akt pathway and ZNF217, provides more values in clinical application.

*ZNF217 and the PI3K/Akt pathway: brothers in arms*

The PI3K/Akt pathway is a pivotal signaling pathway that plays an essential role in the proliferation and inhibition of apoptosis. ErbB3 is a member of the epidermal growth factor receptor (ErbB) family, which is associated with numerous human cancers, and which inhibition results in effective cancer therapies in cancer patients [133, 134]. ErbB3 forms heterodimers with other ErbBs, such as ErbB2 (or Her-2), and stimulates downstream signaling pathways, such as the Ras/MAPK and PI3K/Akt pathways which lead to resistance to multiple therapies, including trastuzumab, paclitaxel, and tamoxifen [135]. Therefore, ErbB3 downregulation or inactivation would be an ideal therapeutic strategy for cancer treatment, whereas ZNF217 may counteract this effect (**Figure 5**).

In breast cancer cell lines, primary human breast tumors and murine mammary tumor models, ErbB3 expression level is positively correlated with ZNF217 expression [71, 72]. ZNF217 upregulates Akt phosphorylation via increasing the transcriptional activation of ErbB3, while ZNF217 downregulation results in reduced Akt and mitogen-activated protein kinase (MAPK) phosphorylation, and ErbB3 expression in MCF-7 and ZR-75-1 cell lines [71, 72, 78]. Intriguingly, though ZNF217 and CtBPs

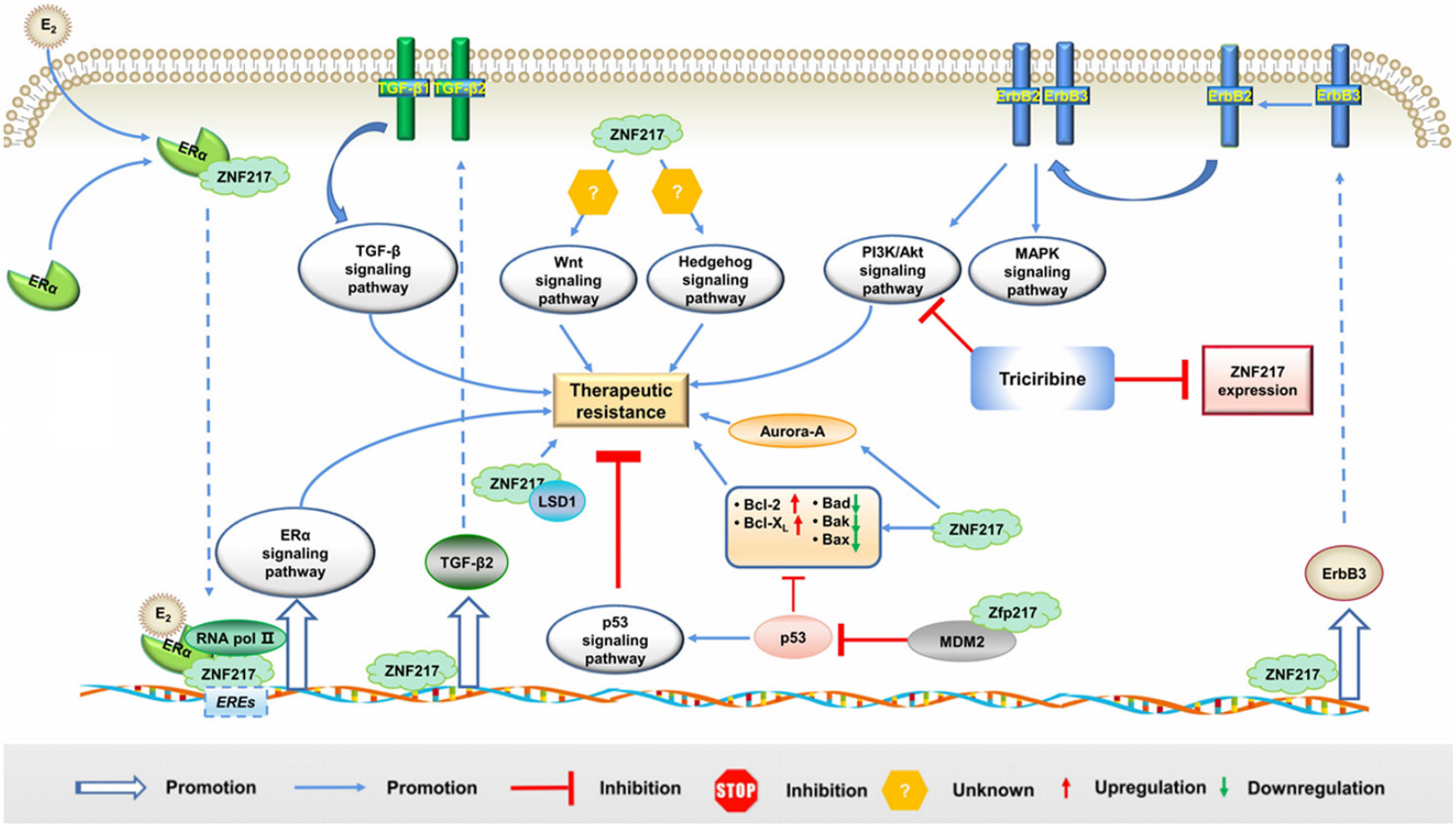


**Figure 5.** ZNF217 initiates therapeutic resistance via multiple signaling pathways. Indeed, ZNF217 induces the activation of proliferation (Aurora-A, ERα signaling pathway, PI3K/Akt signaling pathway, LSD1), heterogeneity (TGF-β signaling pathway) and apoptosis inhibition (p53 signaling pathway) which promotes stress resistance associated with treatments, such as tamoxifen, doxorubicin, paclitaxel, and trastuzumab. Other signaling pathways associated with drug resistance such as Wnt and Hedgehog pathways, would be activated by ZNF217, while whether ZNF217 induction of drug resistance through these two pathways need more studies. Attentionally, the PI3K/Akt pathway plays a significant role in ZNF217-induced drug resistance, while triciribine sufficiently reverses this event. Therefore, anti-ZNF217 treatment shows a great potency to reverse therapeutic resistance in cancer.

were both detected on the *ErbB3* promoter, these molecules acted oppositely [71]. *ErbB3* promoter shows a preservation of H3K9ac and an absence of both H3K9me3 and H3K27me2 in CtBP1/2 null MEFs [71]. Another research demonstrated that ZNF217 overexpression in the MBA-MD-231 cell line increases ErbB2 and ErbB3 expression and the phosphorylation state of the focal adhesion kinase (FAK), a core factor of the integrin associated signaling pathway that stimulate PI3K [40, 136]. Therefore, ZNF217 mainly causes an activation of the PI3K/Akt pathway and could be used as a therapeutic target.

Triciribine is an Akt inhibitor that specifically inhibits the PI3K/Akt pathway, whereas several Phase I/II clinical trials with triciribine demonstrated that a single agent therapy may not efficiently suppress tumor lesions [137-140]. Intriguingly, several studies on ZNF217 may help optimize the effect of triciribine. The combination of triciribine and doxorubicin reverses ZNF217 expression and ZNF217-induced doxorubicin resistance in breast cancer [72]. Furthermore, treatment order critically impacted the effectiveness of triciribine. Zfp217-transfected mice breast cancer cells resisted EAC treatment (microtubule inhibitor epothilone B, doxorubicin, and cyclophosphamide), while treatment with triciribine, followed by paclitaxel treatment (TCN→PAC), is more efficient than treatment with paclitaxel, followed by triciribine treatment (PAC→TCN), and which led to a decrease in tumor burden, CSCs population and an increase of survival in mice with Zfp217-transfected tumors [113]. More importantly, Zfp217-transfected tumors show a decreased microvessel density and a higher percentage of $CD31^+$ (endothelial cell marker) $SMA^-$ (muscle and pericyte cell marker α-smooth muscle actin) vessels, while these vessels become more maturation ($CD31^+SMA^+$) after TCN→PAC treatment [113]. Similar phenomena could be detected in xenograft tumors from ZNF217-overexpressed patients [113]. Without combination with chemotherapy, triciribine abrogated stiff collagen matrix induced mammary epithelial cell proliferation and Akt activity *in vivo* [50]. It is worth noting that studies demonstrated that ZNF217 inhibition causes a decreased Akt phosphorylation and *vice versa*, suggesting the existence of a potential regulatory loop between ZNF217 and the PI3K/Akt signaling pathway [52, 53, 72, 78]. Moreover, the PI3K inhibitor, LY294002, reversed lnc-ATB-induced upregulation of ZNF217 in prostate carcinoma [53]. Thus, the usage of PI3K/Akt inhibitors may increase the efficiency of an anti-ZNF217 treatment.

*ZNF217 and ER: undermining endocrine therapy*

$E_2$, which is synthesized by ovaries and aromatase, mainly induces the activation of ERα and downstream signaling pathway and promotes the progression of ER positive ($ER^+$) breast cancer [141-143]. For decades, ER antagonists were used in basic applications to treat $ER^+$ breast cancer, whereas endocrine-treatment-resistant $ER^+$ breast cancer remains a challenge. As mentioned before, ZNF217 acts as an anti-stress factor that threatens the survival of cancer cells. $E_2$ suppression of ZNF217 expression in breast cancer cell lines, whereas fulvestrant promotes it, also corroborate this hypothesis [48, 49]. Indeed, ZNF217 participates in the maintenance of ERα signaling regardless of $E_2$ presence (**Figure 5**).

In breast cancer, a precise study of ZNF217 chromatin occupancy, identified binding sites of five transcription factors (TCF7L2, NR2F2, GATA3, FOXA1 and ERα) that overlapped with ZNF217, while *in vitro* experimental analysis showed that the expression of genes targeted by ZNF217-ERα, correlated with the progression of multiple malignancies [81]. Significantly, ZNF217-ERα interaction could be detected either in the nucleus and/or cytoplasm of breast cancer cells, indicating that ZNF217 may regulate ERα transcriptional or posttranscriptional function [74]. The C-terminus of ZNF217 physically binds to ERα hinge domain and enhances its recruitment to estrogen response elements (EREs), which triggers the activation of downstream processes, such as growth regulation by estrogen in breast cancer 1 (*GREB1*), an estrogen-responsive gene associated with hormone dependency in cancer, while ZNF217 knockdown results in a significant increase in sensitivity to endocrine therapy [74, 144]. Moreover, a recent study demonstrated that ZNF217 interacts with LSD1 to promote the survival of prostate cancer cells, including those that are castration-resistant, independently of its demethylase function and androgen receptor [145]. Thus, a consolidated relationship between ZNF217 and endocrine

therapy resistance may lead to potential clinical applications.

Several studies investigated ZNF217 characteristics in breast cancer and led to the following conclusions: 1) ZNF217 expression is consistently high in luminal, and low in basal subtype tumors; 2) A high ZNF217 expression is associated with poor prognosis in Luminal, $ER^-$ $HER2^+$, and basal tumor subtypes; 3) A high level of *ZNF217* mRNA expression in primary lesions is consistently associated with a shorter recurrence-free survival (RFS) in $ER^+$/$Her\text{-}2^-$/LN0 breast cancer patients, who received adjuvant and neoadjuvant endocrine therapies; 4) The most powerful prognostic value of ZNF217 is observed in the Luminal-A subgroup [42, 72, 74, 81]. Moreover, ZNF217 showed a better predictive efficiency than the 21-Gene Expression Assay in $ER^+$ breast cancer (a small cohort, n=48, warrant further study), which is used to predict adjuvants' chemotherapy benefit to patients [146, 147]. Compared with other subclasses of breast cancer, *ZNF217* mRNA expression level is informatively associated with bone-metastases in $ER^+$ subclasses [111]. According to the results, clinical databases highlight the role of ZNF217 in predicting breast cancer response to endocrine therapy. Therefore, ZNF217 contributes to the progression, endocrinotherapy-resistance, and development of bone metastatic lesions in $ER^+$ breast cancer, suggesting that ZNF217-monitoring or anti-ZNF217 treatment should be considered as an alternative scheme for Luminal A breast cancer treatment. Overall, ZNF217 shows an ability to protect cancer cells from various therapeutic stresses.

## The role of ZNF217 in diseases other than cancer

We dedicate a significant portion of this review to the role of ZNF217 in promoting the progression and therapeutic resistance of malignant tumors. Additionally, the process of ZNF217-induced immortalization is similar to that of the progression from usual ductal hyperplasia to ductal carcinoma in breast cancer [148]. Moreover, stiffer periductal stroma increases ZNF217 expression in high mammographic density breast tissue [50]. These phenomena imply that ZNF217 aberrant expression may be an early event in the pathological transformation of normal tissues. Here, more observations highlight the significant role of ZNF217/Zfp217 in the pathogenic process of noncancer diseases. The regulatory landscape of this oncogene in diseases may help expand the role of ZNF217 in organisms.

### *Zfp217 and adipogenesis: when oncogene meets metabolic diseases*

Obesity, an excess bodyweight state featured by increased adipose tissues, has been proved to be associated with metabolic diseases and cancer [149]. There exist two ways that increase adipose depots: hypertrophy (increasing adipocyte size) or hyperplasia (generation of new adipocytes from preadipocytes via adipogenesis). Adipogenesis is a complicated process that is regulated by various signaling hormones and ligands and is associated with liposarcomas [150]. Moreover, an aberrant adipocyte metabolism contributes to a more aggressive tumor microenvironment that promotes breast cancer progression [151]. Interestingly, ZNF217 expression is significantly upregulated by beef tallow dietary, a fatty acid associated with cancerogenic properties, such as increased occurrences of colorectal cancer [152]. Furthermore, an indispensable role of Zfp217 in adipogenesis has been unveiled in several recent studies that suggested a novel function of ZNF217 in adipocytes' metabolism (**Figure 4C**).

Unlike in ESCs, Zfp217 expression level is concomitantly upregulated during adipogenesis and positively correlated with Pparg2 expression in pre-adipocytes [75, 153, 154]. The absence of Zfp217 decreases mRNA expression levels of adipocyte marker genes and key adipogenic transcription factors, as well as harms the formation of lipid droplets, especially white adipocyte phenotype droplets, resulting in obesity [153, 154]. Additionally, Zfp217 constrains more adipocytes into G1 phase to suppress their proliferation, and interacts with EZH2, which may contribute to the upregulation of the Wnt signaling pathway to facilitate adipogenesis, whereas microRNAs impair adipocytes' differentiation via *Zfp217* mRNA targeting [154]. However, for cell cycle regulation, another study demonstrated an opposite result and showed that the absence of Zfp217 causes an upregulation of METTL3 expression and a decreased level of *CCND1* mRNA (**Figure 2**), resulting in an increased $m^6A$ level that was

recognized and decayed by YTH domain family 2 (YTHDF2, an $m^6A$ reader protein) [153]. Additionally, a specific interaction and co-localization between Zfp217 and YTHDF2 were observed in the nucleus and cytoplasm, while a delayed adipogenesis that was induced by Zfp217 depletion, could be rescued by YTHDF2 knockdown in pre-adipocytes [75]. At the transcriptional level, Zfp217 directly activates Fat mass- and obesity-associated gene (*FTO*) promoter to upregulate FTO expression, which contributes to the promotion of adipogenesis, while a direct competition between FTO and YTHDF2 in $m^6A$ regulation has been confirmed [75]. Thus, the abovementioned findings suggest that Zfp217 directly stimulates FTO transcription and sequesters YTHDF2 to maintain the $m^6A$ demethylation activity of FTO. It is worth noting that FTO is a canonical obesity gene, which also plays a significant role in carcinogenesis [155-157]. Therefore, the significant role of Zfp217 in adipogenesis sheds light on the function of ZNF217 in adipocyte metabolism related to malignant tumors.

*ZNF217 and PCOS: the safest place turns into dangerous*

Polycystic ovary syndrome (PCOS) features reproductive endocrine abnormalities in women. PCOS correlated with patients' increased obesity and was characterized by an elevated secretion of androgens (hyperandrogenemia) compared with an increased/decreased estrogen, while androgen is a suppressive factor in gynecologic cancers. However, PCOS is associated with an increased risk of gynecologic tumors, such as endometrial, uterine, ovarian, and breast cancers [158-161]. Moreover, treatments, such as oral contraceptive (OC) in PCOS, may promote the development of premenopausal breast cancer [162]. A recent study using Genome-wide association studies (GWAS) identified several PCOS candidate loci, including ZNF217 in PCOS, which are vulnerable to ovarian hyperstimulation syndrome (OHSS), an overreaction to ovulation treatment that is commonly used in PCOS treatment [163]. Further research showed that the ZNF217 overexpression can be detected in ovarian granulosa cells in high risk OHSS patients and mice [164]. *In vitro* experiments showed that of ZNF217 overexpression promotes $E_2$ synthesis through the upregulation of the cAMP response element binding protein (CREB) and aromatase, and negatively regulates TSP-1, causing a suppression of vascular permeability [164]. Moreover, ZNF217 was decreased in the granulosa cells from PCOS-like mice (treated by dehydroepiandrosterone) and women with polycystic ovary syndrome, while ZNF217 suppressed cyclooxygenase 2 (COX2) and Prostaglandin E2 (PEG2) syntheses that were inhibited by PGE2 to form a feedback loop *in vitro* [165]. Therefore, according to the previous section reports, ZNF127 may be a significant factor that connects obesity and breast cancer, while the positive relationship between ZNF217 and $E_2$ synthesis, and the negative relationship between ZNF217 and the inflammation factor PGE2, may contribute to the tumor microenvironment.

*ZNF217 and Barrett's esophagus: more work to do*

Barrett's esophagus (BE) is the pre-malignant histological precursor of esophageal adenocarcinoma (EAC). The identification of BE and early stage of EAC should improve the outcomes of patients with dysplasia and who are at high risk of malignant progression [166]. However, BE diagnostic features still trigger debates. Recent studies demonstrated ZNF217 value in predicting EAC risk in BE. ZNF217 gene amplification could be detected in adenocarcinomas of the gastroesophageal junction [20, 167] and detected and associated with response to endoscopic therapy in BE [168-170]. Moreover, increased *HER-2*, *CDKN2A*, *c-MYC* and *ZNF217* copy numbers that were detected by fluorescence in situ hybridization (FISH) probes, could be used to predict high-grade dysplasia and the development of high risk EAC in BE patients [31-33]. Interestingly, HER-2, CDKN2A and c-MYC contain regulatory associations with ZNF217. Thus, based on the phenomena that are induced by ZNF217 in pre-malignant breast tissues, there exists a high interest in uncovering the oncogenicity of ZNF217 in BE.

*ZNF217 and Alzheimer's disease: fuel inflammation*

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the accumulation of β-amyloid (Aβ) plaques that lead to a cognitive decline [171]. With the increased concentration, maturation, and expansion, Aβ triggers

multiple pathological events that accelerate the progression of AD. Intriguingly, ZNF217 participates in Aβ-induced cell injury. Aβ-induced neurotoxicity significantly inhibited viability and induced apoptosis via the lncRNA-ATB/miR-200/ZNF217 axis in PC12 cells [172]. Moreover, the lncRNA-SNHG1/miR-361-3p/ZNF217 axis was positively regulated by Aβ [173]. It is worth noting the two studies showed that pathogenic factors induced by Aβ, could be influenced by ZNF217 knockdown, such as decreased inflammatory responses (TNF-α, IL-1β, IL-6 and Malondialdehyde) and oxidative stress (Superoxide dismutase, SOD) [172, 173]. According to the discovery in AD, a relationship between ZNF217 and inflammation has been unveiled and may contribute to investigating the role of ZNF217 in tumoral immune response.

Although attacks from immunocytes are effective in eliminating tumor cells, immune escape that is associated with tumors' heterogeneity, significantly affects this response. Thus, cancer immunotherapy attracts more attention. For instance, targeted therapies, such as trastuzumab prevents the activation of the HER-2-dependent cell signaling pathway and induces antibody-dependent cell-mediated cytotoxicity. Immune checkpoint inhibitors and oncolytic viruses also contribute to solid tumors' immune sensitivity. Though no research showed a role of ZNF217 in tumoral immune escape, this could be enlightened by the regulatory network induced by ZNF217. For instance, TGF-β contributes to the immune exclusion and a lack of immunogenicity in tumor masses [174]. FTO is associated with the response to anti-programmed death-1 (PD-1) blockade, while the inhibition of FTO attenuates self-renewal and reprograms immune response in CSCs [175, 176]. Moreover, *ZNF217* aberrant gene amplification may be associated with a more favorable response to PD-1 blockade in primary mediastinal large B-cell lymphomas (PMBL) [177]. Thus, the oncogene ZNF217 inclines to compose variations of immune microenvironment and immunogenicity that impact cancer progression.

## Conclusion

In this review, we discussed the role of ZNF217 in various and significant cancer processes, such as somatic immortalization, cell cycle acceleration, heterogeneity formation and inhibition of apoptosis. ZNF217 also possesses a huge transcriptional, post-transcriptional and post-translational regulatory network. It is worth noting that ZNF217 interacting factors that co-occupy gene promoters are mostly gene suppressors. Though some studies demonstrated a transcriptional activator role of ZNF217, the precise mechanism has yet to be unveiled [71]. Interestingly, ZNF217/Zfp217 also plays a significant role in $m^6A$ regulation, which is the most prevalent internal modification on eukaryotic mRNAs and that alters mRNA activity to regulate target gene expression and that plays a significant role in carcinogenesis [122, 157, 178]. Hence, it is possible that ZNF217 transcriptionally suppresses gene expression, while also post-transcriptionally stimulates mRNA translation to control gene expression and promote malignant phenotypes.

When ZNF217 fulfills its function, cells seem to acquire an ability to resist several types of stresses, which impedes their cell growth and survival. The role of ZNF217 in drug resistance suggests that its presence is a guarantee of normal cellular processes in somatic cells, while in malignancy, it impedes anti-neoplastic treatments. Thus, anti-ZNF217 treatments, including miRNA, triciribine and others, may constitute an alternative anti-neoplastic treatment strategy.

Early diagnosis and individualized treatment feature the most effective way to reduce cancer mortality. Here, we highlighted the value of ZNF217 as a biomarker that predicts treatments' sensitivity and outcomes in pre-malignant and cancer patients. ZNF217 may be a biomarker for CDK4/6 or other CDKs inhibitors. The Akt inhibitor, triciribine, reversed ZNF217 mediated drug resistance, while ZNF217 could act as a biomarker for the designation of future triciribine clinical trials. For breast cancer induced bone metastasis, ZNF217 expression level could be used to select specific anti-BMP drugs for further clinical trials. More importantly, the ZNF217 regulatory network may contribute to immune escape in cancer cells. Therefore, monitoring ZNF217 may contribute to the precise selection of therapeutic regimen.

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## Disclosure of conflict of interest

None.

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