#### REVIEW

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## ZNF217: An Oncogenic Transcription Factor and Potential Therapeutic Target for Multiple Human Cancers

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**Abstract:** Zinc finger protein 217 (ZNF217) is one of the well-researched members of the Krüppel-like factor transcription factor family. ZNF217 possesses a characteristic structure of zinc finger motifs and plays a crucial role in regulating the biological activities of cells. Recent findings have revealed that ZNF217 is strongly associated with multiple aspects of cancer progression, impacting patient prognosis. Notably, ZNF217 is subject to regulation by non-coding RNAs, suggesting the potential for targeted manipulation of such RNAs as a robust therapeutic avenue for managing cancer in the future. The main purpose of this article is to provide a detailed examination of the role of ZNF217 in human malignant tumors and the regulation of its expression, and to offer new perspectives for cancer treatment.

Keywords: oncogene, regulation, non-coding RNA, targeted therapy

### Introduction

Cancer is a major public health challenge worldwide with significant morbidity and mortality.<sup>1–3</sup> Carcinogenesis is a complex multi-stage process in different signaling pathways.<sup>4,5</sup> The identification of specific biomarkers for multiple tumors could facilitate early detection and personalized therapy, which may improve the prognosis and survival of cancer patients by reducing the risk of tumor recurrence, metastasis, and drug resistance.<sup>6,7</sup> However, the efficacy of anti-tumor therapy is not always guaranteed due to the heterogeneity and complexity of tumor biology and the variability of patient response.<sup>8,9</sup>

The ZNF217 protein is a member of the Kruppel-like family of transcription factors and contains eight predicted C2H2 zinc finger motifs, as well as a region rich in proline.<sup>2</sup> The ZNF217 gene is located on chromosome region 20q13, which is frequently amplified in multiple types of human cancers.<sup>10</sup> Moreover, ZNF217 amplification may provide selective advantages to cancer cells.<sup>11</sup> Recent evidence suggests that ZNF217 has been implicated in regulatory functions of gene expression across diverse cancer types, leading to increased cell proliferation, invasion, and metastasis, as well as inhibition of apoptosis.<sup>12</sup> Therefore, ZNF217 represents a promising target for molecular targeted therapy, although further research is required to fully elucidate its mechanisms of action.

Amplifications of DNA are a common occurrence in human cancers, resulting in elevated gene expression levels.<sup>4</sup> These amplified segments often contain oncogenes, which could provide host cells with increased proliferative and/or survival advantages. In 1998, Collins<sup>13</sup> and his team achieved a significant breakthrough by cloning a 1-Mb section of chromosome 20q13, wherein they discovered a ~260 kb segment that was frequently amplified in breast tumors. The team also identified a novel gene, ZNF217, located within this amplified segment. Amplifications involving human chromosome 20q13 are commonly detected in multiple types of cancer, including breast cancer,<sup>14,15</sup> polycystic ovary

syndrome,<sup>16</sup> ovarian cancer,<sup>17–20</sup> gastric,<sup>21</sup> prostate,<sup>22,23</sup> esophagus,<sup>24</sup> pancreatic,<sup>25</sup> and colorectal carcinomas,<sup>26–28</sup> glioblastoma,<sup>29</sup> hepatoma,<sup>30</sup> lung cancer,<sup>31</sup> lymphoma,<sup>32</sup> Barrett's esophagus,<sup>33–35</sup> head and neck squamous cell carcinoma,<sup>36</sup> osteosarcoma,<sup>37</sup> and melanoma.<sup>38</sup>

The transcription factor known as ZNF217 has been identified as a potential oncogene located within the amplicon on chromosome 20q13, which is found in multiple types of primary human tumors and has been linked to a negative prognosis.<sup>13,20,28,30,39</sup> Additionally, ZNF217 is not restricted to the nucleus, as multiple studies have demonstrated that it interacts with proteins in both the nucleus and cytoplasm to regulate various phenotypes.<sup>37,40,41</sup> ZNF217 is involved in regulating multiple characteristics of cancer cells, including persistent signals for cell proliferation, circumvention of growth-inhibiting factors, continuous replication, resistance to cell apoptosis, promotion of cancer stem cell populations, and initiation of invasion and metastasis.<sup>42</sup> (Figure 1) The mechanism underlying the relationship between ZNF217 and cancer is complex.

Although only a few direct target genes of ZNF217 have been officially identified, these genes play a crucial role in controlling tumor progression and cancer cell plasticity.<sup>43</sup> For instance, ZNF217 activates the PI3K/AKT pathway, thereby increasing the expression of the oncogene C-Myc, and modulates genes associated with epithelial-mesenchymal transition to promote cell migration, invasion, and growth in glioma cells.<sup>44</sup> Additionally, implanting breast gland tumor cells that express ZFP217 into the breast adipose tissue of immune-compromised mice has been shown to increase tumor burden.<sup>45</sup> Apart from what has been discussed above, the inhibition of ZNF217 has been shown to impede the growth of liver cancer cells in both laboratory experiments (in vitro) and living organisms (in vivo).<sup>30</sup> This evidence strongly suggests that ZNF217/ZFP217 is pro-oncogenic. A comprehensive understanding of the regulatory mechanisms of tumorigenesis will lead to new and more effective treatment strategies. However, successful anti-tumor treatment is often hindered by the stage of cancer progression and the development of drug resistance. Therefore, it is crucial to find ways to overcome these obstacles.<sup>46</sup> It is necessary to gain a deeper understanding of the functions of ZNF217 to explore potential treatment options based on ZNF217.



Figure I ZNF 217 plays a role in cancer and other diseases through specific pathways with different expression levels. Created with BioRender.com.

## Effect of ZNF217 on N6-Methyladenosine Modification

As widely acknowledged, tumor formation is a complex biological phenomenon that involves various factors related to genomics and epigenetics.<sup>42</sup> Epigenetic alterations include DNA methylation, histone modifications, RNA modifications, and non-coding RNA.<sup>47,48</sup> Among these, N6-methyladenosine (m6A) is the most prevalent biochemical modification for mRNA, and it plays a crucial role in RNA metabolism, including mRNA stability, translation, splicing, export, and folding.<sup>49</sup> m6A is introduced by "writer" proteins belonging to a methyltransferase complex that consists of the methyltransferase-like 3 catalytic subunit (METTL3) as the catalytic subunit, as well as other accessory subunits, including METTL14.<sup>49</sup> However, emerging research suggests that abnormal m6A modification is strongly linked to cancer and leads to cancer progression.<sup>50,51</sup> Additionally, decreased expression of METTL3, increased expression of AlkB Homolog 5 (ALKBH5), or dysregulated regulation of YTH domain-containing protein family (YTHDF)2 have been linked to unfavorable prognoses in multiple cancer types.<sup>50,52</sup> ZFP217 interacts with METTL3 to inhibit m6A RNA modification, while low levels of m6A in transcripts related to embryonic stem cells (ESCs) allow for the regulation of ESC pluripotency and somatic cell reprogramming.<sup>53</sup>

## ZNF217 Affects the Expression of Oncogenes

ZNF217 is a protein with approximately 1000 residues and has been identified as a candidate cancer protein. ZNF217 contains seven predicted classical zinc fingers, found in two clusters of the N-terminal half of the protein. A recent report indicates that clusters containing zinc finger 6 and 7 (ZNF217F67) can bind to double stranded DNA.<sup>54</sup> DNA methylation status is a well-known process catalyzed by DNA methyltransferases (DNMTs) and recycled during active demethylation by the 10–11 translocation (TET) family of enzymes. DNA methylation primarily adds a methyl group to DNA at the 5-carbon position of cytosine (5mC) and occurs almost exclusively in the context of CpG dinucleotides.<sup>11</sup> An increasing number of studies indicate that epigenetic processes control ZNF 217/Zfp 217 expression levels and ZNF 217/Zfp 217-driven functions. Indeed, deregulation of the DNA methylation status of the ZNF 217 locus or complex crossalk between the ZNF 217 locus and the non-coding RNA network could explain the abnormal upregulation of ZNF 217.<sup>49</sup>

ZNF217 was initially described as a transcriptional inhibitor,<sup>11</sup> but further research has shown that it can also have a harmful effect by positively regulating specific gene expression programs.<sup>55</sup> These findings demonstrate that ZNF217 is a dual-function transcription factor. Additionally, ZNF217 promoter methylation has been found to have an inverse correlation with its expression at the transcriptional level. A comprehensive genome-wide analysis of glioblastoma has shown that DNA methylation decreases its expression.<sup>42</sup> Research has demonstrated that ZNF217 exerts regulatory control over the expression of its target genes via its ability to bind to distinct DNA sequences in a specific manner.<sup>56</sup> Furthermore, studies have revealed that ZNF217 could activate certain promoters, such as the ErbB3 promoter in MCF-7 and mouse embryonic fibroblasts (MEFs) as well as mesenchymal genes including SNAIL1, SNAIL2, and Vimentin<sup>43,57,58</sup> (Figure 2). To fully comprehend the pathogenesis mediated by ZNF217/ZFP217, it is crucial to recognize that the level of expression of ZNF217/ZFP217 is influenced not only by gene duplication but also by promoter region methylation and miRNA regulation.<sup>44</sup> As of yet, no reports have indicated any modifications of the ZNF217 protein. However, we obtained the post-translational modification sites(PTM) map of ZNF217 through the PhosphoSitePlus database. As shown in the figure, the most common post-translational modification type of ZNF217 is phosphorylation modification (Figure 3).

## The Effect of ZNF217 on the Proliferation of Cancer Cells

During the biological development process, cells undergo limited proliferation through periodic cell cycles. Telomeres are conservative structures composed of nucleoproteins that can be found at the tips of linear chromosomes in eukaryotes.<sup>59</sup> Telomeres play a crucial role in cell division. In fact, due to the inability of DNA polymerase to complete the complete replication of linear chromosome ends, telomeres gradually shorten with the continuous division of somatic cells until reaching the critical length, and cells exit the cell cycle and experience aging or apoptosis.<sup>60,61</sup> In a serum-free medium, some human mammary epithelial cells(HMECs) spontaneously proliferate without expressing p16 (INK4a). These HMECs could undergo prolonged proliferation but eventually reach growth arrest when telomeres become



Figure 2 Interactions between ZNF217 and other genes.



Figure 3 Post-translational modifications of ZNF217. (This figure is cited from the PhosphoSite Plus database).

critically short.<sup>62</sup> Telomeric repeat-binding factor 2 (TRF2), telomerase expressed in immortalized HMECs, protects telomeres and potentially enhances telomere stability via ZNF217.<sup>63</sup> Meanwhile, aberrant expression of ZNF217 is highly likely to trigger unlimited growth and uncontrolled proliferation, leading to cancer, by circumventing the activation mechanism of progressive telomere shortening. Additionally, some studies suggest that abnormal ZNF217 expression downregulates differentiation-associated genes, resulting in cell dedifferentiation and promoting development toward a more proliferative and pluripotent phenotype.<sup>56</sup>

Another study showed that the tumor suppressive role of P15 (ink4b) is mediated through the inhibition of cellular progression from the G1 to the S phase of the cell cycle,<sup>64</sup> and the ZNF217/CoREST transcription complex has been identified as a direct regulator of the P15 (ink4b) tumor suppressor gene.<sup>65</sup> This complex suppresses the transcription of the p15ink4b gene by recruiting DNMT3A DNA methyltransferase and causing hypermethylation of the promoter region.<sup>66</sup> Notably, ZNF217 overexpression could impair TGF- $\beta$ -dependent anti-proliferative programs by hindering the recruitment of cofactors responsible for the active demethylation of p15ink4b.<sup>67</sup> Disruption of the TGF- $\beta$  pathway is thought to promote early malignant development by enabling cancer cells to evade the growth-inhibitory effects of TGF- $\beta$ .<sup>67,68</sup> Thus, the observed changes in DNA methylation patterns in specific genes, such as p15ink4b, are involved in the dismantling of ZNF217-dependent anti-proliferative signaling in early tumorigenesis. Additionally, ZNF217 upregulates elongation factor 1- $\alpha$  2 (eEF1A2), which is co-located with ZNF217 at the 20q13 locus during the process of immortalization. Conversely, silencing eEF1A2 reverses ZNF217-transduced immortalization in immortalized ovarian surface epithelial cells (IOSEs)<sup>17</sup> (Table 1).

### The Effect of ZNF217 on Tumor Invasion, Migration, and Metastasis

The acquisition of EMT not only increases the metastatic potential of cancerous cells but also enhances the likelihood of relapse after surgery.<sup>69</sup> One study found that overexpression of ZNF217 results in a significant rise in both EMT and invasion of hepatoma cells.<sup>30</sup> ZNF217 suppresses gene expression through both direct and indirect methods. For instance, E-Cadherin is suppressed by two mechanisms: direct binding of ZNF217 to the proximal promoter and recruitment of the CtBP co-repressor complex. This ultimately leads to the promotion of cancer cell migration, invasion, and anchorage-independent growth.<sup>45</sup> Recent research has revealed that ZNF217 has the potential to promote the growth of metastatic

| Tumor or Cell                                   | Changes of ZNF217 | Key Result   | References |
|---|-------------------|--|------------|
| Human breast tumor                              | Upregulated       | ZNF217 stimulates metastatic bone growth in breast cancer by modulating the bone morphogenetic protein (BMP) signaling pathway.  | [14,15]    |
| Immortalized ovarian<br>surface epithelial cell | Upregulated       | ZNF217 acts early in ovarian tumor progression through upregulation of EEF1A2 to promote tumor cell immortalization.   | [17]       |
| Hepatocellular carcinoma                        | Upregulated       | ZNF217 inhibits the expression of CDH1 by recruiting LSD1, thereby affecting the synthesis of E-cadherin and promoting tumor EMT.  | [30]       |
| Osteosarcoma                                    | Upregulated       | ZNF217 promotes osteosarcoma development and in situ growth and metastasis<br>through the regulation of an oncogene network regulated by activation of the PI3K-<br>AKT signaling pathway. | [37]       |
| Human breast tumor                              | Upregulated       | ZNF217 drives overexpression of erbB3 and leads to activation of AKT and MAPK pathways, thereby promoting tumor growth and chemoresistance.  | [57,58]    |
| Human mammary<br>epithelial cell                | Upregulated       | ZNF217 inhibits tumor cell apoptosis by promoting overexpression of telomerase TRF2 and maintaining telomere stability.  | [63]       |
| Human breast tumor                              | Upregulated       | ZNF217 accelerates the proliferation of tumor cells by negatively regulating the expression of P15 (ink4b) tumor suppressor.   | [65,66]    |

 Table I Regulatory Effect of ZNF217 Expression on Cancer Progression

bone and facilitate the formation of osteolytic lesions in breast cancer by modulating the bone morphogenetic protein (BMP) signaling pathway.<sup>14,15</sup> Furthermore, data suggest that the treatment of osteosarcoma cell lines expressing ZNF217 with inhibitors that specifically target the PI3K-AKT signaling pathway leads to potent cytotoxic effects in vitro.<sup>37</sup> ZNF217 regulates osteosarcoma development and in situ growth/metastasis in part by activating an oncogene network regulated by the PI3K-AKT signaling pathway. Significantly, targeting the PI3K-AKT signaling axis with the small molecule AKT inhibitor triciribine holds great potential for the treatment of osteosarcoma, and ZNF217 is part of a feedforward loop involving PI3K–AKT signaling.<sup>37</sup> (Table 1) These studies highlight the significant regulatory role that ZNF217 plays in the process of tumor invasion and metastasis.

## ZNF217 Specific Role and Biomarker Value in Cancer

The initial study on the ZNF217 gene revealed that breast tumor specimens had higher levels of ZNF217 transcription than their respective normal epithelial cell counterparts.<sup>13</sup> Additionally, increased ZNF217 expression was linked to the proliferation, metastasis, apoptosis, and drug resistance in breast cancer. ZNF217 mRNA levels could serve as a powerful and novel biomarker for predicting patient response to chemotherapy and determining outcome-dependent subgroups in breast cancer. It is noteworthy that in breast cancer studies, the immunohistochemistry (IHC) ZNF217 index is defined through the utilization of nuclear as well as cytoplasmic ZNF217 staining.<sup>70</sup> Nuclear staining has confirmed the transcriptional regulator effect of ZNF217, which was also observed in several cellular models upon ZNF217 overexpression.<sup>71</sup> However, the function of ZNF217 in cytoplasm remains unclear. In conclusion, the evaluation of ZNF217 protein biomarkers in cancer samples is complex but crucial.

## Effects of ZNF217 on Drug Resistance to Cancer

Chemotherapy, which utilizes cytotoxic drugs to trigger tumor cell apoptosis, is a treatment modality.<sup>72</sup> Although cytotoxic drugs and targeted therapy have greatly enhanced the prognosis of cancer patients as anti-tumor therapies, their efficacy is hampered by treatment inefficacy and drug resistance. To improve treatment outcomes, it is critical to identify patients who are more responsive to treatment and to discover novel targets to impede tumorigenesis and cancer progression. ZNF217, along with factors such as eEF1A, induces an anti-apoptotic effect, resulting in reduced sensitivity to chemotherapy.<sup>73</sup> The p53 gene acts as a tumor suppressor by regulating apoptosis in cells.<sup>74</sup> However, mutations in the p53 gene or increased expression of its inhibitor MDM2 could cause defects in cells' response to chemotherapy.<sup>74</sup> The overexpression of ZNF 217 leads to the formation of the ZNF 217/MDM2 complex, which significantly reduces the acetylation level of p53.<sup>75</sup> This complex also binds to and restricts the promoter of CDKN1A, which encodes p21 (CIP1), an inhibitor of CDK2 and CDC2, in the H1299 cell line.<sup>75</sup> Therefore, ZNF217 may play an important role in the resistance of tumors to chemotherapy. However, mutant p53 is prevalent in a variety of tumor tissues, and it is unclear whether p53 plays a crucial role in ZNF217-triggered drug resistance and warrants further investigation.

## The Role of ZNF217 in Tumor-Targeted Therapy

For cancer treatment, targeted therapy has led to significantly improved outcomes for cancer patients. Given that cancer initiation and maintenance are driven by several genetic abnormalities affecting oncogenes or tumor suppressor genes, targeting these oncogenic pathways represents a promising approach for impeding tumor progression. Selectively targeting cancer cells remains a major challenge in cancer therapy. To overcome this challenge, it is crucial to identify novel targets that can inhibit tumorigenesis and cancer progression. A study investigated the genotype-phenotype correlation of ovarian cancer cells using ZNF217 siRNA. The study found that ovarian clear cell carcinoma (OCCC) with ZNF217 amplification was more susceptible to growth inhibition and apoptosis induction caused by ZNF217 siRNA.<sup>18</sup> As mentioned previously, ZNF217 is known to promote cancer and has been identified as an oncogene. Additionally, targeting ZNF217 directly or targeting BMP signaling has shown to have increased potential in managing the risk of further bone metastases in ZNF217-positive breast cancer.<sup>14</sup> Recent studies have demonstrated the therapeutic potential of targeting the PI3K-AKT signaling axis in ZNF217-positive and active PI3K-AKT osteosarcoma by using the small-molecule AKT inhibitor triciribine.<sup>37</sup> Research has shown that inhibiting ZNF217 and the PI3K/Akt signaling

pathway.<sup>59,76</sup> Furthermore, the PI3K inhibitor LY294002 has been found to reverse the upregulation of ZNF217 induced by lnc-ATB in prostate cancer. Therefore, using PI3K/Akt inhibitors may enhance the effectiveness of anti-ZNF217 treatment.

The aforementioned studies demonstrate the significant potential of ZNF217 in targeted tumor therapy. Despite the absence of direct ZNF217-targeting drugs, inhibitors that target genes or pathways linked to ZNF217 hold promise as a future treatment in vivo or clinical trials. Additionally, as this review expresses, non-coding RNAs (ncRNAs) are vital regulators in the development and advancement of multiple cancers.<sup>77</sup> Hence, research on ncRNAs is also highly significant for forthcoming cancer therapies.

# Regulation of the Expression Level of ZNF217 and Its Subsequent Driving Function by Non-Coding RNA

Genes transcribed into non-coding RNA (ncRNA) make up the majority of human genes and are categorized based on their length, shape, and location. The four main types of ncRNA are long stranded ncRNA (lncRNA), microRNA (miRNA), circular RNA (circRNA), and PIWI interacting RNA (piRNA), which all have different functions in cancer. While there is currently no reported evidence of a relationship between ZNF217 and piRNA, we will discuss ZNF217's association with three other mRNAs separately during tumorigenesis. This section reviews literature data on the formal validation of miRNA binding to ZNF217/Zfp217 mRNA and its impact on molecular events controlled by ZNF217/Zfp217. Some of these validated miRNAs were sponged by specific lncRNAs or circRNAs, revealing the complex ceRNA/miRNA/ZNF217 axis that controls ZNF217 expression levels and downstream ZNF217-dependent functions.<sup>49</sup> These ncRNAs are essential regulators in the onset and progression of multiple cancers,<sup>77</sup> and some of them may serve as new markers and therapeutic targets for cancer treatment in the future.

### Long Non-Coding RNA Regulates the Expression of ZNF217

Long non-coding RNAs (lncRNAs) are a vast group of transcripts that do not code for proteins (approximately 55,000 human genes). They participate in the regulation of gene expression through multiple functions.<sup>78,79</sup> At the posttranscriptional level, lncRNAs have a significant function in controlling the expression of ZNF217. Specifically, lncRNAs promote the expression of ZNF217. For example, studies have demonstrated that the long non-coding RNA CTBP1-AS2 promotes cervical cancer progression by upregulating ZNF217 expression through sponge miR-3163 activity.<sup>80</sup> Conversely, research has also shown that OIP5-AS1 acts as a competitive RNA molecule by absorbing miR-137, which in turn increases ZNF217 expression and exacerbates malignant activities in epithelial ovarian cancer (EOC).<sup>81</sup> Additionally, the long non-coding RNA induced by Transforming Growth Factor β (Lnc-ATB) plays a role in Epithelial-Mesenchymal Transition (EMT) associated with trastuzumab resistance and metastasis in breast cancer through involvement in the pathways of miR200c/ZEB1 and miR-200c /ZNF217.82 Furthermore, the overexpression of Lnc-ATB is strongly linked to poor prognosis in prostate cancer, independent of other factors, as it upregulates the expression of ZNF217.83 Therefore, LncRNA-ATB holds great potential as a novel target for the diagnosis and treatment of prostate cancer. However, it is worth noting that long non-coding RNAs also play a significant role in keloid fibroblasts. A recent study has demonstrated that the reintroduction of ZNF217 into keloid fibroblasts transfected with miR-182-5p could promote the proliferation, migration, and survival of fibroblasts that were inhibited by miR-182-5p, indicating that the overexpression of ZNF217 could enhance the cell growth and migration of keloid fibroblasts. Furthermore, ZNF217 is a downstream target of miR-182-5p.<sup>84</sup> In keloid fibroblasts, long non-coding RNA HOXA11-AS indirectly regulates the expression of ZNF217 by competitively binding to miR-182-5p, which in turn controls the formation and development of keloids<sup>84</sup> (Figure 4).

### microRNA Regulates the Expression of ZNF217

Xiang et al have identified 172 potential miRNAs that target the mRNA of ZNF217, out of which 42 are conserved across both human and mouse species.<sup>85</sup> Some of these miRNAs are themselves absorbed by specific lncRNA or circRNA, revealing the complex competing endogenous RNA (ceRNA)/miRNA/ZNF217 axis that regulates the expression level of ZNF217 and its downstream functions. Additionally, miRNAs could interact with the 3' untranslated region



Figure 4 LncRNA inhibits the negative regulation of ZNF217 by miRNA either by acting as a miRNA sponge or directly promoting ZNF217 expression. This enhances ZNF217 expression, thereby promoting disease progression, such as in tumors. Created with BioRender.com.

(UTR) of target genes through specific sequences called microRNA response elements (MREs). A study indicates that ZNF217 can significantly increase tumor invasion and EMT. The main reason is that during the progression of liver cancer, ZNF217 can hinder the expression of CDH1 at the transcriptional level by enlisting LSD1 to decrease the dimethylation level of histone H3K4 on the promoter of CDH1. MiR-101 could suppress ZNF217 expression by binding to its 3'untranslated region (3'UTR), inhibiting the progression of hepatocellular carcinoma. This suggests that abnormal regulation of the miR-101/ZNF217/CDH1 axis is linked to the progression of hepatocellular carcinoma.<sup>30</sup> These studies have further confirmed the important role of miRNA in regulating the expression of ZNF217. In breast cancer, in contrast to lncRNAs, the expression of ZNF217 is negatively correlated with miR-503.<sup>86</sup> Previous research has shown that miR-503 can inhibit tumor cell proliferation by targeting ZNF217.86 Additionally, another study indicated that overexpression of miR-503, which is driven by GATA3, can impede the progression of prostate cancer by repressing the expression of ZNF217.<sup>22</sup> The aforementioned research suggests the potential applications of miRNA in the treatment of cancer. Furthermore, recent study data provide evidence that ZNF217 inhibits the methylation of m6A by interacting with the METTL3 protein, which in turn promotes the expression of NANOG.<sup>87</sup> However, miR-135 targets and inhibits ZNF217, resulting in the down-regulation of NANOG, and thus inhibits cancer growth and metastasis.<sup>87</sup> (Figure 5) This discovery suggests the potential use of the miR-135/ZNF217/NANOG axis as a therapeutic target for breast cancer, although the clinical effectiveness of miR-135 has not yet been verified.

### Circular RNA Regulates the Expression of ZNF217

Circular RNAs (circRNAs) are a recently discovered class of molecules that possess complex molecular functions. There is a significant association between specific circRNAs and tumor characteristics, and there is increasing evidence to indicate that cyclic RNA may become an essential regulator of tumor progression, controlling cellular proliferation, migration, programmed cell death, and division.<sup>88</sup> CircRNAs have multiple mechanisms for regulating cell function, including acting as a competing endogenous RNA (ceRNA) that could sponge miRNA.<sup>89</sup> A study has demonstrated that circCSNK1G1 enhances the expression of ZNF217 in gastric cancer cells by sponging miR-758.<sup>90</sup> Additionally, a recent study revealed that HSA\_CIRC\_0069094 competes with ZNF217 for the binding site of miR-758-3P, indicating that HSA\_CIRC\_0069094 promotes breast cancer by indirectly activating the expression of ZNF217 through competitive binding with miR-758-3P.<sup>91</sup> This discovery opens up new possibilities for treating breast cancer. Furthermore, in the investigation of Alzheimer's disease pathogenesis, it has been confirmed that miR-212-3p is the target of ZNF217, and circLPAR1 can increase the expression of ZNF217 by sponging miR-212-3p. In vitro, circLPAR1 accelerates apoptosis,

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Figure 5 miRNAs negatively regulate ZNF217 expression by targeting ZNF217, thereby inhibiting cancer development and EMT. Created with BioRender.com.

inflammation, and oxidative stress induced by A $\beta$ 25-35 via the miR-212-3p/ZNF217 axis.<sup>92</sup> (Figure 6) This study provides further insight into the role of circLPAR1 in Alzheimer's disease pathogenesis.

### The Role of ZNF217 in Non-Cancer Diseases

This chapter emphasizes the important role of ZNF 217/Zfp 217 in the pathogenesis of non-cancer diseases such as obesity, Alzheimer's disease(AD), and polycystic ovary syndrome(PCOS).



Figure 6 Circular RNA functions as a sponge for miRNA to counteract its inhibitory effect on ZNF217, leading to increased expression of ZNF217 and ultimately promoting the progression of tumors and other diseases. Created with BioRender.com.

Adipogenesis is a complex process regulated by various signaling hormones and ligands, and it is associated with liposarcoma.<sup>93</sup> The differentiation of fat cells involves a series of gene regulatory processes, and more than 100 transcriptional regulators participate in various levels of regulatory mechanisms.<sup>94</sup> Several recent studies have revealed the crucial role of Zfp217 in adipogenesis, showing that ZNF217 has novel functions in adipocyte metabolism.ZFP217 and EZH2 synergistically promote fat production, indicating that Zfp217 has potential effects on obesity.<sup>85</sup> Through extensive research, it has been found that the deletion of Zfp217 could reduce the levels of crucial fat-generating factors and thus impede fat synthesis. Furthermore, Zfp217 also regulates adipogenesis through m6A-dependent and YTH domain family 2(YTHDF2)-mediated mechanisms.<sup>95</sup> At the transcriptional level, Zfp217 directly activates the fat mass and obesity-related gene (FTO) promoter to upregulate the expression of FTO, thereby promoting adipogenesis.<sup>41</sup> These findings suggest that ZFP217 could be a valuable tool in the future for treating Obesity.

AD is an age-related neurodegenerative disorder that is genetically complex and is characterized by a gradual decline in memory function. The pathogenesis of AD involves the accumulation of  $\beta$ -amyloid plaques and the formation of neurotoxic oligomers of the amyloid- $\beta$  (A $\beta$ ) peptide,<sup>96,97</sup> as reported in previous studies. Interestingly, the long noncoding RNA, lncRNA-ATB, has been found to exert a negative regulation on miR-200 expression in PC12 cells. In turn, the miR-200 can downregulate the expression of its target gene ZNF217. The miR-200/ZNF217 axis could be regulated by inhibiting the expression of lncRNA-ATB to prevent neurotoxicity induced by A $\beta$ 25-35 in PC12 cells.<sup>98</sup> Additionally, SNHG1 boosts cell damage in AD by regulating the miR-361-3p/ZNF217 axis.<sup>99</sup> Notably, when ZNF217 is knocked out, A $\beta$ -induced pathogenic factors such as inflammatory response (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and malondialdehyde) and oxidative stress (superoxide dismutase, SOD) will also be reduced accordingly.<sup>98,99</sup> According to the AD research results, the relationship between ZNF217 and inflammation was revealed, which may help study the role of ZNF217 in tumor immune response.

PCOS is a hormonal disorder characterized by an excess of male sex hormones (hyperandrogenism), impaired ovulation (ovulatory dysfunction), and enlarged ovaries with fluid-filled sacs (polycystic ovaries). PCOS occurs in 6% to 10% of females of childbearing age, according to the diagnostic criteria.<sup>100</sup> Genome-wide association study (GWAS) has identified ZNF217 as one of the candidate genes for polycystic ovary syndrome.<sup>101</sup> A recent study has indicated that PCOS is a result of alterations in the expression of a cluster of genes linked to PCOS GWAS, comprising LHCGR, ZNF217, DENND1A, and RAB5B. The decrease in the expression of ZNF217 in PCOS theca cells leads to the upregulation of other related genes DENND1A.V2 and CYP17A1 mRNA, thereby promoting androgen synthesis.<sup>102</sup> Additionally, ZNF217 could indirectly impact the expression of DENND1A.V2 and RAB5B, successively influencing CYP17A1 expression by the mediation of miR-130b-3p. However, it should be noted that miR-130b-3p also has the potential to regulate the expression of ZNF217.<sup>102</sup>

### Conclusion

Numerous studies have indicated that ZNF217 plays a critical role in cancer initiation and progression. ZNF217 is involved in genetic expression, cell proliferation, invasion, migration, metastasis, and drug resistance, making it a potential target for cancer therapy. Additionally, ZNF217 has extensive transcriptional and post-transcriptional regulatory networks. Notably, numerous studies have shown that mRNA is also involved in the regulation of ZNF217 expression, indicating that mRNA could also regulate the expression of target genes in a specific way and play an important role in the progression of cancer. This may be one of the ways mRNA participates in tumor development by affecting gene expression.

To put it simply, early diagnosis and personalized treatment are the most effective means of reducing cancer mortality. This article emphasizes the significance of ZNF217 as a biomarker in predicting treatment sensitivity and prognosis for cancer patients. Additionally, the presence of ZNF217 has been shown to promote drug resistance, hindering anti-tumor treatments. As a result, targeted therapies that aim to inhibit ZNF217 may serve as a viable alternative in the fight against cancer.

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