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Zinc Finger Proteins in Colorectal and Breast Cancer: Diagnostic, Prognostic, and Therapeutic Approaches with a Current Literature Review

Seda BEYAZ[1*], Abdullah JM AKMAKJI[2], Ayşenur BÜYÜKSUNGUR[3], İrem Nur GÖZEL[4], Ali Atshan Raheel ALABEDI[5], Abdullah ASLAN[6]

[1*,2,3,4,5,6] Fırat University, Department of Biology, Molecular Biology and Genetic Program, Elazığ, Türkiye

[1]https://orcid.org/0000-0003-0436-8112
[2]https://orcid.org/0000-0002-8223-7743
[3]https://orcid.org/0009-0003-2510-8683
[4]https://orcid.org/0000-0002-3661-7753
[5]https://orcid.org/0009-0001-5807-7102
[6]https://orcid.org/0000-0002-6243-4221
*Corresponding author: sbeyaz@firat.edu.tr

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ABSTRACT

Cancer is one of the leading causes of death worldwide and poses a significant burden on healthcare systems. ZFPs play crucial roles in regulating gene expression and are involved in key processes in cancer biology. This study examines the molecular functions of ZFPs in colorectal and breast cancers and their potential as therapeutic targets. In colorectal cancer, ZFP36 acts as a tumor suppressor, while ZFPs such as ZNF143, ZNF460, ZNF677, ZNF281, and ZNF384 regulate processes such as cell proliferation, metastasis, epithelial-mesenchymal transition (EMT), and drug resistance. In breast cancer, ZFPs like ZEB1, ZNF703, and ZBTB33 are directly associated with tumor progression, treatment resistance, and poor prognosis. Clinical and experimental data indicate that these proteins are considered crucial biomarkers and targets in diagnostic and therapeutic strategies. The functional and structural diversity of ZFPs deepens the molecular understanding of cancer and provides a strong foundation for personalized medical approaches.

Kolorektal ve Meme Kanserlerinde Çinko Parmak Proteinleri: Tanısal, Prognostik ve Terapötik Yaklaşımlar ile Güncel Literatür Taraması

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ÖZ

Kanser, dünya genelinde en önemli ölüm nedenlerinden biri olmakta ve sağlık sistemleri üzerinde ciddi bir yük oluşturmaktadır. ZFP'ler, gen ekspresyonunun düzenlenmesinde görev almakta ve kanser biyolojisinde temel roller üstlenmektedir. Bu çalışma, ZFP'lerin kolorektal ve meme kanserlerindeki moleküler işlevlerini ve terapötik hedef olarak taşıdıkları potansiyeli incelemektedir. Kolorektal kanserde ZFP36 tümör baskılayıcı olarak görev yapmaktadır; ZNF143, ZNF460, ZNF677, ZNF281 ve ZNF384 gibi ZFP'ler ise hücre proliferasyonu, metastaz, epitel-mezenkimal geçiş (EMT) ve ilaç direnci süreçlerini düzenlemektedir. Meme kanserinde ZEB1, ZNF703 ve ZBTB33 gibi ZFP'lerin tümör ilerlemesi, tedavi direnci ve kötü prognoz ile doğrudan ilişkili olduğu gösterilmektedir. Klinik ve deneysel veriler, bu proteinlerin tanı ve tedavi stratejilerinde belirleyici biyobelirteçler ve hedefler olarak değerlendirildiğini ortaya koymaktadır. ZFP'lerin fonksiyonel ve yapısal çeşitliliği, kanserin moleküler düzeyde anlaşılmasını derinleştirmekte ve kişiselleştirilmiş tıbbi yaklaşımlar için güçlü bir temel sunmaktadır.

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Introduction

Worldwide, cancer continues to be a major cause of mortality across nations, regardless of their economic status (Figures 1, 2). In addition to the existing health burden, a significant increase in cancer cases is expected due to population growth and aging. Moreover, the widespread adoption of lifestyle factors that increase cancer risk further accelerates this rise. Low and middle-income countries (LMICs) are particularly affected by this trend due to economic transformations. Factors such as increased mechanization in transportation and labor, shifts in women's social and financial roles, and greater access to international markets are changing lifestyles and fostering the spread of cancer risk factors. As a result, risk factors more commonly observed in high-income countries (HICs), including tobacco use, physical inactivity, overweight, and reproductive behaviors, are becoming increasingly prevalent in LMICs, contributing to a growing cancer burden in these regions. This situation poses a significant global health challenge, underscoring the need to develop preventive strategies that account for these diverse economic and social contexts (Torre et al., 2016).

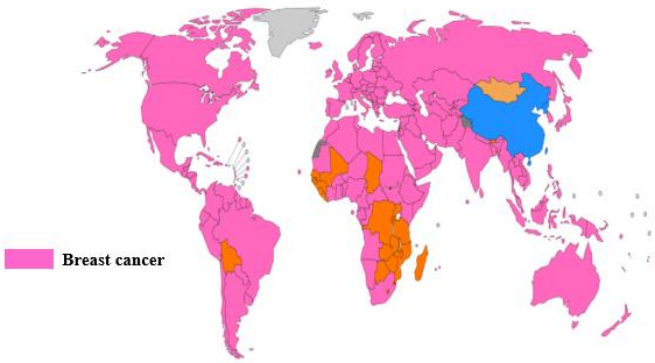

Figure 1. Most common cancer site by country in females in 2022, with absolute case numbers and incidence rates (Globocan, 2022)

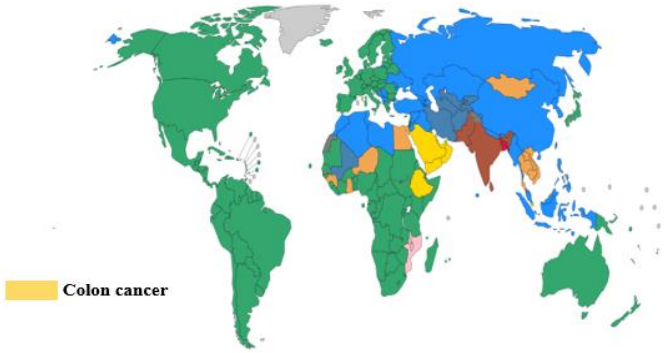

Figure 2. Most common cancer site by country in females in 2022, with absolute case numbers and incidence rates (Globocan, 2022)

Zinc finger proteins (ZFPs) are recognized as the largest and most diverse family of transcription factors, accounting for approximately 5% of the human genome (Figure 3). ZFPs comprise a broad and heterogeneous group of proteins characterized by zinc-coordinated finger-like (ZnF) domains that enable DNA binding and play critical roles in numerous biological processes. These proteins possess the capacity to interact with DNA, RNA, poly-ADP-ribose, proteins, and lipids. Functioning as multifunctional proteins that facilitate DNA binding and gene regulation, ZFPs are crucial regulators of fundamental cellular processes such as development, differentiation, metabolic homeostasis, and programmed cell death (Ye et al., 2019; Hong et al., 2023). Numerous cellular processes, including transcriptional control, chromatin remodeling, proteostasis, cellular signaling, proliferation, and differentiation, are mediated by the more than 30 different types of ZFPs that have been identified to date (Cassandri et al., 2017; Singh and Van Attikum, 2021). Increasing research highlights the crucial role of zinc finger proteins (ZFPs) in cancer, affecting various phases, including tumor initiation, growth, and metastasis. Aberrations in intracellular signaling pathways, a hallmark of cancer, are frequently driven or modulated by ZFPs, thereby contributing to tumorigenesis (Ye et al., 2019; Hong et al., 2023).

The present study aims to elucidate the specific functions of ZFPs within colorectal and breast cancer pathophysiology and to evaluate their promise as viable molecular targets for the development of innovative, targeted cancer therapies.

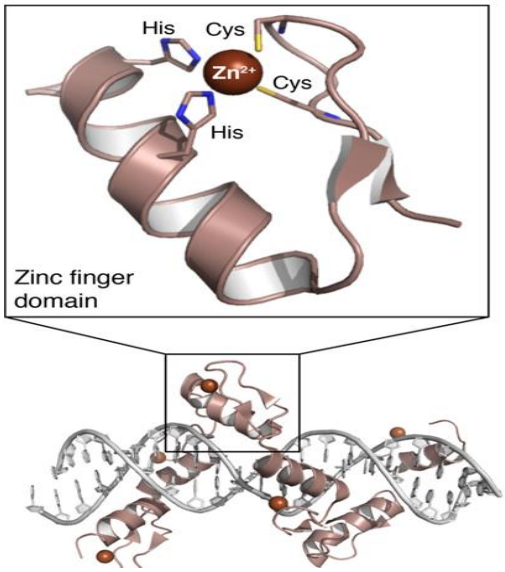

Figure 3. Structure of zinc finger proteins (Gersbach et al., 2014)

The Role of Zinc Finger Proteins in Colon Cancer: Diagnosis, Prognosis, and Therapeutic Potential

Colorectal Cancer

Colorectal cancer represents a major worldwide public health issue, comprising about 10% of all cancer cases and deaths annually. It ranks as the third most frequent cancer among men and the second among women. Epidemiological data indicate that women experience roughly 25% lower rates of incidence and mortality than men. Geographically, these rates vary, with industrialized nations often showing the highest incidence and fatality rates. Lifestyle-related risk factors like smoking, obesity, lack of physical activity, food choices in high-income countries, and an aging population are linked to the increased prevalence of colorectal cancer. Treatment options for both localized and advanced-stage colorectal cancer have expanded due to a better understanding of the disease's pathogenesis, allowing for more individualized therapeutic approaches (Figure 4). Palliative chemotherapy, targeted therapies, immunotherapies, extensive surgical procedures for locoregional and metastatic disease, endoscopic and surgical local resection, preoperative radiotherapy, and systemic neoadjuvant treatments are some of the current treatment approaches (Dekker et al., 2019). Furthermore, colon cancer’s prognosis is greatly impacted by distant metastases, which primarily target the liver. Colorectal liver metastases account for almost half of colorectal cancer patients’ deaths (Tinguely et al., 2020).

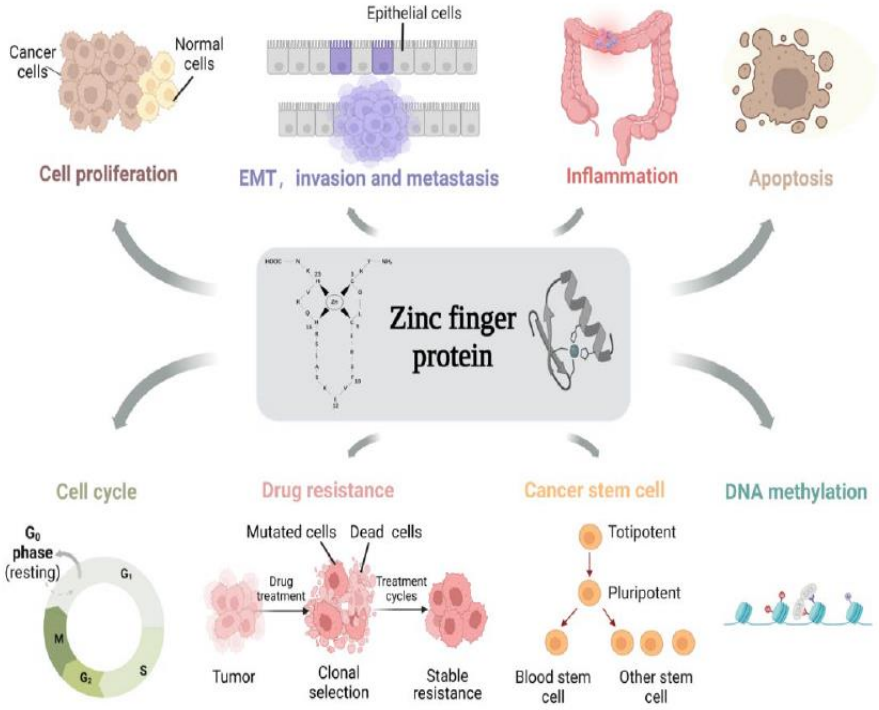

Figure 4. The role of ZFPs in shaping cellular processes in the pathogenesis of colorectal cancer (Liu et al., 2022)

Diagnosis and Prognosis of Colorectal Cancer

Computed Tomography Colography (CT) is a non-invasive imaging technique that creates high-resolution images of the colon using CT scanners and specific software. Despite being more convenient and comfortable for patients than colonoscopy, tissue collection is not feasible; hence, colonoscopy is still necessary to confirm worrisome lesions. Because they are non-invasive, blood-based biomarkers like carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are frequently employed in clinical practice. Their specificity is constrained, though, as levels may also rise in other medical disorders, and their sensitivity falls between 40 and 60%. Consequently, a sizable fraction of patients with colorectal cancer might be incorrectly classified, which would decrease the efficacy of screening initiatives (Serras et al., 2024).

Particularly in detecting distant metastases, diagnostic sensitivity and specificity in colorectal cancer patients can be significantly improved by combining CEA levels with microRNA-141 (miR-141), as demonstrated by research aiming to overcome current diagnostic limitations (Cheng et al., 2011). One common first-line diagnostic method in colorectal cancer screening programs is the fecal occult blood test (FOBT). It can lower mortality rates by 15% to 33% and is crucial in identifying high-risk individuals, even if it

does not directly diagnose colorectal cancer. Despite the possibility of false positives brought on by outside variables, including diet, exercise, and some medications, FOBT is nevertheless a practical, affordable, and non-invasive technique that is favored in extensive screening initiatives. According to conventional FOBTs, fecal immunochemical assays (FIT) have a better sensitivity. They are instrumental in early-stage screening because they can identify a greater percentage of individuals with colorectal cancer sooner due to their capacity to detect microscopic bleeding from lesions in the gastrointestinal region selectively. FIT tests, however, are not very sensitive in identifying advanced adenomas and stage I colorectal cancer. Furthermore, storage and shipping circumstances can cause the antibodies employed in FIT to become unstable, which could result in false-negative results and lower the screening's overall dependability. The use of DNA-based analysis in feces samples has enabled the detection of genetic and epigenetic changes released by tumor cells in recent years. This method has shown promise as a diagnostic tool for colorectal cancer detection that is more sensitive and specific (Cao et al., 2024).

Zinc Finger Protein-36 (ZFP36/TTP): The Regulatory Role of Tristetraprolin in Colorectal Cancer

Controlling post-transcriptional gene expression requires the well-characterized RNA-binding protein tristetraprolin (TTP), commonly referred to as ZFP36, NUP475, G0/G1 switch regulatory protein 24 (GOS24), and TPA-inducible sequence 11 (TIS11) (Shukla et al., 2017). The gene encoding TTP is mapped to chromosome 19q13.2 and comprises two exons separated by a single intron. It transcribes a 1.7-kilobase mRNA that translates into a protein with an approximate molecular mass of 34 kDa (Guo et al., 2017). Structurally, TTP harbors three proline-rich regions and two highly conserved tandem CCCH-type zinc finger (TZF) motifs defined by the $CX_8CX_5CX_3H$ consensus sequence. Additionally, the protein contains multiple phosphorylation sites located on serine and threonine residues, notably at positions S88, S186, S66, T92, S169, S228, and S197, which are implicated in the modulation of its biological activity (Lai et al., 2019). ZFP36 is identified as a tumor suppressor whose expression is reduced during colorectal cancer progression, and it functions by regulating mRNA stability. Re-expression of ZFP36 suppresses epithelial-mesenchymal transition (EMT) and increases the sensitivity of cells to anoikis. Additionally, ZFP36 has been shown to inhibit the expression of three key transcription factors involved in the EMT process: ZEB1, MACC1, and SOX9. Furthermore, ZFP36 expression is negatively correlated with the Wnt/β-catenin signaling pathway, which is frequently activated in colorectal cancer. EMT is

facilitated by decreased ZFP36 expression, while it is suppressed by re-expression of ZFP36. ZFP36's capacity to suppress the expression of oncogenic transcription factors implicated in EMT, including SOX9, MACC1, and ZEB1, is linked to this antitumor impact. Interestingly, ZFP36 had not been found to directly target SOX9. According to recent research, ZFP36 reduces the stability of SOX9 mRNA, which lowers the transcription factor's levels and aids in the prevention of EMT. These findings offer a significant molecular framework for understanding how ZFP36 exerts its tumor-suppressive functions (Montorsi et al., 2016)

Zinc Finger Protein-143 (ZNF143): A Transcriptional Regulator of Cell Proliferation and DNA Replication

One transcription factor that is essential to the advancement of the cell cycle is zinc finger protein-143 (ZNF143). A new inhibitor that targets ZNF143, YPC-21661, promotes apoptosis by halting the cell cycle during the G2/M phase, hence exerting lethal effects on cancer cells. This is in contrast to small compounds that block the transcriptional activity of E2F or c-Myc, which arrest the cell cycle in the G0/G1 phase. In colorectal cancer cells, YPC-21661 downregulates the expression of ZNF143 target genes by preventing its binding to DNA. It is also known that ZNF143 can bind to cisplatin-modified DNA, and this interaction contributes to the development of cisplatin resistance. Accordingly, the suppressive effect of YPC-21661 on ZNF143 has been reported to enhance the therapeutic efficacy of cisplatin. This study identifies YPC-21661 as the first ZNF143 inhibitor to exhibit anticancer activity both *in vitro* and *in vivo*, suggesting its potential as a therapeutic agent in colorectal cancer treatment. Additionally, silencing ZNF143 suppresses IL-8 expression, while activation of the IL-8–CXCR axis promotes colorectal cancer progression (Lan et al., 2025)

Zinc Finger E-box Binding Homeobox Transcription Factors 1/2 (ZEB1/ZEB2): Critical Roles in the Epithelial-Mesenchymal Transition (EMT) Process

The epithelial-mesenchymal transition (EMT), in which epithelial cells go through several molecular alterations and take on mesenchymal traits, is mostly regulated by zinc finger E-box-binding homeobox 1 (ZEB1) (Poonaki et al., 2022). ZEB1 has been identified as a central gene in the EMT process across various tumor types, including lung, breast, cervical, and prostate cancers (Savci-Heijink et al., 2019). The lncRNA ZFAS1/miR200b/ZEB1 protein axis may control EMT in colorectal adenocarcinoma, according to a prior study. However, its potential as a non-invasive diagnostic biomarker for colorectal cancer in its early stages has not yet been thoroughly investigated (O’Brien et al., 2021).

ZEB2 is thought to primarily function during embryogenesis and promote EMT and metastasis in various cancer types (Katsura et al., 2017). But an increasing amount of data indicates that ZEB2 plays new roles in both healthy and malignant adult tissues, upending the conventional wisdom that sees ZEB2 only as an oncoprotein that promotes metastases. Both ZEB1 and ZEB2 play critical roles in the metastasis process, which is the leading cause of cancer-related mortality. Many human malignancies exhibit unusually high levels of ZEB1 expression. ZEB1 is impacted by extracellular signals released into the tumor microenvironment, such as TGF-β, FGF, EGF, HGF, Wnt, Notch, and Hedgehog, and it also promotes metastatic processes, including cell migration and invasion. Moreover, by activating EMT helps regulate several signaling pathways, including MAPK, PI3K, NF-κB, Wnt/β-catenin, and Notch. The loss of E-cadherin, a protein involved in intercellular adhesion, as a result of transcription factors directly suppressing the CDH1 gene, is one of the defining events of EMT. ZEB1 and ZEB2 are two of these variables that are especially significant (Caramel et al., 2017). Both ZEB1 and ZEB2 regulate their target genes by binding to E-box motifs in promoter regions. For example, both ZEB factors are known to suppress the expression of E-cadherin, P-cadherin, and gap junction proteins such as connexin 26 (GJB2) and connexin 31 (GJB3) (Parfenyev et al., 2025).

Recent Studies on the Role and Clinical Relevance of Zinc Finger Proteins in Colorectal Cancer

Hao et al. (2021) employed bioinformatic strategies to investigate ZNF460 expression, revealing its upregulation at both transcriptomic and proteomic levels. Elevated ZNF460 levels were statistically correlated with deeper tumor infiltration, regional lymphatic dissemination, distant organ metastasis, and increased circulating CA19-9 concentrations (all $P<0.05$). The study established that ZNF460 overexpression is predictive of unfavorable clinical outcomes, showing a significant association with reduced overall survival (OS) and relapse-free survival (RFS). Multivariate statistical assessments confirmed that ZNF460 acts as an independent prognostic indicator for both OS (HR = 1.636; 95% CI: 1.028–2.603; P = 0.038) and RFS (HR = 2.215; 95% CI: 1.227–3.997; P = 0.008). Functional assays demonstrated that silencing ZNF460 diminished the invasive and metastatic behavior of colon cancer cells. Mechanistic exploration indicated that ZNF460 facilitates tumor progression by activating the JAK2/STAT3 axis. Altogether, these insights underscore the oncogenic role of ZNF460 in colorectal cancer and propose it as a candidate for targeted therapy development.

Siraj et al. (2021) used immunohistochemistry to examine ZNF677 protein expression in a sizable cohort of 1,158 individuals with colorectal cancer. In contrast to normal tissues (5.1%, 11/214; $p<0.0001$), they found that ZNF677 loss was substantially more prevalent in CRC tissues (45.3%, 525/1158). Mucinous histology ($p = 0.0311$), advanced clinical stage ($p<0.0001$), and lymph node (LN) metastases ($p = 0.0374$) were all substantially correlated with this reduction of expression. Additional analysis showed that, in comparison to the entire population, ZNF677 loss was significantly higher in CRC cases with LN metastases ($p = 0.0258$). ZNF677 loss was an independent predictor of lymph node metastasis in colorectal cancer (CRC) (odds ratio = 1.41; 95% CI: 1.05–1.87; $p = 0.0203$), according to multivariate logistic regression analysis. In CRC cell lines, functional gain-and loss-of-function tests showed that whilst ZNF677 overexpression restored these effects, decreased ZNF677 expression markedly boosted cell proliferation, EMT, and chemoresistance. Consequently, the authors suggested that ZNF677 be taken into account as a possible target for tailored treatment approaches in addition to being a predictive biomarker.

Qin et al. (2019) revealed that ZNF281 expression at both mRNA and protein levels was markedly upregulated in colorectal carcinoma tissues in comparison to adjacent non-cancerous colonic tissues. This overexpression was significantly correlated with poor cellular differentiation and more aggressive disease features, including advanced T and N categories and elevated TNM staging. Based on these correlations, the authors proposed that ZNF281 may act as an independent prognostic factor in colorectal cancer patients. Functional analyses further demonstrated that silencing ZNF281 expression resulted in a pronounced decline in tumor cell proliferation, motility, and invasive capacity, which was primarily mediated through the downregulation of the Wnt/β-catenin signaling pathway. According to Yan et al. (2022), colorectal cancer samples had significantly higher levels of the transcription factor ZNF384, which belongs to the zinc finger protein family, and this was linked to a worse prognosis. Notably, ZNF384 inhibition prevented the development of CRC cells, while overexpression enhanced their capacity for invasion and migration. Additionally, they showed that ZNF384 controls Matrix Metalloproteinase-2 (MMP2) expression. ZNF384-mediated invasion and migration were inhibited by MMP2 inhibition, although the inhibitory effects of ZNF384 knockdown were reversed by MMP2 overexpression. Additionally, MMP2 and Hypoxia-Inducible Factor-1α (HIF-1α), a transcription factor that is increased in hypoxic environments, showed favorable correlations with ZNF384 expression levels in human colorectal cancer samples.

The Role of Zinc Finger Proteins in Breast Cancer: Diagnosis, Prognosis, and Therapeutic Potential

Diagnosis and Prognosis of Breast Cancer

Breast cancer is one of the most significant threats to women's health. Although diagnostic and treatment methods have made some progress, the pathogenic factors of breast cancer, like other cancers, remain unclear (Akyolcu et al., 2019). Despite many causes, the exact etiology is not yet determined, leading to variations in diagnosis and treatment approaches. Over 1.2 million cases are diagnosed worldwide each year, affecting 10-12% of the female population (Benson et al., 2009). Advanced age and female gender are among the most common risk factors. Genetic mutations, particularly in BRCA-1 and BRCA-2, account for approximately 10% of breast cancers (Watkins, 2019).

Diagnostic imaging methods such as mammography, magnetic resonance imaging (MRI), and ultrasonography play a significant role in breast cancer diagnosis. Mammography is widely used for detecting early-stage cancers and is particularly recommended for specific age groups. Digital mammography and computer-aided detection systems are improving diagnostic accuracy. MRI provides high-resolution imaging without using ionizing radiation and is preferred in patients with a genetic predisposition or cases with ambiguous findings. Ultrasonography determines the size and location of intramammary masses but has limitations in differentiating benign from malignant lesions, while biopsy guidance reduces unnecessary invasive procedures. Definitive diagnosis is established through fine-needle aspiration and core needle biopsy; vacuum-assisted biopsy is enhancing diagnostic precision in uncertain cases. Surgical treatment plays a critical role in tumor excision and staging; breast-conserving surgery involves the removal of the tumor with limited surrounding tissue, whereas mastectomy entails the complete removal of the breast. Sentinel lymph node biopsy is reducing surgical complications. Radiotherapy is generally applied following breast-conserving surgery, targeting tumor cells, and is also used for symptom management in advanced stages. Systemic therapies include chemotherapy, hormone therapy, and targeted therapies. Emerging approaches such as nanotechnology, gene therapy, and immunotherapy are being noted as promising modalities in breast cancer treatment (Kumar, 2021).

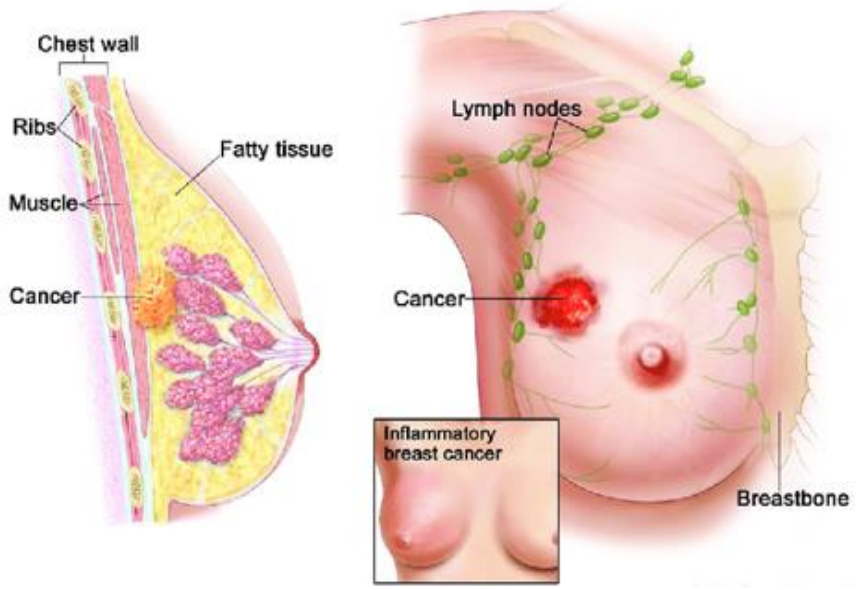

Figure 5. Demonstration of proliferation in breast tumor cells (Kumar, 2021)

Zinc Finger E-Box Binding Homeobox 1/2 (ZEB1): Metastasis in Breast Cancer

One of the most common protein families is zinc finger proteins (ZNFs), which are distinguished by their diverse range of molecular functions. They may attach to a variety of biomolecules, such as DNA, RNA, poly(ADP-ribose) (PAR), and other proteins, thanks to their structural diversity (Cassandri et al., 2017). ZNFs were first identified as repetitive zinc-binding domains with conserved cysteine and histidine residues in the transcription factor IIIA (TFIIIA) of Xenopus. Numerous physiological processes, such as membrane association, protein–protein interactions, and nucleic acid recognition, are mediated by these proteins (Laity et al., 2001). In conditions such as laryngeal squamous cell carcinoma, glioma, non-small cell lung cancer, gastric cancer, oral squamous cell carcinoma, gallbladder cancer, and breast cancer, overexpression of ZNF X (ZFX) has been shown to stimulate cell proliferation and metastasis (Jen and Wang, 2016). According to earlier research, several ZNFs participate in transcriptional suppression via corepressors, which alters how different downstream genes are regulated (An, 2022). The process by which epithelial cells turn into mesenchymal-like cells as a result of modifications in the expression levels of important markers like vimentin and E-cadherin is known as the EMT. EMT-inducible transcription factors from the SNAIL, SLUG, TWIST, and ZEB families are the main regulators of EMT (Cho et al., 2019). Zinc finger E-box binding homeobox 1 (ZEB1) is highly linked to aggressive characteristics, metastasis, and poor clinical prognosis in a variety of tumor types, including breast, lung, and pancreatic malignancies, according to data acquired about EMT-inducible transcription

factors. Two zinc finger clusters found in ZEB1 attach to particular DNA sequences called E-box elements (Cho et al., 2019).

ZEB1 is a key initiator of the EMT and a potent regulator of gene expression, influencing both embryonic development and cancer progression. Elevated ZEB1 mRNA levels and EMT-associated phenotypes are frequently observed in patients with triple-negative breast cancer. In addition to driving tumor progression, ZEB1 promotes metastasis in both pancreatic and breast cancers. Notably, ZEB1 has been shown to facilitate bone-specific metastasis of breast cancer by upregulating extracellular antagonists such as chordin-like 1, follistatin, and noggin. These factors inhibit activin ligand signaling and bone morphogenetic proteins, which are members of the TGFβ family, thereby creating a microenvironment conducive to metastatic colonization in bone tissue (Maturi et al., 2018).

Zinc Finger Protein-703 (ZNF703): Oncogene in Estrogen Receptor-Positive (ER+) Subtypes

Steroid hormones regulate cell growth and differentiation, affecting normal physiology, reproductive events, and behaviors. Estrogens exert their effects on target tissues through two members of the nuclear receptor superfamily: estrogen receptor-α (ERα) and ERβ. ERα is considered an important biological marker for the response of breast cancers to hormone therapy. The shortened isoform ERα-36 has been observed to confer resistance to tamoxifen. Current studies aim to clarify the prognostic and predictive roles of ERβ. Existing literature indicates that nuclear wild-type ERβ supports ERα in predicting endocrine therapy response and is associated with better overall outcomes and metastatic potential in breast and prostate cancers. The cytoplasmic ERβ2 isoform (also known as ERβcx) is linked to poorer survival rates and metastatic characteristics (Thomas and Gustafsson, 2011). ZNF703 is known to be highly prevalent in breast cancer, identified by genome-wide measurement of DNA copy number using genomic hybridization, alongside ERBB2 and CCND1. ZNF703 expression has been discovered in a subset of triple-negative breast cancers (TNBC), both in human tumor samples and cancer cell lines (Zhang et al., 2022).

Recent studies have demonstrated that inhibition of ZNF703 in breast cancer cells induces apoptosis. Moreover, overexpression of ZNF703 has been shown to modulate downstream signaling of estrogen receptor alpha (ERα), a receptor that, despite being typically absent in triple-negative breast cancer (TNBC), still plays a notable role in this context (Wang et al., 2025).

Zinc Finger and BTB Domain-Containing Protein-33 (ZBTB33-Kaiso): Epigenetic Regulation

ZBTB33 (Kaiso) was initially identified as a transcription factor and is considered a member of the BTB/POZ subgroup of zinc finger proteins. It contains a dual-mode DNA-binding domain that recognizes both sequence-specific consensus regions and methylated CpG nucleotides. Its nuclear function has been found to influence transcriptional programs that promote the development and progression of breast cancer. Subsequent studies revealed that a large portion of the sequence motifs within the nucleus are unmethylated and located in open chromatin regions. Due to its crucial role in transcriptional regulation, ZBTB33 is generally regarded as a nuclear protein. Numerous studies have demonstrated that the atomic localization of ZBTB33 is dynamically regulated through its interaction with p120 (CTNND1) (Singhal et al., 2021).

Studies on the Role and Clinical Associations of Zinc Finger Proteins in Breast Cancer in the Literature

Bassey-Archibong et al. (2016) analyzed breast cancer samples from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) datasets to assess the clinical significance of ZBTB33 expression. Silencing ZBTB33 in breast cancer cell lines such as MDA-MB-231 and Hs578T led to decreased levels of proteins associated with epithelial-mesenchymal transition (EMT) and inhibited the TGFβ signaling-induced EMT process. Furthermore, ZBTB33 deficiency reduced the metastatic potential of TNBC cells in mouse models. High expression of ZBTB33 and TGFβR1 in breast cancer patients correlated with poorer overall survival, while overexpression of TGFβR1 in ZBTB33-deficient cells was insufficient to restore metastatic potential. In conclusion, ZBTB33 plays a critical role in TGFβ signaling and TNBC metastasis. Using RT-qPCR and western blot analysis, Guo et al. (2021) assessed the expression of MIR-491-5p and ZNF703 in breast cancer tissues and cells. They used Transwell assays to confirm ZNF703's cellular activity and investigated its expression using immunohistochemistry. Western blot analysis was also used to examine protein levels associated with the AKT/mTOR signaling pathways. ZNF703 and MIR-491-5p interacted, as demonstrated by a dual-luciferase reporter experiment. The findings indicated that ZNF703 was significantly expressed in breast cancer, and MIR-491-5p was expressed at low levels; this pattern was linked to a poor prognosis for the patients.

Zhang et al. (2018) reported that breast tumors with elevated ZEB1 expression exhibit a markedly reduced response to chemotherapy. Their findings further revealed a positive

correlation between ZEB1 and the proteins cyclin D1 and Bcl-xL, both of which are key mediators of chemotherapy resistance. In vitro experiments demonstrated that forced overexpression of ZEB1 diminished the sensitivity of breast cancer cells to genotoxic agents such as epirubicin (EPI). Mechanistically, ZEB1 was shown to promote the transcription of ataxia–telangiectasia mutated (ATM) kinase by recruiting a ZEB1/p300/PCAF complex to its promoter, thereby enhancing DNA damage repair via the homologous recombination (HR) pathway. Consistent with these results, ectopic ZEB1 expression reduced the therapeutic efficacy of EPI in vivo, as evidenced by studies using a nude mouse xenograft model. Collectively, these findings underscore the pivotal role of ZEB1 in driving chemotherapy resistance in breast cancer.

Udu-Ituma et al. (2023) developed antisense oligonucleotides (ASO) against ZNF703 mRNA and demonstrated that these downregulated ZNF703 protein expression. ZNF703 inhibition reduced cell proliferation and induced apoptosis; moreover, when used in combination with cisplatin, ASO9 enhanced anticancer effects. They reported that ASO technology holds potential for increasing the number of targetable cancer genes. Singhal et al. (2021) investigated the intracellular distribution of the transcriptional regulator ZBTB33 in breast cancer tumors using quantitative automated imaging and computational methods. Multivariate analyses revealed that the intracellular localization of ZBTB33 uncovered new functional and predictive links among tumor immune microenvironment, survival, ethnic origin, and LC3A/B proteins associated with autophagy. Luo et al. (2020) found significantly increased expression of ZEB1-AS1 in triple-negative breast cancer (TNBC) tissue samples and cell lines by RT-qPCR analyses. Inhibition of ZEB1-AS1 suppressed cell proliferation, migration, and invasion, and also promoted apoptosis. RT-qPCR data showed elevated ZEB1 gene expression in TNBC tissues, and silencing ZEB1 inhibited TNBC progression. Mechanistic analyses demonstrated that ZEB1-AS1 interacts with the ELAVL1 protein to maintain the stability of ZEB1 mRNA. Similarly, ZEB1 binds to ELAVL1, supporting mRNA stability. These findings suggest a critical regulatory role of the ZEB1-AS1/ELAVL1/ZEB1 axis in TNBC pathogenesis.

Conclusion

Zinc finger proteins (ZFPs) are important transcriptional regulators involved in cancer development, progression, and treatment resistance due to their structural and functional diversity. In colorectal and breast cancers, specific ZFPs such as ZFP36, ZNF143, ZEB1/2, ZNF703, and ZBTB33 regulate key oncogenic pathways, including EMT, Wnt/β-catenin,

JAK/STAT, and DNA damage response. Their altered expression in tumors and association with clinical outcomes like metastasis and drug resistance make them promising biomarkers for diagnosis and prognosis. Novel therapeutic strategies such as small-molecule inhibitors, antisense oligonucleotides, CRISPR/Cas9 gene editing, and epigenetic modulators target ZFPs to improve treatment outcomes. For example, inhibiting ZNF143 may enhance chemotherapy sensitivity, while targeting ZNF703 can reduce tumor cell proliferation. These approaches aim to selectively target cancer cells while minimizing side effects on healthy tissues. However, successful clinical translation requires a deeper understanding of ZFP-related molecular mechanisms and validation in larger patient groups. Integrating genomic, proteomic, and epigenetic data with AI-assisted bioinformatics will help clarify the roles of ZFPs in cancer biology and support the development of personalized therapies.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contributions

The authors declare that they have contributed equally to the article.

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