International Journal of General Practice Nursing, 2025, Volume 3, No Special
https://ojs.bbwpublisher.com/index.php/IJGPN
ISSN Online: 2981-9423
ISSN Print: 2981-9415

Epigenetic Regulatory Mechanisms of ZNF304 in Colorectal Cancer and Its Role in Migration and Invasion

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Abstract: Colorectal cancer is one of the leading causes of cancer-related deaths worldwide, and its development involves complex genetic and epigenetic mechanisms. Epigenetic regulation, especially DNA methylation, plays a crucial role in tumorigenesis, progression, and metastasis. Epithelial-mesenchymal transition (EMT) is an important process promoting tumor cell invasion and metastasis, and epigenetic regulators such as TRIM28 and ZNF304 play key roles in this process. TRIM28 can regulate the expression of EMT-related genes by activating the TGF-β signaling pathway and histone modification; ZNF304, as a member of the C2H2 zinc finger transcription factor family, is closely related to cell survival, migration, and metastasis in various tumors. This review summarizes the epigenetic regulatory mechanisms of TRIM28 and ZNF304 in colorectal cancer, exploring their roles in the EMT process and tumor migration and invasion, providing new insights for the study of colorectal cancer metastasis mechanisms and targeted therapy.

Keywords: Colorectal cancer; ZNF304; TRIM28; Epigenetics; Epithelial-mesenchymal transition

Online publication: December 31, 2025

1. Introduction

In more than half of the world's countries, malignant tumors have become one of the leading or secondary causes of death in people over 70 years of age [1]. According to data from the National Cancer Center of China in 2019, the number of new malignant tumor cases in my country reached 3.929 million in 2015, of which colorectal cancer accounted for 388,000 cases, ranking third; and the number of deaths reached 187,000, ranking fifth [2]. The occurrence of colorectal cancer is a complex process involving multiple factors, multiple steps, and multiple stages. Although genetic factors play an important role, most colorectal cancer cases are sporadic and develop gradually over several years through adenomas-carcinoma sequences [3].

Epigenetics refers to the phenomenon of heritable changes in gene expression without altering the gene's nucleotide sequence [4]. Its forms include DNA methylation, genomic imprinting, maternal effects, gene

silencing, and RNA editing [5]. Among these, DNA methylation, as one of the most thoroughly studied epigenetic modifications, plays an important regulatory role in tumor development and progression.

Epithelial-mesenchymal transition (EMT) is a key biological process by which tumor cells acquire invasiveness and migration capabilities [6,7]. During EMT, epithelial cells lose their cell polarity and adhesive properties, acquiring a mesenchymal-like morphology, thereby gaining the ability to invade and migrate [8]. Studies have shown that EMT activation is closely related to tumor progression, drug resistance, and poor prognosis [9–11]. Therefore, in-depth exploration of the relationship between epigenetic factors and EMT is of great significance for revealing the metastatic mechanism of colorectal cancer.

2. Results

2.1. Molecular mechanisms and signaling pathways of EMT

During EMT, cells transition from an epithelial phenotype to a mesenchymal phenotype, characterized by decreased expression of E-cadherin, ZO-1, and cytokeratin, while increased expression of mesenchymal markers such as Vimentin, N-cadherin, fibronectin, and ZEB1 [12,13]. The loss of E-cadherin is considered a core event in EMT [10]. After EMT activation, cell morphology changes from polygonal to spindle-shaped, with significantly enhanced migration and invasion capabilities.

Sun *et al. found that EMT mainly occurs in the early stages of tumor invasion, at which point E-cadherin is absent, while Vimentin is occasionally upregulated* [14]. ZEB1 is considered one of the most potent EMT activators [15,16], which can inhibit epithelial gene expression and is closely related to tumor invasion, metastasis, drug resistance, and poor prognosis [17–19]. Multiple signaling pathways are involved in EMT regulation, including TGF-β, Wnt, Notch, PI3K, MAPK, and Hedgehog [20–22]. Among them, the TGF-β signaling pathway is particularly crucial in tumor progression [23–25]. TGF-β is usually secreted by cells in the tumor microenvironment (TME) and regulates various biological processes such as cell proliferation, differentiation, apoptosis, and migration through Smad-dependent and Smad-independent pathways [20,26,27]. It can also maintain cancer stem cell homeostasis, suppress immune responses, and induce EMT and metastasis [28].

2.2. Epigenetic regulatory role of TRIM28

The tripartite motif (TRIM) family contains more than 80 members, with its typical structure being an N-terminal RBCC motif, including the RING, B-box, and helical domains [29]. The RING domain possesses E3 ubiquitin ligase activity, mediating post-translational modifications of proteins [30], thereby regulating the stability of key molecules in TGF-β signaling [31].

Multiple studies have shown that members of the TRIM family are involved in tumor cell proliferation, differentiation, transcriptional regulation, and chromatin remodeling [25,32]. TRIM28 (also known as transcriptional mediator 1β, TIF1-β) can synergistically regulate the transcription of multiple genes with KRAB domain transcription factors [25]. Fitzgerald *et al. found that TRIM28 can activate the TGF-β signaling pathway by inhibiting the translation of KRAB transcription factors, thereby promoting EMT and cell migration* [33–36]. Furthermore, TRIM28 can regulate the transcriptional activity of more than 700 KRAB transcription factors, exhibiting broad co-inhibition or co-activation effects [37,38], and is overexpressed in various tumors, closely associated with recurrence and poor survival [39,40].

2.3. Function of ZNF304 and its research progress in colorectal cancer

C2H2 zinc finger proteins are the largest family of transcription factors in the human genome, with about two-thirds of transcription factors containing the C2H2 structure, half of which carry an N-terminal KRAB repressive domain [41,42]. ZNF304, as a member of this family, belongs to the Kruppel-associated box (KRAB) type transcription factor and has transcriptional repression function [43].

In KRAS-positive colorectal cancer cells, ZNF304 is upregulated and binds to the promoter of the tumor suppressor gene INK4-ARF, leading to its silencing [44]. Aslan *et al. found that ZNF304 promotes cell migration and survival and inhibits anoikis in ovarian cancer, and its high expression is closely related to poor patient prognosis* [45]. Studies have shown that the coexistence of genome-wide hypomethylation and promoter-specific DNA hypermethylation is an important characteristic of colorectal cancer [46]. EMT activation promotes tumor cell invasion and metastasis [47–49]. TGF-β upregulates TRIM28 expression, regulates the expression of EMT marker genes (such as Cdh1 and Cdh2) through histone modification, and further enhances the EMT process [36].

Furthermore, TRIM28 overexpression in colorectal cancer is closely associated with disease recurrence and poor prognosis [39,50]. Although ZNF304 has been shown to promote cell survival and migration in ovarian cancer through multiple oncogene pathways [45], its mechanism of action in colorectal cancer remains unclear.

3. Conclusion

The occurrence and progression of colorectal cancer involve a complex molecular regulatory network, among which the epigenetic regulators TRIM28 and ZNF304 play key roles in EMT induction and tumor metastasis. TGF-β promotes EMT by upregulating TRIM28, while ZNF304 may affect tumor suppressor gene silencing and cell migration through specific transcriptional repression mechanisms. In-depth research on the epigenetic regulatory role of ZNF304 in colorectal cancer will help reveal the molecular mechanisms of tumor invasion and metastasis, and provide new theoretical basis and potential strategies for the early diagnosis and targeted treatment of colorectal cancer.

Disclosure statement

The author declares no conflict of interest.

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