REVIEW

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Epigenetic Landscapes and Stromal Epithelial Crosstalk in Colorectal Adenocarcinoma: Histomorphological Signatures of Tumor Progression

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ABSTRACT

To comprehensively review the current understanding of epigenetic regulation and stromal–epithelial crosstalk in colorectal adenocarcinoma and to elucidate their correlation with histomorphological signatures of tumor progression. A systematic narrative review was conducted using PubMed, Scopus, and Web of Science databases for articles published between 2021 and 2026. Keywords included colorectal cancer, epigenetic regulation, tumor microenvironment, cancer-associated fibroblast, stromal epithelial interaction, metabolic reprogramming, and histopathology. Only peer-reviewed articles focusing on molecular mechanisms and histological correlations were included. Recent evidence demonstrates that DNA methylation, histone modification, and non-coding RNA networks orchestrate transcriptional reprogramming in colorectal adenocarcinoma. These epigenetic alterations interact dynamically with cancer-associated fibroblasts, immune cells, extracellular matrix components, and metabolic pathways within the tumor microenvironment. Crosstalk mechanisms mediated by cytokines, growth factors, and extracellular vesicles contribute to epithelial–mesenchymal plasticity, tumor budding, desmoplastic reaction, and vascular remodeling. Spatial transcriptomics further reveals that stromal activation correlates with aggressive histomorphological patterns and unfavorable clinical outcomes. Epigenetic landscapes and stromal–epithelial communication are central determinants of colorectal adenocarcinoma progression. Their integration with histopathological evaluation offers promising opportunities for biomarker development and targeted therapeutic strategies.

Keywords: colorectal adenocarcinoma, epigenetic regulation, tumor microenvironment, cancer-associated fibroblast, histomorphology.
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INTRODUCTION

Colorectal adenocarcinoma represents one of the leading causes of cancer-related mortality worldwide. Despite advances in surgical techniques, chemotherapy, and immunotherapy, disease progression and therapeutic resistance remain significant clinical challenges. Traditionally, colorectal carcinogenesis has been explained through genetic instability pathways, including chromosomal instability, microsatellite instability, and CpG island methylator phenotype. However, growing evidence suggests that epigenetic dysregulation and tumor microenvironment remodeling play equally critical roles in tumor evolution.[1]

Epigenetic regulation refers to heritable changes in gene expression that occur without alterations in DNA sequence. In colorectal adenocarcinoma, DNA methylation, histone modification, and non-coding RNA networks orchestrate transcriptional programs that regulate proliferation, differentiation, apoptosis, and immune evasion. Importantly, these alterations are reversible, rendering them attractive therapeutic targets.

Simultaneously, the tumor microenvironment has emerged as a dynamic ecosystem composed of cancer-associated fibroblasts, immune infiltrates, endothelial cells, and extracellular matrix components. Stromal epithelial crosstalk is mediated through soluble factors, extracellular vesicles, metabolic intermediates, and direct cell–cell interactions. These interactions shape tumor behavior and are reflected in distinct histomorphological patterns, including tumor budding, desmoplastic stroma, glandular heterogeneity, and vascular remodeling.

Understanding how epigenetic landscapes intersect with stromal signaling is essential for elucidating tumor progression and identifying clinically relevant biomarkers.

MATERIALS AND METHODS

This article was compiled using a systematic narrative review approach with a comprehensive and structured literature search strategy. The search was conducted in PubMed, Scopus, and Web of Science

databases for articles published between January 2021 and February 2026. The search strategy employed a combination of Boolean keywords including colorectal cancer, epigenetic regulation, DNA methylation, histone modification, non-coding RNA, tumor microenvironment, cancer-associated fibroblast, stromal epithelial interaction, metabolic reprogramming, and histopathological features.

The literature selection process involved evaluation, and methodological quality assessment using a critical approach focusing on study design, sample size, molecular analysis techniques, and clinical relevance. Included articles included original research, systematic reviews, and meta-analyses addressing epigenetic mechanisms and tumor microenvironment interactions in colorectal adenocarcinoma. Articles published before 2021, case reports, editorials, and studies irrelevant to the topic were excluded.

Data extraction was performed systematically to identify specific epigenetic alterations, the molecular signaling pathways involved, the stromal and immune components involved, and their correlation with histopathological parameters and clinical outcomes. Data synthesis was performed narratively with an integrative approach to generate a conceptual framework linking molecular alterations to tumor morphological manifestations.

RESULTS

The Epigenetic Landscape in Colorectal Carcinogenesis

Epigenetic changes in colorectal adenocarcinoma not only act as a secondary mechanism to genetic mutations but also as a primary determinant regulating the transcription of genes involved in neoplastic transformation, tumor progression, and therapy resistance. Promoter hypermethylation of tumor suppressor genes such as MLH1 leads to microsatellite instability through inactivation of the mismatch repair system, which contributes to the accumulation of somatic mutations and an increased tumor neoantigen burden. This phenomenon not only influences carcinogenesis pathways but also determines response to immunotherapy, as tumors with high microsatellite instability exhibit higher lymphocyte infiltration and sensitivity to immune checkpoint inhibitors.

In addition to focal hypermethylation, global genomic hypomethylation is also an important characteristic of colorectal cancer, associated with the activation of retrotransposon elements, chromosomal instability, and the expression of genes associated with invasion and metastasis. Studies based on high-resolution methylome analysis have shown a correlation between specific methylation patterns and molecular subtypes of colorectal cancer, which significantly differ in prognosis and therapy response.

Histone modifications play a role in regulating chromatin structure and the accessibility of transcription factors to DNA. Decreased H3K27 trimethylation, mediated by increased histone demethylase activity, is associated with the activation of genes involved in the epithelial-mesenchymal transition and tumor cell stemness. Conversely, increased histone acetylation at proliferative gene promoters creates a more open chromatin environment, supporting the expression of genes regulating the cell cycle and angiogenesis. In experimental models, histone deacetylase inhibitors have been shown to induce epithelial differentiation and suppress tumor cell proliferation through global transcriptional reprogramming.

The role of non-coding RNAs in the epigenetic landscape is gaining increasing attention due to their ability to regulate gene expression post-transcriptionally and epigenetically. Certain microRNAs, such as miR-21 and miR-155, are known to play a role in suppressing the expression of tumor suppressor genes and increasing the activity of the PI3K/AKT and TGF-β pathways, which are associated with tumor invasion. Long non-coding RNAs such as HOTAIR and MALAT1 function as scaffolds for histone modification complexes, facilitating the formation of repressive chromatin at epithelial differentiation genes. Furthermore, circular RNA acts as a sponge for microRNAs, modulating the complex gene regulatory network involved in colorectal carcinogenesis.

The interplay between metabolic reprogramming and epigenetic regulation is a crucial aspect explaining the phenotypic plasticity of tumor cells. Metabolites such as acetyl-CoA, S-adenosylmethionine,

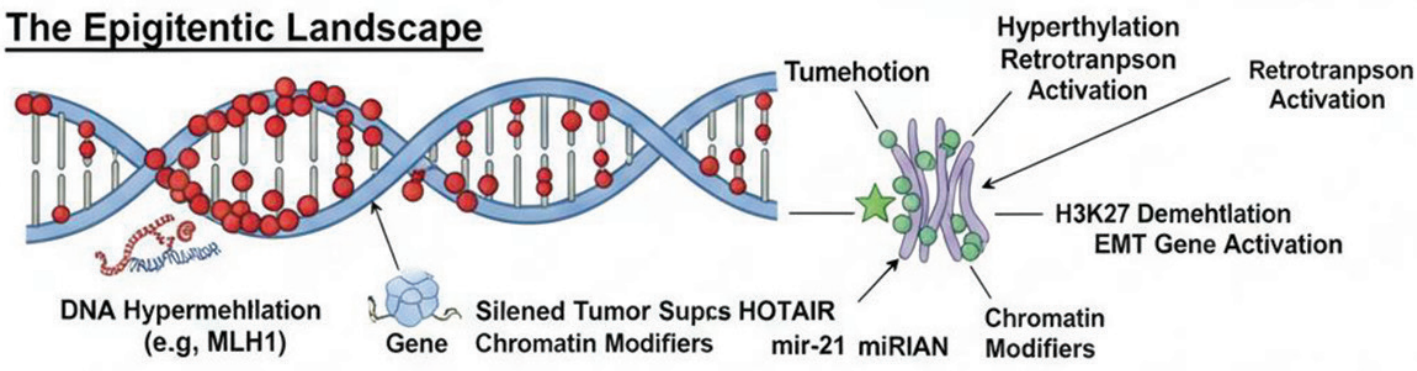

Figure 1. A chemical modification mechanism of DNA and histone proteins that controls gene expression without changing the DNA base sequence.

and α-ketoglutarate serve as acetyl or methyl group donors for epigenetic enzymes, enabling changes in tumor cell metabolism to directly influence the epigenome. Hypoxic conditions in the tumor microenvironment increase lactate production, which inhibits histone deacetylase activity and promotes the expression of genes related to angiogenesis and invasion.[2,3]

Fibroblast Heterogeneity and Epithelial-Strom Crosstalk

Cancer-associated fibroblasts are a major component of the tumor microenvironment, exhibiting extensive phenotypic and functional heterogeneity. Single-cell RNA sequencing analysis identified several fibroblast subpopulations, including myofibroblastic cancer-associated fibroblasts, which play a role in tissue contractility and extracellular matrix remodeling; inflammatory cancer-associated fibroblasts, which produce pro-inflammatory cytokines such as IL-6 and CXCL12; and antigen-presenting cancer-associated fibroblasts, which interact with immune cells through MHC class II expression.

The interaction between fibroblasts and tumor cells is mediated by various growth factors such as TGF-β, HGF, and FGF, which induce the activation of signaling pathways related to proliferation, migration, and apoptosis resistance. Furthermore, cancer-associated fibroblasts produce a stiffer extracellular matrix through the deposition of collagen types I and III and the activation of lysyl oxidase, which enhances mechanotransduction and the activation of the YAP/TAZ pathway in tumor cells. The activation of this mechanosignaling is associated with increased invasiveness and stemness of cancer cells.

Crosstalk between fibroblasts and immune cells also plays a crucial role in creating an immunosuppressive environment. Fibroblasts produce chemokines that recruit regulatory T cells and M2-phenotype macrophages, which suppress the cytotoxic activity of CD8+ T lymphocytes and natural killer (NK) cells. Furthermore, fibroblasts express immune checkpoint ligands that contribute to resistance to immunotherapy.

Exosomes derived from cancer-associated fibroblasts contain microRNAs and proteins capable of inducing epithelial-mesenchymal transition in tumor cells and enhancing metastatic potential. Conversely, exosomes from tumor cells can activate normal fibroblasts into cancer-associated fibroblasts through epigenetic reprogramming.[4,5]

Metabolic Reprogramming and Epigenetic Regulation in the Tumor Microenvironment

Metabolic reprogramming is a crucial adaptation of tumor cells to meet their energy and biosynthetic needs in hypoxic and nutrient-limited microenvironments. Increased aerobic glycolysis results in lactate accumulation, which not only serves as an alternative energy source for stromal cells but also as a signaling mediator that induces angiogenesis and immunosuppression.

Metabolites produced by tumor cell metabolic pathways act as cofactors for epigenetic enzymes. S-adenosylmethionine, as a methyl group donor, influences DNA and histone methylation, while α-ketoglutarate is a cofactor for histone and DNA demethylase enzymes. Changes in the concentrations

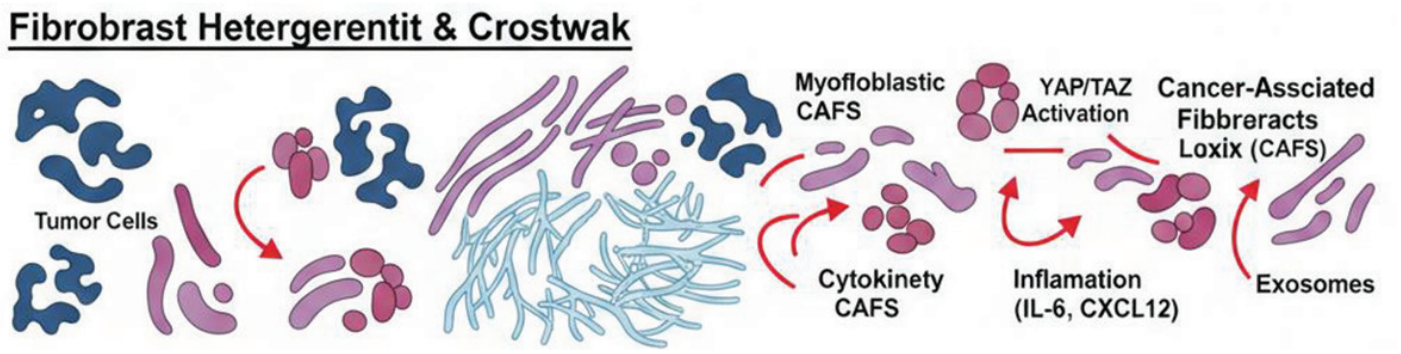

Figure 2. Dynamics between cancer cells and stromal components, particularly Cancer-Associated Fibroblasts (CAFs).

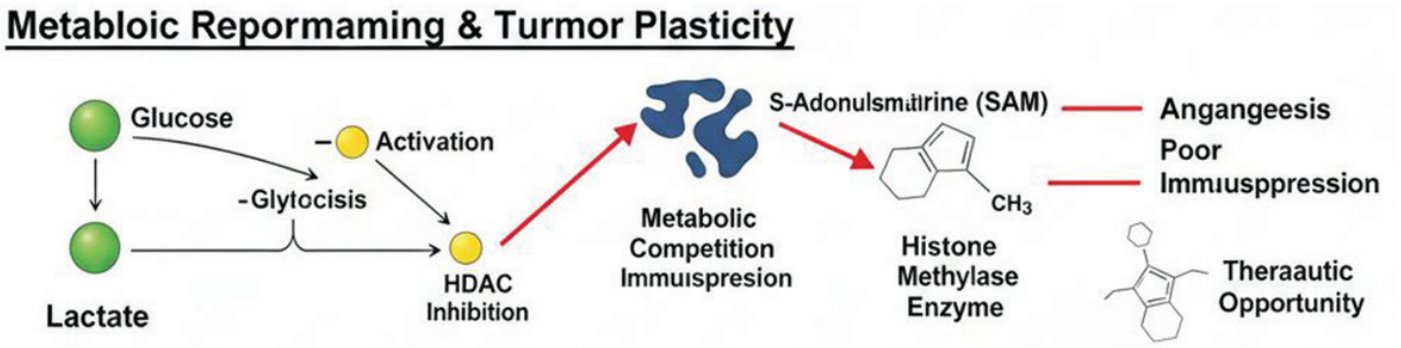

Figure 3. Changes in tumor cell metabolism affect genetic regulation and the immune environment.

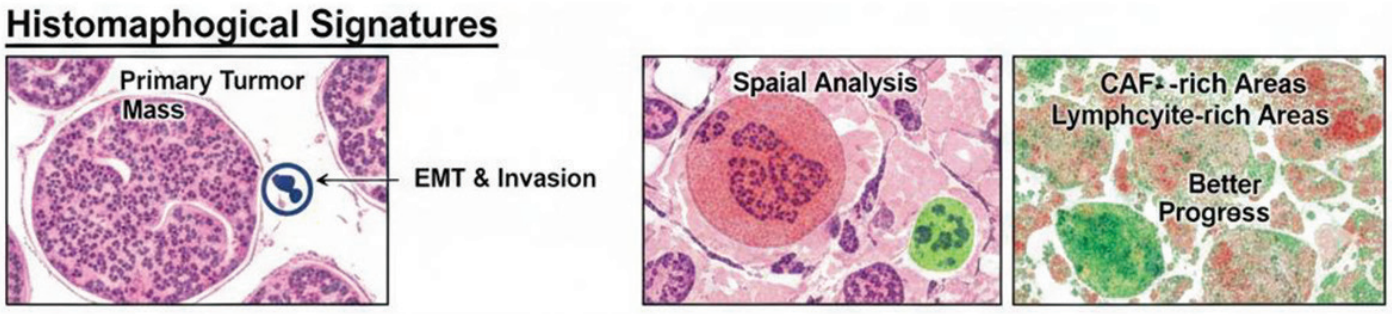

Figure 4. Relating the above molecular mechanisms to what is seen under the microscope (pathology).

of these metabolites lead to epigenome remodeling that supports the expression of genes related to tumor proliferation and invasion.

Furthermore, metabolic competition between tumor cells and immune cells in the tumor microenvironment leads to dysfunction of effector immune cells. Glucose deprivation and lactate accumulation inhibit the activity of T lymphocytes and natural killer (NK) cells, thus creating an environment conducive to tumor growth.[6,7]

Epithelial Mesenchymal Plasticity and Correlation with Tumor Budding

Epithelial-mesenchymal plasticity is a dynamic process that allows tumor cells to switch between epithelial and mesenchymal phenotypes. This process is controlled by transcription factors such as SNAIL, TWIST, and ZEB1, which are epigenetically regulated through histone modifications and regulation of non-coding RNA. This transition plays a role in enhancing migration, invasion, and resistance to apoptosis.

Histopathologically, this process appears as tumor budding, defined as small clusters of tumor cells or single cells at the invasion front. Tumor budding is correlated with an increased risk of lymph node metastasis, lymphovascular invasion, and poor prognosis. Recent studies have shown that tumor budding has a distinct epigenetic profile from the primary tumor mass, reflecting a higher degree of phenotypic plasticity.[7]

Histomorphological Signatures of Tumor Progression and Spatial Analysis

Molecular changes in the tumor microenvironment are reflected in various histomorphological patterns observable microscopically. A desmoplastic reaction characterized by increased fibroblast density and extracellular matrix deposition reflects intense stromal activation and is associated with tumor invasion. Heterogeneity in glandular differentiation indicates the presence of tumor cell subclones with distinct molecular profiles.

Spatial analysis based on digital pathology and spatial transcriptomics technology shows that the distribution of stromal and immune cells within tumor tissue significantly correlates with patient clinical outcomes. Tumor areas with high lymphocyte infiltration and low stromal activation indicate a better prognosis compared to tumors dominated by cancer-associated fibroblasts and M2 macrophages.[1,7]

Implications of Epigenetic Based Therapies and the Tumor Microenvironment

Understanding the interaction between the epigenetic landscape and the tumor microenvironment opens up opportunities for the development of more effective targeted therapies. DNMT and HDAC inhibitors have been shown to reactivate tumor suppressor genes and enhance cancer cell immunogenicity by increasing tumor antigen expression. Combining epigenetic therapy with immunotherapy has shown promise in improving therapeutic responses in colorectal cancer patients.

Targeting cancer-associated fibroblasts and signaling pathways involved in extracellular matrix remodeling is also a potential therapeutic approach. Furthermore, strategies to inhibit exosome transfer between tumor cells and stroma may disrupt pro-tumorigenic communication within the tumor microenvironment.[1]

DISCUSSION

The integration of epigenetic regulation and stromal–epithelial communication represents a paradigm shift in understanding colorectal adenocarcinoma progression. DNA methylation patterns influence immune infiltration and response to checkpoint inhibitors. Histone modification enzymes serve as modulators of chromatin accessibility and therapeutic targets.

Cancer-associated fibroblasts display functional heterogeneity, contributing to immunosuppression, matrix remodeling, and therapeutic resistance. Metabolic intermediates act as epigenetic cofactors, linking hypoxia and nutrient availability to gene regulation.

Histomorphological manifestations such as tumor budding reflect underlying epithelial–mesenchymal plasticity governed by epigenetic reprogramming. Desmoplastic reaction represents stromal activation and fibroblast proliferation. These morphological features possess prognostic significance and may serve as surrogate markers for molecular alterations.

Targeting epigenetic machinery combined with modulation of tumor microenvironment components offers promising therapeutic avenues.

CONCLUSION

Epigenetic landscapes and stromal–epithelial crosstalk are central drivers of colorectal adenocarcinoma progression. Their molecular interplay is reflected in distinctive histomorphological patterns

that hold diagnostic and prognostic value. Integrating molecular epigenetics with histopathological assessment may enhance precision oncology strategies and guide targeted therapeutic interventions.

CONFLICT OF INTEREST

All authors declared that there is no conflict of interest about this article

AUTHOR CONTRIBUTION

All authors contributed equally in the writing of this article

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ETHICS APPROVAL

Not Applicable

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