



Review

The Roles of Zinc Finger Proteins in Colorectal Cancer

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Abstract: Despite colorectal cancer remaining a leading worldwide cause of cancer-related death, there remains a paucity of effective treatments for advanced disease. The molecular mechanisms underlying the development of colorectal cancer include altered cell signaling and cell cycle regulation that may result from epigenetic modifications of gene expression and function. Acting as important transcriptional regulators of normal biological processes, zinc finger proteins also play key roles in regulating the cellular mechanisms underlying colorectal neoplasia. These actions impact cell differentiation and proliferation, epithelial–mesenchymal transition, apoptosis, homeostasis, senescence, and maintenance of stemness. With the goal of highlighting promising points of therapeutic intervention, we review the oncogenic and tumor suppressor roles of zinc finger proteins with respect to colorectal cancer tumorigenesis and progression.

Keywords: zinc finger protein; colorectal cancer; transcription factor; oncogene; tumor suppressor



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1. Zinc Finger Proteins Are Transcriptional Regulators in Colorectal Cancer (CRC)

With more than 1.9 million new cases of CRC worldwide in 2020 [1] and 150,000 new cases projected in the US in 2023 [2], CRC is the third most prevalent cancer and second leading cause of cancer-related death in the world [3]. Potential contributors to increased CRC risk include the increasing prevalence of aging populations, ingestion of so-called Western diets, obesity, and insufficient physical exercise—all clearly interrelated factors. For currently unknown reasons, there has also been a shift towards the development of colorectal cancer in younger people, i.e., those younger than age 50 years [2]. Prior colon adenomas, inflammatory bowel disease, and a family history of CRC, including hereditary disorders (e.g., familial adenomatous polyposis and Lynch syndrome), further increase CRC risk [4]. Various molecular mechanisms are implicated in the development of CRC, including altered cellular signaling pathways, epigenetic modifications, genomic instability, and metabolic dysfunction. The complexity of CRC pathogenesis is further confounded by extensive cross-talk between these and other mechanisms [5]. The observation that zinc finger proteins play a key role as transcriptional regulators in the development and progression of CRC prompted the current review.

For the purposes of this review, a zinc finger (ZNF) is defined as a small, functional, autonomously folded domain that requires the coordination of one or more zinc ions to stabilize its structure [6]. In 1985, xenopus transcription factor IIIA (TFIIIA) was the first protein shown to possess such a zinc finger domain [6]. ZNFs are DNA-binding domains that comprise the largest family of transcription factors. They can also bind RNA, facilitate interactions between proteins, have structural roles, and provide other,

as-yet-undefined biological functions [6]. Hence, zinc finger proteins (ZFP) can act as transcriptional repressors and activators for a wide array of genes, thus modulating a multitude of biological processes, including cell differentiation, cell proliferation, migration, invasion, epithelial–mesenchymal transition (EMT), apoptosis, and stemness (Figure 1). As fundamental regulators of cancer progression via both oncogenic and tumor suppressor functions, ZFPs may also serve as therapeutic targets [7]. In this review, we discuss the roles of ZFPs in the development and progression of CRC, as either tumor suppressors or oncogenes, and highlight potential points of therapeutic intervention.

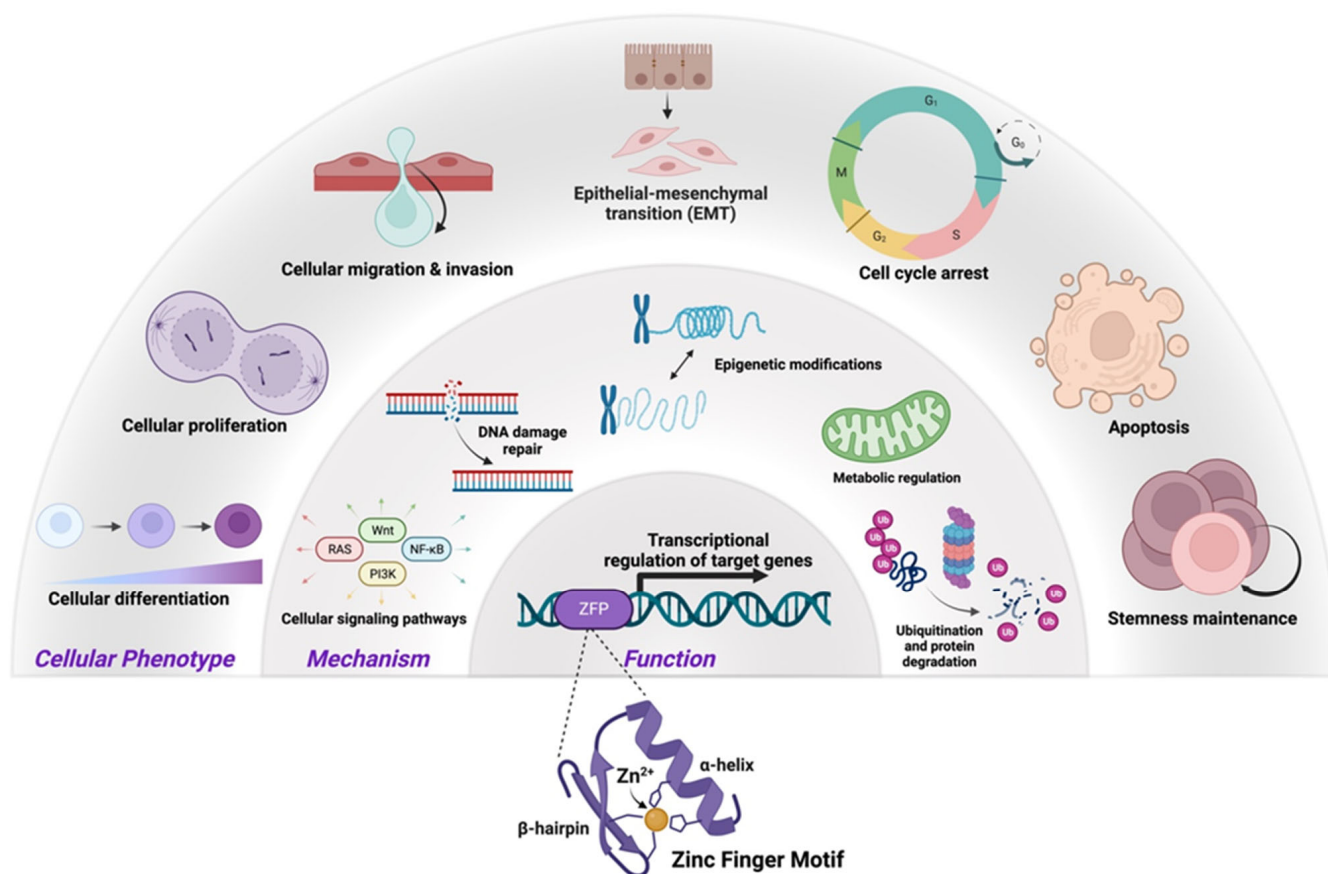


Figure 1. The roles of zinc finger proteins (ZFPs) in maintaining cellular homeostasis. ZFPs contain a zinc finger motif, vital for binding DNA and executing transcriptional regulation of target genes involved with mechanisms that maintain normal cellular physiology (i.e., signaling, DNA damage response, etc.). This figure illustrates the mechanisms whereby ZFP regulation of target gene transcriptional activity alters key cellular phenotypes. Created with Biorender.com.

2. ZFPs Modulate CRC Cell Proliferation, Differentiation, Migration, Invasion, and EMT (Table 1)

Most ZFPs implicated in CRC progression are involved in manipulating the cellular phenotype to promote proliferative and invasive behavior and achieve metastatic potential through multiple mechanisms.

Table 1. ZFPs controlling cell proliferation, differentiation, migration, invasion, and EMT.

Molecular Mechanism	Gene	Common Alias(es)	Function	Additional Molecular Mechanisms	Cellular Targets	Role in Additional Cell Phenotypes or Behavior	Refs.
Wnt/ β -catenin	ZNRF3	RNF203	TS		Frizzled, LRP6		[8,9]
	OVOL2	CHED; CHED1; CHED2; PPCD1; ZNF339	TS		TCF4, SLUG; MAP3K8/AKT/NF- κ B signaling, CXCL16		[10,11]
	FLYWCH1		TS		β -catenin, TCF4, E-cadherin; γ H2AX, ATM, p53	DNA damage response	[12,13]
	ZFP36	Tristetraprolin, TIS11, TTP, NUP475, RNF162A, GOS24	TS		MACC1, ZEB1, SOX9		[14]
	RSPO2	HHRD; TETAMS2; CRISTIN2	TS		LGR5; Wnt5a/Fzd non-canonical pathway		[15,16]
	ZIC2	HPE5	O		Axin2; cyclin D1, CD44, LGR5	Apoptosis, cell cycle	[17]
	ZBTB17	MIZ-1, ZNF151, ZNF60, pHZ-67	O	Myc-signaling	Dpr1, Dvl2	Cell cycle	[18,19]
	BMI1	FLVI2/BMI1, PCGF4, RNF51	O		p16 ^{INK4a} , p14 ^{ARF} ; IDAX, E-cadherin		[20–23]
	PLAGL2	ZNF900	O		ASCL2, Wnt4A, Wnt5A; Wnt6; CD44		[24–26]
	ZNF281	GZP1, ZBP99, ZNP-99	O			Cell cycle	[27]
	GATA6		O		Sp1, urokinase-type plasminogen activator (uPA)		[28]
	TRIM37	MUL, POB1, TEF3	O		β -catenin, c-Myc, cyclin D1		[29]
	ZNF277	NRIF4	O		β -catenin, p21 ^{WAF1}	Cell senescence, cell cycle	[30,31]
Ras/ERK	ADNP	ADNP1, HVDAS, MRD28	TS		Under investigation		[32]
	ZC3H13	Xio	TS		Snail, cyclin D1, cyclin E1, occludin, Zo-1		[33]
	ZDHHC9	DHHC9, MMSA1, MRZSR, MRXSZ, ZDHHC10, ZNF379, ZNF380	O				[34]

Table 1. Cont.

Molecular Mechanism	Gene	Common Alias(es)	Function	Additional Molecular Mechanisms	Cellular Targets	Role in Additional Cell Phenotypes or Behavior	Refs.
JAK/STAT	ZNF143	SBF, STAF	TS		IL-8, ZEB1		[35,36]
	ZNF460	HZF8, ZNF272	O				[37]
NF-κB	ZCCHC10		TS				[38]
	ZFP91	DSM8, FKSG11, PZF, ZNF757	O		HIF-1α	Angiogenesis, cell cycle	[39]
PI3K/AKT	ZNF549		TS				[40]
	GLI1	PAPA8, PPD1	O	NF-κB		Stemness	[41,42]
	ZNF692	AREBP, Zfp692	O		cyclin D1, CDK2, MMP9, p27 ^{Kip1}	Cell cycle	[43]
	ZBED6	MGR	TS	Hippo, TGF-β, EGFR, PI3K	IGF-2	Cell cycle	[44]
TGF-β	ZNF37A	KOX21, ZNF37	O		THSD4		[45]
	ZNF326	ZAN75, ZIRD	O		LTBP4, p-Smad2/3, N-cadherin, Snail, Slug, vimentin, E-cadherin, Zo-1		[46]
Hippo/YAP	ZNF367	AFF29, CDC14B, ZFF29	O				[47]
	ZNF280A	SUHW1, ZNF280, ZNF636	O			Cell cycle	[48]
YAP	ZMYND8	PRKCBP1, PRO2893, RACK7	O			Metabolism	[49,50]
DNA or histone methylation	ZBTB18	MRD22, RP58, TAZ-1, ZNF238	TS				[51]
	GATA4	ASD2, TACHD, TOF, VSD1	TS				[52]
	GATA5	CHTD5, GATAS					
	ZNF677		TS				[53]
	ZFP82	ZNF545	TS	Wnt/β-catenin, PI3K/AKT, MAPK/ERK, NF-κB, AP1 signaling	KAP1	Apoptosis, ribosome biogenesis	[54]

Table 1. Cont.

Molecular Mechanism	Gene	Common Alias(es)	Function	Additional Molecular Mechanisms	Cellular Targets	Role in Additional Cell Phenotypes or Behavior	Refs.
	<i>SPOP</i>	<i>BTBD32, TEF2, NSDVS1</i>	TS	Hh/GLI2 pathway	SP1/PI3K axis, HDAC6; MMP2	Apoptosis	[55–57]
	<i>PRDM5</i>	<i>BCS2, PFM2</i>	TS				[58]
	<i>UHRF1</i>	<i>ICBP90, Np95, RNF106, hNP95, TDRD22</i>	O				[59]
Epigenetic modifications	<i>MTA1</i>		O		VEGF-1, histone deacetylase	Angiogenesis	[60,61]
	<i>MORC2</i>	<i>CMT2Z, DIGFAN, ZCW3, ZCWCC1</i>	O		NDRG1		[62]
	<i>ZNF518B</i>		O		Histone methyltransferases		[63]
	<i>ZNF146</i>	<i>OZF</i>	O		hRAP		[64,65]
	<i>ZNF382</i>	<i>KS1</i>	TS		HP1, NF-κB, and AP1 signaling	Apoptosis	[66]
	<i>KLF5</i>	<i>BTEB2, CKLF, IKLF</i>	O		SNHG12	Stemness, DNA damage response, cell cycle	[67]
	<i>Sp1</i>		O		ZFAS1, VEGFA, miR-150-5p	Apoptosis	[68,69]
	<i>THAP11</i>	<i>RONIN</i>	O		HCF-1		[70]
	<i>ZBTB48</i>	<i>TZAP, HKR3, ZNF855</i>	O		Telomere dysregulation, mechanism under investigation		[71]
DNA Damage Response	<i>KLF4</i>	<i>EZF, GKLF</i>	TS	Wnt, ERK signaling	p53, histone acetylases; NDRG2, cyclin D1; u-PAR	Cell cycle	[72–75]
	<i>ZEB1</i>	<i>AREB6, BZP, DELTAEF1, FECD6, NIL2A, PPCD3, TCF8, ZFHEP, ZFHX1A</i>	O	Wnt pathway	MPG; LOXL2; uPA, PAI-1; miR-200	Stemness	[76–80]
	<i>HLTF</i>	<i>HIP116, HIP116A, HLTF1, RNF80, SMARCA3, SNF2L3, ZBU1</i>	TS				[81]

Table 1. Cont.

Molecular Mechanism	Gene	Common Alias(es)	Function	Additional Molecular Mechanisms	Cellular Targets	Role in Additional Cell Phenotypes or Behavior	Refs.
p53	ZBTB7A	FBI1, LRF, ZBTB7, ZNF857A, pokemon, TIP21	TS/O		ETS-1, MMPs; NF-κB	Glycolysis	[82–85]
	GLI3	ACLS, GCPS, GLI3-190, GLI3FL, PAPA, PAPB, PHS, PPDIV	O	ERK1/2 cascade			[86,87]
	ZNF398	p51, p71, ZER6	O		MDM2	Cell cycle	[88]
E-cadherin	SNAI1	SNAH, SLUGH2, SNAI1, SNAI1	O	Wnt/β-catenin signaling	VDR; lncRNA WiNTRLINC1, MYB	Stemness	[89–91]
	SPRY2	SPROUTY2, IGAN3	O		ZEB1, E-cadherin		[92]
	NANOS1	NOS1, SPGF12, ZC2HC12A	O		p120ctn		[93]
	ZC3H12C	MCPIP3	TS		Vimentin, VCAM-1, MMP2		[94]
Metabolism	YY1	DELTA, NF-E1, UCRBP, YIN-YANG-1	O	Wnt/β-catenin signaling	GLUT3; p53	Cell cycle, apoptosis	[95,96]
	ZBTB7C	APM1, ZBTB36, ZNF857C	TS	Ras, Wnt signaling	Myc	Inflammation	[97,98]
	ZFP1	ZNF475, PITA	O		p53	Apoptosis	[99]
	ZNF568	PISA	O		p53	Apoptosis	[99]
Angiogenesis	ZNF384	CAGH1, CAGH1A, CIZ, ERDA2, NMP4, NP, TNRC1	O		MMP2		[100]
	SNAI2	SLUG, SNAI2, WS2D, SLUGH1	O		MMPs; MDM2, p53/p21; VDR		[89,101–104]
	ZEB2	SMADIP1, SIP1, ZFHX1B	O	miR-192, E-cadherin	MMP-2/9	Metastasis, EMT	[105–108]
	ZNF24	ZNF191, ZSCAN3, KOX17	TS		VEGF		[109]
	ZKSCAN3	ZF47, ZFP306, ZNF306, ZNF309, ZSCAN13, ZSCAN35	O		VEGF, integrin β4		[110,111]

Table 1. Cont.

Molecular Mechanism	Gene	Common Alias(es)	Function	Additional Molecular Mechanisms	Cellular Targets	Role in Additional Cell Phenotypes or Behavior	Refs.
Under investigation	WT1	AWT1, GUD, NPHS4, WAGR, WIT-2, WT33	O				[112,113]
	ZBTB4	Kaiso-L1, ZNF903	TS				[114]
	FOXP1	12CC4, HSPC215, MFH, QRF1, hFKH1B	TS			Inflammation	[115,116]
	ZNF185	SCell	O				[117]
	ZNF217	ZABC1	O				[118]
	ZNF703	NLZ1, ZEPP01, ZNF503L, ZPO1	O				[119]
	CRIP1	CRHP, CRIP	O		GSK3/mTOR		[120,121]
	ZFC3H1	CCDC131, CSRC2, PSRC2	O				[122]
	ZFR	SPG71, ZFR1	O		FAM49B		[123]
	ZNF350	ZBRK1, ZFQR	TS		ATXN2		[124]

TS = tumor suppressor, O = oncogene; the NCBI Gene database was utilized to determine common alias(es).

2.1. ZFPs Modulate Wnt Signaling

The canonical Wnt pathway modulates β -catenin/T cell factor (TCF) transcription factor complex activity to regulate target gene expression and promote cell differentiation, proliferation, and migration. Briefly, after Wnt binding to its target receptor, comprising LRP5/6 and Frizzled (Fzd), Dishevelled (Dvl) is recruited to block cytosolic β -catenin phosphorylation and subsequent degradation by a destruction complex comprising glycogen synthase kinase β (GSK3 β), axin, casein kinase I (CK1), and adenomatous polyposis coli (APC). β -catenin then undergoes nuclear translocation where it complexes with TCF to induce target gene expression [9]. Inhibition of this pathway is commonly regulated by **ZNRF3**/RNF43, an E3 ubiquitin ligase, that degrades FZD and LRP6 to promote β -catenin ubiquitination [8,9].

Non-canonical Wnt pathways encompassing cascades independent of the β -catenin/TCF complex classically control cell migratory and polarity phenotypes; the two most common non-canonical pathways are the planar cell polarity and calcium-activated pathways [9,125].

Numerous ZFPs downregulate Wnt signaling by different mechanisms, thereby attenuating CRC cell motility and invasive behavior. This can occur by restricting the expression of EMT-promoting genes, e.g., blocking pro-EMT Wnt signaling via **OVOL2**-mediated recruitment of histone deacetylase to the TCF4- β -catenin complex [10]. **FLYWCH1** stimulates reduced cell motility and enhances cell attachment through β -catenin interactions and transcriptional modulation of β -catenin/TCF4 to impede the expression of downstream genes including **ZEB1**, **EPHA4**, and *E-cadherin* [13]. **ZFP36**, negatively correlated with Wnt/ β -catenin signaling activity, represses the expression of EMT-related transcription factors including **MACC1**, **ZEB1**, and **SOX9** [14]. While R-spondin proteins usually enhance Wnt signaling through **ZNRF3** turnover, **RSPO2** promotes the stabilization of membrane-associated **ZNRF3** through LGR5-dependent interactions [15]. These interactions reduce CRC cell motility and proliferation, likely by inhibiting the Wnt5a-activated non-canonical pathway [16]; this highlights the complexity and interactions between signaling pathways underlying CRC pathogenesis.

Many other ZFPs function to augment Wnt signaling. **ZIC2** promotes transcriptional repression of *Axin2*, a vital component of the β -catenin destruction complex, and/or direct interactions with β -catenin [17]. **ZBTB17** downregulates *Dapper1*, a protein that degrades Dvl, thereby enhancing Wnt signaling [18], while **BMI1** suppresses *IDAX*, a CXXC-type zinc finger domain-containing protein and Wnt pathway repressor, to increase cell proliferation [22]. **PLAGL2** facilitates both canonical and non-canonical Wnt signaling by activating Wnt6 and *ASCL2* to promote intestinal epithelial stem cell identity, and activating Wnt4a and Wnt5a, actions that promote enteroid growth [24,26]. Other ZFPs that augment Wnt signaling and promote cell proliferation and CRC metastatic potential include **ZNF281** [27], **GATA6** [28], and **TRIM37** [29].

ZNF277, a senescence-regulating transcription factor upregulated in CRC, is also a transcriptional target of β -catenin. Previous work by our group demonstrated that **ZNF277** mRNA and protein expression modulate key cancer pathways, including the HOXD family and p21^{WAF1}, and play a key role in M₃ muscarinic receptor-dependent murine CRC progression [30,31].

2.2. ZFPs Modulate Other Signaling Pathways

While Wnt signaling is a key modulator of colon cancer progression, many other pathways are also exploited by ZFPs. Notably, the Ras/ERK pathway, mutated in many cancers, is inhibited by **ZC3H13**, an anti-oncogene downregulated in CRC, thus attenuating cell proliferation and invasion [33]. Conversely, **ZDHHC9**, which is upregulated in CRC, potentially modulates the N-Ras and H-Ras pathway via its palmitoyl transferase activity; the precise mechanism of how this promotes tumorigenicity remains obscure [34].

Activation of intracellular Janus kinases (JAKs) via ligand-mediated receptor activation leads to downstream phosphorylation and dimerization of STAT proteins; this STAT

complex functions as a nuclear transcription factor that promotes the expression of genes beneficial for tumorigenesis [126]. For example, in addition to regulating the Ras/ERK pathway, **ZNF143** controls the JAK/STAT pathway to alter the expression of IL-8, a pro-angiogenic cytokine, thereby curtailing tumor progression [35]. **ZNF460** promotes CRC metastasis by stimulating JAK2/STAT3 signaling [37].

In the absence of an inhibitor, I κ B, the NF- κ B transcription factor, comprising p65 and p50 subunits, is translocated to the nucleus where it modulates the expression of target genes that promote cell proliferation, migration, and invasion [127]. Activation of NF- κ B signaling can occur via transcriptional repression of **ZCCHC10** by miR-410-3p [38]. Alternatively, ZFPs such as **ZFP91** can interact with the p65 subunit of NF- κ B to stimulate transcription of the alpha-subunit of the transcription factor hypoxia-inducible factor 1 (HIF-1 α) to regulate processes that promote tumorigenesis, including cell proliferation, invasion, metastasis, angiogenesis, and cell cycle progression [39].

Phosphatidylinositol 3-kinase (PI3K) is activated downstream of many receptor types to phosphorylate cell membrane-adherent phosphoinositides. Following a series of subsequent recruitment and binding events, involving various enzyme complexes, the AKT kinase is ultimately turned on to induce mTOR, MDM2, and FOXO activation resulting in accelerated cell differentiation and proliferation [128]. miR-708-5p, an enhancer of PI3K/AKT signaling, negatively regulates **ZNF549** to induce CRC cell proliferation and migration [40]. Interestingly, while **ZNF549** expression in primary tumors is reduced compared to normal tissue, its expression is increased in advanced-stage tumors, suggesting additional roles for this ZFP in CRC progression [40]. Conversely, **GLI1**, a vital player in Hedgehog signaling, enhances PI3K/AKT signaling in a Foxm1-dependent manner to increase CRC metastasis [42], while **ZNF692** promotes cell proliferation and invasion by altering the expression of proteins involved in cell cycle regulation and angiogenesis, including cyclin D1, CDK2, and p27^{Kip1}, via the PI3K/AKT pathway [43]. **ZBED6**, a repressor of IGF2 expression, attenuates cell proliferation, likely via PI3K signaling, and has also been implicated as a modulator of the Wnt, Hippo, TGF, and EGFR pathways [44].

TGF- β ligand–receptor binding results in the phosphorylation of cytosolic SMAD proteins and the formation of SMAD multimer complexes that are translocated to the nucleus and bind specific DNA motifs, thus regulating target gene expression [129]. Interestingly, the enhancement of TGF- β signaling by **ZNF37A**-induced repression of the tumor microenvironment regulator *THSD4* stimulates cytokine generation by cancer-associated fibroblasts to promote tumor spread [45]. TGF- β pathway activation to increase invasive potential can also occur via upregulation of **ZNF326** target genes, e.g., LTBP4, a TGF- β 1 receptor activator [46]. Both **ZNF367** [47] and **ZNF280A** [48] inhibit the Hippo tumor suppressor pathway, augmenting Yes-associated protein (YAP) signaling to enhance CRC cell proliferation. **ZMYND8**, a multifunctional transcription factor, histone reader, and DNA repair protein, is also a target of YAP-mediated signaling that induces the cholesterol synthesis necessary for CRC cell proliferation [50].

2.3. ZFPs Modulate Epigenetic Modifications

Epigenetic modifications are broadly characterized by altered gene expression in the absence of DNA sequence changes. The most well studied modifications involved in CRC pathogenesis include altered target gene promoter methylation status and/or recruitment of histone modifiers (i.e., acetylators and methylators) to alter gene expression levels [130]. Non-coding RNAs such as long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) have also emerged as epigenetic modulators [131]. Promoter methylation often inactivates or downregulates target tumor suppressor ZFPs, including **ZBTB18** [51], **GATA4/GATA5** [52], and **ZNF677** [53], to promote CRC pathogenesis via CRC cell proliferation and invasion. This can also occur via promoter hypermethylation, as seen with **ZFP82**, which normally interacts with the corepressor KAP1, to attenuate rRNA transcription and ribosome biogenesis via histone deacetylation [54], and **SPOP**, which facilitates polyubiquitination and subsequent degradation of histone deacetylase 6 (HDAC6) to reduce

deacetylation of non-histone proteins and prevent EMT [56,57]. Interestingly, **PRDM5**, a tumor suppressor underscored by its ability to inhibit cell proliferation after its transfection into human CRC cells, is also inactivated by trimethylation of histone H3 lysine [58]. Conversely, **UHRF1**, an E3 ubiquitin ligase, can initiate and maintain DNA hypermethylation to silence tumor suppressor genes and promote metastasis [59].

Interactions with histone deacetylases by ZFPs can also promote CRC metastasis. **MTA1**, whose expression is increased in CRC liver metastases, was shown to interact with histone deacetylase and modulate chromatin structure and transcriptional repression [61]. Similarly, **MORC2** interacts with the histone deacetylase Sirutin1 to suppress downstream Myc-regulated gene 1N (*NDRG1*) transcription, ultimately promoting EMT and CRC lung metastasis [62]. Alternatively, **ZNF518B** expression promotes CRC metastasis and recurrence by recruiting histone methyltransferases (e.g., EZH2 and G9A) to silence downstream tumor suppressor genes [63]. **ZNF146** enhances CRC cell proliferation and motility [65] by telomere dysregulation through interactions with hRAP, a telomeric protein that modulates telomere length [64]. Heterochromatin silencing via heterochromatin protein 1 interactions is a potential mechanism whereby **ZNF382** inhibits tumorigenesis by altering the expression of oncogenes and other factors involved in NF- κ B signaling [66].

Epigenetic modifications of DNA or chromatin are not the only mechanisms utilized to induce CRC oncogenicity. **KLF5**, a downstream mediator of activated K-Ras and H-Ras, targets lncRNAs to modulate the expression of protein-coding genes via interactions with co-regulatory transcription factors, such as AR and HSF1 [67]. Similarly, **Sp1** induces expression of the lncRNA ZFAS1, which binds miR-150-5p, to upregulate VEGFA and subsequently promote cell proliferation, migration, and invasion [68,69]. Primary tumors and metastases overexpress **THAP11** which binds to host cell factor-1 (HCF-1), a transcriptional coregulator, to target promoters, ultimately modulating transcription and cell proliferation via histone modifications [70].

2.4. ZFPs and the DNA Damage Response

Evasion of DNA damage response pathways during cell growth and proliferation is important for CRC progression. Non-homologous end joining (NHEJ) and homologous recombination (HR) are the major double-strand DNA break repair pathways, the latter requiring proto-oncogenes BRAC1 and BRCA2 for successful repair [132]. Other types of DNA damage, such as single-stranded DNA mishaps, utilize mismatch repair (MMR) and base excision repair (BER) to repair or remove mismatched nucleotides [133]. Defects in any of these pathways contribute to genomic instability and the accumulation of mutations that promote cancer cell phenotypes. **ZEB1**, a well-studied ZFP, promotes colitis-associated CRC by repressing transcriptional repair molecules, including N-methyl-purine glycosylase, involved in the BER pathway. ZEB1 upregulation in CRC cells also stimulates macrophages to generate reactive oxygen species and IL-1 β , which results in a positive feedback loop of increased DNA damage and impaired DNA repair [78].

KLF4 counteracts the suppressive effects of p53 on NHEJ and HR mechanisms to modulate DNA repair [74], and in colitis-associated CRC models, it maintains genomic stability by directing p53 to centrosomes [72]. Meanwhile, the inactivation of the DNA helicase protein **HLTF** in CRC promotes genomic instability and subsequent malignant transformation [81].

2.5. ZFPs Modulate p53 Levels

To maintain cell homeostasis through regulation of the cell cycle, DNA repair response, and cell death pathways, p53, a vital tumor suppressor, modulates numerous cell processes via its role as a transcription factor. p53 levels are tightly regulated by numerous proteins, including MDM2, an E3 ubiquitin ligase responsible for p53 degradation, thus maintaining p53 levels appropriate for the cell state [134]. **ZBTB7A**, a tumor suppressor [84], can also function as an oncogene by downregulating p53, thereby enhancing ETS proto-oncogene 1 (ETS-1) function and stimulating CRC cell proliferation and invasion [82]. Both **GLI3** [86]

and the p52 isoform of **ZFP398** [88] help stabilize the p53–MDM2 complex by binding to p53 and MDM2. The resulting ubiquitination and exosomal removal of p53 facilitate neoplasia and cell proliferation [88].

2.6. ZFPs Modulate E-Cadherin Expression

The transmembrane glycoprotein E-cadherin, a well-studied cell-adhesion molecule, is commonly expressed in epithelial cells to prevent metastatic behavior [135]. In CRC, **SNAI1** upregulation induces EMT and metastasis by inhibiting transcription and subsequent expression of the vitamin D receptor and E-cadherin, and promoting β -catenin nuclear translocation to potentiate Wnt pathway signaling [89]. **SPRY2**, a receptor tyrosine kinase modulator, also downregulates vitamin D₃-dependent E-cadherin expression to augment cellular invasion and de-differentiation [92]. **NANOS1**, a downstream target gene of E-cadherin, can also compromise the anti-migratory properties of E-cadherin. hNanos1, inversely correlated with E-cadherin expression, induces cytoplasmic translocation of p120 catenin (p120ctn), a regulatory protein that complexes with cadherin proteins at the cell membrane to maintain adherens junctions, subsequently disrupting cell-cell adhesion stability [93]. However, to attenuate cell migration and invasion, **ZC3H12C** overexpression enhances E-cadherin expression and suppresses vimentin expression in human CRC cells without altering cell survival [94].

2.7. ZFPs Modulate CRC Cell Metabolism

As opposed to metabolic pathways such as oxidative phosphorylation, CRC cells, like many other cancer cell types, utilize aerobic glycolysis for energy generation. Glutaminolysis, the breakdown of glutamine, is upregulated in CRC to maintain anaplerosis, which sustains glycolytic pathways needed for tumor cell growth and proliferation [136]. **ZBTB7C**, downregulated in CRC, is thought to block Myc and tumor cell glutaminolysis, thus increasing immune cell proliferation due to the glutamine surplus in the tumor microenvironment and attenuating CRC cell proliferation [98]. Enhanced tumor cell aerobic glycolysis is also exploited by several oncogenes to promote cell proliferation and metastasis, e.g., **YY1**, via *GLUT3* transcription upregulation [95], and **ZFP1**, via p53-dependent glycolysis [99]. **ZNF568** can accomplish this by inhibiting p53-mediated mitochondrial metabolism [99].

2.8. ZFPs Modulate the Expression of Factors That Stimulate Angiogenesis

A major mechanism underlying CRC metastasis is angiogenesis, the formation of new blood vessels, via modulation of vascular endothelial growth factor (VEGF) signaling [137]. VEGF targets tyrosine kinase receptors to regulate downstream signaling cascades that alter pro-angiogenic behavior such as vascular permeability and cell survival [137]. The availability of VEGF can be upregulated by matrix metalloproteinase-2 (MMP2), a multifunctional protein in cancer [138]. **ZNF384** [100], **SNAI2** [103], and **ZEB2** [107] are upregulated in CRC and enhance MMP2 expression and/or activity, promoting angiogenesis. **SNAI2**, which expedites p53/p21 degradation by upregulating MDM2 [101], is essential for mutant-KRAS cancer cell survival after EMT [104]. **ZNF24** represses VEGF expression [109] to suppress angiogenesis, while **ZKSCAN3**, an inducer of VEGF to promote CRC development and invasion, is implicated in carcinoembryonic antigen (CEA)-producing tumor liver metastasis [110].

3. ZFPs Coordinate Cell Cycle Regulation and Apoptotic Mechanisms in CRC (Table 2)

Cell cycle regulation, essential to maintain cell integrity, is monitored at key checkpoints. This process is highly dependent on cyclins, cyclin-dependent kinases (CDKs), and p53, which regulate cell cycle progression and prevent inappropriate cell growth and genomic replication [139]. Apoptosis, induced by cell stress signals, can occur via either the intrinsic or extrinsic pathway; the former is mediated by mitochondrial and Bcl-2 proteins, and the latter is executed by activation of cell death receptors (e.g., TRAIL). Both pathways ultimately activate caspase signaling cascades that promote programmed cell death [140]. Evading cell cycle arrest and apoptosis is essential for CRC cell survival and proliferation and tumor expansion and spread.

Table 2. ZFPs modulating cell cycle arrest and apoptosis.

Molecular Mechanism	Gene	Common Alias(es)	Function	Additional Molecular Mechanisms	Cellular Targets	Role in Additional Cell Phenotypes or Behavior	Refs
Checkpoint	<i>ZFP36L1</i>	<i>BRF1, Berg36, ERF1, RNF162B, TIS11B, cMG1</i>	TS		p53, cyclin A, cyclin B, cyclin D	Cell proliferation	[141]
	<i>ZFP36L2</i>	<i>BRF2, ERF2, OOMD13, OZEMA13, RNF162C, TIS11D</i>					
	<i>XAF1</i>	<i>BIRC4BP, HSXIAPAF1, XIAPAF1</i>	TS		Cyclin B, Chk1, Cdc25; XIAP		[142,143]
	<i>KLF6</i>	<i>BCD1, CBA1, COPEB, CPBP, GBF, PAC1, ST12, ZF9</i>	TS		p21, Bax	Cell proliferation	[144]
	<i>PATZ1</i>	<i>ZNF278, MAZR, RIAZ, ZBTB19, ZSG</i>	O	ERK/MAPK pathway	p21, p53, cyclin D1/E1	Cell proliferation	[145]
	<i>MZF1</i>	<i>MZF-1, MZF1B, ZFP98, ZNF42, ZSCAN6</i>	O		p55 ^{PIK} ; <i>Axl</i>	Migration, invasion	[146–148]
Bcl-x _L pathway	<i>ZIC1</i>	<i>BAIDCS, CRS6, ZIC, ZNF201</i>	TS	PI3K/AKT, MAPK pathways	Bcl-x _L /Bad/Caspase 3 cascade; GADD45B	Cell proliferation	[149]
	<i>MECOM</i>	<i>AML1-EVI-1, EVI1, MDS1, MDS1-EVI1, PRDM3, RUSAT2, MDS1 and EVI1 complex locus, KMT8E</i>	O	TGF-β; TIMP2, DNMT1	BCl-x _L , ΔNp63	Cell proliferation, invasion, metastasis	[150–153]
	<i>CPEB4</i>	<i>CPE-BP4</i>	O		Bcl-x _L , Bax	Cell proliferation, invasion	[154]
Epigenetic modifications	<i>ZBTB33</i>	<i>Kaiso, ZNF348</i>	O	cyclin D1/cyclin E1, MTG16	CDKN2A	Cell proliferation	[155–157]
	<i>ZNF304</i>		O		<i>p14^{ARF}, p15^{INK4B}, p16^{INK4A}</i>		[158]
	<i>ZC3HAV1</i>	<i>ZAP; ZC3H2; ARTD13; PARP13; FLB6421; ZC3HDC2</i>	TS		<i>TRAILR4</i>		[159]
	<i>PRDM2</i>	<i>HUMHOXY1, KMT8, MTB-ZF, RIZ, RIZ1, RIZ2</i>	TS				[160,161]

Table 2. Cont.

Molecular Mechanism	Gene	Common Alias(es)	Function	Additional Molecular Mechanisms	Cellular Targets	Role in Additional Cell Phenotypes or Behavior	Refs
Other	<i>PLAGL1</i>	<i>LOT1, ZAC, ZAC1</i>	TS		PPAR γ	Cell differentiation	[162,163]
	<i>KLF9</i>	<i>BTEB, BTEB1</i>	TS		ISG15	Cell proliferation, differentiation	[164]
	<i>ZFX</i>	<i>ZNF926</i>	O		DUSP5, MAPK signaling	Cell proliferation	[165–167]
	<i>ZNF746</i>	<i>PARIS</i>	O		GSK3 β , FWB7, c-Myc	Cell proliferation	[168]
	<i>RBBP6</i>	<i>MY038, P2P-R, PACT, RBQ-1, SNAMA</i>	O		p53		[169]
	<i>GLI2</i>	<i>CJS, HPE9, PHS2, THP1, THP2</i>	O		TGF- β , HIF1- α	Stemness, cell differentiation	[170]
	<i>GLIS2</i>	<i>NKL, NPHP7</i>	O		PUMA	Cell proliferation, migration	[171]
Under investigation	<i>GFI1</i>	<i>SCN2, ZNF163, GFI1A</i>	TS			Cell proliferation	[172]
	<i>ZBTB16</i>	<i>PLZF, ZNF145</i>	O			Stemness, cell proliferation	[173]
	<i>CIZ1</i>	<i>LSFR1, NP94, ZNF356</i>	O			Cell proliferation	[174,175]

TS = tumor suppressor, O = oncogene; the NCBI Gene database was utilized to determine common alias(es).

3.1. ZFPs and Cell Cycle Checkpoint Regulation

The backbone of cell cycle regulation consists of CDKs activated by cyclins in the presence of mitogenic signals [176]. **ZFP36L1** and **ZFP36L2**, both downregulated in CRC, are postulated to promote G1-phase cell cycle arrest without triggering cell death, likely by downregulating cyclin D expression [141]. Other regulatory components, such as checkpoint kinase 1 (Chk1), are vital to ensure cell cycle arrest until DNA damage is repaired [139]. To achieve G2-M cell cycle arrest, **XAF1** activates Chk1 and then inactivates Cdc25C, a CDK activator, and the Cdc2–cyclin B complex [143].

Other promoters of cell cycle arrest following DNA damage include cyclin-dependent kinase inhibitors, such as p21^{Cip1/Waf1}, which is upregulated by p53 [139]. **KLF6** (particularly the SV2 splice variant implicated in sporadic CRC) induces apoptosis by upregulating p21^{Cip1/Waf1} and Bax, a pro-apoptotic Bcl-2 family protein [144]. Alternatively, **PATZ1**, upregulated in CRC, downregulates p21^{Cip1/Waf1} expression and prevents cell cycle arrest by upregulating cyclin D1 and E1 [145]. **MZF1** induces p55^{PIK} gene transcription by attaching to the cis-element “TGGGGA”, which in turn promotes cell cycle progression through p55^{PIK}–Rb interactions [146]. Interestingly, **MZF1** is also implicated in sulindac sulfide-mediated TRAIL receptor (death receptor 5) transcription, leading to apoptosis—A potential strategy for cancer therapy [147].

3.2. Homeostasis Governed by the Bcl-2 Protein Family Can Be Modulated by ZFPs

Bcl2 family proteins, comprising pro- and anti-apoptotic proteins, are differentially regulated to maintain cellular homeostasis. When apoptosis is induced by cell stress, anti-apoptotic proteins (e.g., Bax, Bcl-x_L) are upregulated by p53-induced BH3-only proteins, which target mitochondrial proteins to initiate caspase activation and programmed cell death [140]. **ZIC1**, downregulated by promoter hypermethylation in CRC, induces apoptosis by triggering the Bcl-x_L/Bad/Caspase 3 cascade [149]. **MECOM** upregulation in CRC inhibits apoptosis by inducing Bcl-x_L protein transcription and augmenting cells in the G0/G1 phase [151]. **CPEB4** promotes CRC development by downregulating Bax and increasing Bcl-x_L expression, thus suppressing apoptosis [154].

3.3. Epigenetic Modifications Modulated by ZFPs

As discussed above, epigenetic modifications provide a common mechanism to regulate ZFP function and can be manipulated by ZFPs to suppress CRC progression. Both **ZBTB33** [157] and **ZNF304** [158] promote tumor suppressor gene silencing by directly binding to CpG island methylator phenotype gene promoters and recruiting corepressor complexes to methylate target genes, thereby preventing CRC cell cycle arrest. In contrast, to induce apoptosis in an exosome-dependent manner, **ZC3HAV1** binds directly to and degrades the mRNA transcript of anti-apoptotic TRAIL decoy receptor 4 (*TRAILR4*) [159]. Interestingly, the tumor-suppressive effects of **ZC3HAV1** are dictated by the tumor microenvironment. In the presence of TRAIL signals, **ZC3HAV1** stimulates apoptosis, but in their absence, **ZC3HAV1** suppresses cell growth. **PRDM2**, frequently inactivated by DNA methylation, has been shown to promote cell apoptosis and G2/M arrest in colon cancer cells [160].

3.4. Other Mechanisms Whereby ZFPs Modulate CRC Progression

ZFPs can modulate CRC pathogenesis by modulating cell signaling and dependency on the tumor microenvironment. **PLAGL1**, an anti-proliferative gene, modulates apoptosis and cell cycle arrest in a PPARγ-dependent manner by upregulating the expression of target genes involved in cell growth [162]. **KLF9** inhibits ISG15, an apoptosis-inhibiting cytokine, thereby suppressing tumorigenesis [164], while **ZFX** downregulates DUSP5, permitting constitutive MAPK signaling, to promote apoptotic resistance and cell cycle progression [166].

ZNF746 upregulation in CRC likely inhibits GSK3β and FWB7 to modulate site-specific phosphorylation and dephosphorylation of oncogenic c-Myc, an action that blocks

c-Myc ubiquitination and degradation to ultimately evade G1 cell cycle arrest [168]. **RBBP6** upregulation in CRC facilitates MDM2-mediated p53 ubiquitination and degradation to promote tumorigenesis [169].

GLI2 activation by HIF-1 α and cancer-associated fibroblast-secreted TGF- β 2 recruits anti-apoptotic molecules, allowing evasion of chemotherapy-induced apoptosis in a hypoxic tumor microenvironment [170]. To augment cell migration and retard apoptosis, **GLIS2**, a GLI2-related KLF protein, inhibits transcription of the apoptotic gene *PUMA* and focal adhesion genes (e.g., cadherins), likely by modulating acetylation levels of gene enhancers [171].

4. ZFPs Aid in Maintaining Cell Stemness to Propagate CRC-Promoting Cell Behaviors (Table 3)

Maintenance of stemness allows the self-renewal, differentiation, and propagation of a specific cell lineage. Cancer cells adopt this phenotype to enhance cell survival, cloning, and proliferation [177]. In CRC, many ZFPs contribute to this stem-like maintenance by manipulating Wnt signaling and epigenetic pathways.

Table 3. ZFPs involved in regulating cell stemness.

Molecular Mechanism	Gene	Common Alias(es)	Function	Additional Molecular Mechanisms	Cellular Targets	Role in Additional Cell Phenotypes or Behavior	Refs.
Wnt	<i>JADE3</i>	<i>PHF16</i>	O		LGR5		[178]
	<i>PRDM1</i>	<i>BLIMP1</i> , <i>PRDI-BF1</i>	O		IGFBP3, ERK1/2		[179]
	<i>SALL4</i>	<i>DRRS</i> , <i>HSAL4</i> , <i>IVIC</i> , <i>ZNF797</i>	O		β -catenin, GLI2	Metastasis	[180–182]
Epigenetics	<i>ZRANB1</i>	<i>Trabid</i>	O	Wnt signaling, APC	EZH2	Cell proliferation	[183]
	<i>UPF1</i>	<i>HUPF1</i> , <i>NORF1</i> , <i>RENT1</i> , <i>UTF</i> , <i>pNORF1</i> , <i>smg-2</i>	O		TOP2A		[184]
	<i>SALL3</i>	<i>ZNF796</i>	O		Under investigation		[185,186]
Under investigation	<i>PRDM14</i>	<i>PFM11</i>	O			Invasion	[187]
	<i>RBCK1</i>	<i>HOIL1</i> , <i>PBMEI</i> , <i>PGBM1</i> , <i>RBCK2</i> , <i>RNF54</i> , <i>UBCE7IP3</i> , <i>XAP3</i> , <i>XAP4</i> , <i>ZRANB4</i>	O			Migration and invasion	[188]

O = oncogene; the NCBI Gene database was utilized to determine common alias(es).

4.1. ZFPs Modulate Wnt Signaling

To maintain stemness, upregulation of **JADE3** expression in CRC potentiates canonical Wnt signaling and subsequent transcriptional upregulation of the stem cell regulator and marker *LGR5* by recruiting histone acetylases at the *LGR5* promoter [178]. Conversely, **PRDM1** contributes to cancer cell stemness by preferential regulation of the non-canonical Wnt pathway, specifically the planar cell polarity pathway, detected by the presence of upregulated downstream targets such as *Wnt5A* and *Fzd4* [179]. **SALL4** was shown to promote metastasis [180] and stem cell self-renewal via its ability to modulate GLI1 expression [181] and potentiate the canonical Wnt/ β -catenin pathway by direct interactions with β -catenin [182].

4.2. ZFPs Modulate Epigenetic Modifications

When recruited by lncRNA FAM83C-AS1, **ZRANB1** de-ubiquitinates and stabilizes histone methyltransferase EZH2 to downregulate the expression of the metastasis suppressor *SEMA3F* and increase CRC cell stemness, proliferative, and metastatic capabilities [183]. Interestingly, **UPF1** upregulation induces oxaliplatin chemoresistance by augmenting topoisomerase enzyme activity, thereby sustaining CRC stemness [184].

5. ZNF Structure and Function in CRC

In addition to highlighting the vital functions of ZFPs in CRC pathogenesis, it is important to recognize the role ZNF motifs play as core domains enabling ZFPs to execute specific tasks. ZNF motifs house consensus sequences commonly comprising cysteine (Cys) and histidine (His) residues coordinated by one or more zinc ions. The configuration of the ZNF structural fold varies depending on the combination and location of coordinated residues within the consensus sequence. Thirty types of ZNFs are classified based on structural composition, each type likely contributing to specific ZFP functions [189], particularly in CRC progression.

The majority of ZNFs belong to the Cys2His2 (C2H2)-type family. This ZNF family structurally comprises a single α -helix and anti-parallel β -sheet containing pairs of Cys and His residues coordinated by one zinc ion, which is necessary for target DNA sequence recognition and binding [190]. ZNF281, KLF4, and SNAI2 are among several ZFPs that harbor C2H2-type domains and modulate Wnt signaling, DNA damage response mechanisms, and angiogenesis, respectively, to modify CRC cell behavior [189].

E3-ubiquitin ligases, an abundant type of ZFP, can possess RING finger domains, characterized by a consensus sequence containing multiple Cys residues and a single His residue coordinated by two zinc ions. This domain is vital for ZNRF3, which regulates cytoplasmic β -catenin levels to negatively modulate Wnt signaling and cell proliferation [8]. UHRF1 possesses both RING finger and PHD domains responsible for silencing CRC metastatic tumor suppressor genes via epigenetic modifications [189].

Conserved Mutations in C2H2-Type ZFPs in CRC

The structural importance of ZNF motifs in ZFP function in CRC is evidenced by the functional consequences of ZNF-localized mutations. Computational and functional genomic analyses of CRC tumor samples reveal a high somatic mutation frequency at specific, conserved amino acid residues within C2H2-containing ZFP transcription factors, including ZNF382, ZNF281, and ZEB1 [191]. The most common mutation, an arginine-to-isoleucine missense mutation at position 9, is predicted to alter the necessary orientation of the ZNF with respect to neighboring domains and impair the specificity of target DNA recognition and binding [191]. This, in concert with the finding that adjacent residues (i.e., position 8) are not frequently mutated in CRC [191], highlights the integral role of highly conserved residues in maintaining crucial ZNF structure and ZFP functions. It is possible that there is a threshold for the types of ZNF mutations tolerable for cells, particularly for ZFPs necessary for essential cellular functions. Additional studies are necessary to elucidate the molecular underpinnings by which such mutations modify ZFP-specific functions and downstream target gene expression; this will help lay the groundwork for personalized, targeted therapeutic development.

6. Evaluating the Potential of ZFPs as CRC Therapeutic Targets

As these multidimensional proteins play diverse roles in promoting CRC, ZFPs are poised to serve as targets for therapeutic development. A potential approach is the design and use of metallo-compounds to alter zinc coordination properties within the crucial ZNF motif. Several metal-based compounds are approved to treat various conditions, including rheumatoid arthritis, cancer (e.g., cisplatin), and parasitic infestation [192]. In vitro studies targeting SP1 [193] and ZFP36 [194] with copper complexes have demonstrated therapeutic potential by diminishing chemoresistance and modulating inflammation, respectively.

Future studies must evaluate the potential side effects of metal-complex treatments and monitor for metal toxicity. Another potential approach to modulate ZFP activity in CRC is to repurpose thalidomide analogs, already approved to treat select hematologic cancers. These small-molecule drugs degrade C2H2-type ZFPs by activating the E3 ubiquitin ligase CRL4^{CRBN} in vitro [195]. The use of thalidomide analogs to target oncogenic C2H2-containing ZFPs involved in promoting CRC may be a promising avenue of exploration.

7. Current Limitations to Targeting ZFPs for CRC Therapy

While we highlighted specific roles of ZFPs throughout this review, it is important to note that these proteins play multiple roles in the promotion of tumorigenic cell phenotypes (Tables 1–3). The ability of ZFPs to cross-regulate multiple different mechanisms, including signaling pathways, cell cycle checkpoints, and angiogenic markers, demonstrates the complexity of investigating the role of distinct ZFPs in CRC pathogenesis and identifying ZFPs as targets with therapeutic potential. While altered expression of certain ZFPs is linked to CRC survival (Figure 2), the precise underlying mechanisms remain elusive for most proteins. Additionally, there are conflicting data regarding whether some ZFPs, e.g., SALL1 [185,196], ZIC5 [197,198], ZNF148 [199–201], and ZNF750 [202,203], are CRC tumor suppressors or oncogenes; this raises the possibility they have dual functions depending on tumor stage—additional studies are needed to explore this possibility.

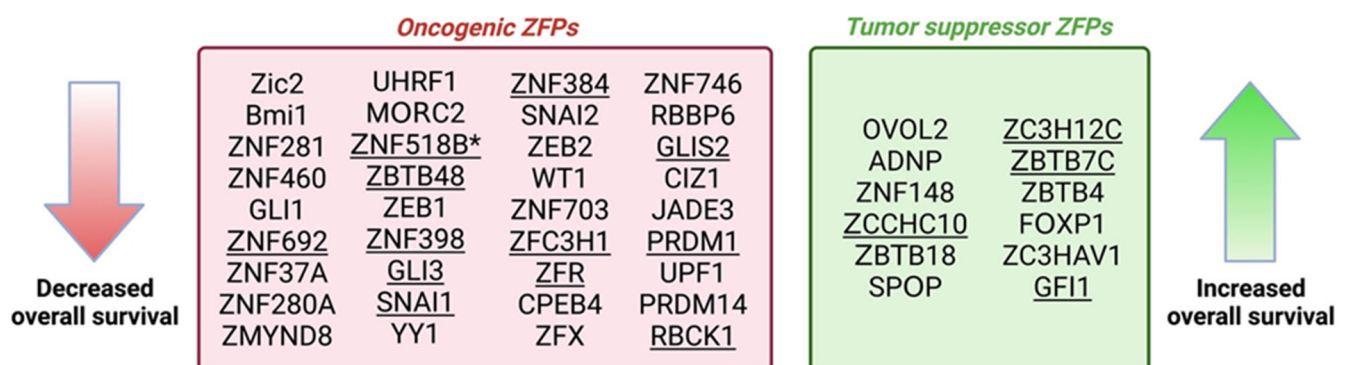


Figure 2. ZFPs implicated in overall survival (OS) outcomes for individuals with colorectal cancer. Increased expression of tumor suppressor ZFPs increased OS, while upregulation of oncogenic ZFPs decreased OS. Underlined ZFPs indicate expression of mRNA transcripts, instead of protein levels. Asterisk (*) indicates a decreased ratio of mRNA isoform 2 to 1. Created with Biorender.com.

Many studies performed to understand the pathways and signaling mechanisms by which ZFPs suppress or promote CRC behavior stem are limited by the reliance on cell lines or murine models to draw conclusions regarding human disease. Additional work using human tissue, perhaps organoids, will help confirm their putative roles and mechanisms of action. While ZFPs play a complex role in CRC, ZFP lncRNA antisense (AS) transcripts are also emerging as players. ZFAS1 [204], ZEB2-AS1 [205], and ZEB1-AS1 [206] are among the lncRNA transcripts upregulated in CRC. Future studies investigating ZFPs, and their AS transcripts, will expand our understanding of their role in CRC development and progression and the potential to develop novel therapeutics based on this information.

8. Conclusions

ZFPs play key roles in CRC development and progression, primarily acting as oncogenes or tumor suppressors, by regulating cell proliferation, senescence, apoptosis, cell cycle, EMT, cell migration, invasion, stemness, and Wnt signaling. Future research can be directed at understanding the interactions between various ZFPs and identifying those with the most important effects on CRC metastasis and survival, thus identifying novel therapeutic opportunities.

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