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Contrasting molecular pathways in colorectal carcinogenesis: insights from the Cancer Stem Cell paradigm

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Introduction

In the Western world, colorectal cancer (CRC) ranks as the second most common malignancy in women, following breast cancer, and the third most common in men, after lung and prostate cancer [1]. The most significant risk factor for CRC development is age, with approximately 99% of cases occurring in individuals over 40 years. Following age, a family history of the disease is the most common and well–established risk factor for CRC. Traditional models of tumorigenesis propose that every cell within a tumor has the potential to initiate and sustain tumor growth. In contrast, the cancer stem cell (CSC) model suggests that only a small subset of tumor cells possesses the capacity for self–renewal and propagation [2]. This paradigm shift challenges the effectiveness of current diagnostic and therapeutic approaches, highlighting the need for novel, targeted strategies in diagnosis, treatment, and disease monitoring [3].

In this review, we explore in depth the molecular characteristics of colorectal carcinogenesis and compare the conventional model of tumor development with the cancer stem cell model, integrating and summarizing the latest findings from recent literature.

Normal Colon Stem Cells

The concept of cancer stem cells (CSCs) was first experimentally supported in 1997, when Bonnet and Dick identified a subpopulation of leukemia cells expressing CD34 but lacking CD38, which possessed the exclusive ability to initiate leukemia [4]. Anatomically, the colon is divided into four distinct regions, and its inner luminal surface is lined by a single layer of epithelial cells organized into ring–shaped invaginations. These invaginations extend into the submucosal connective tissue, forming the functional units of the colon known as the crypts of Lieberkühn [5]. Each crypt contains approximately 2,000 cells and comprises three major differentiated epithelial cell types: enterocytes, goblet cells, and enteroendocrine cells, which are primarily located in the upper two–thirds of the crypt. Paneth cells are also present at the base of the crypt and play a critical role in maintaining the stem cell niche. Intestinal stem cells (ISCs) are undifferentiated, multipotent, and self–renewing cells that reside at the crypt base. They are responsible for tissue homeostasis and regeneration, continuously replenishing the epithelial lining through asymmetric division and subsequent lineage commitment [6].

Stem Cell Division and Intestinal Crypt Dynamics

Intestinal stem cells typically undergo asymmetric division, producing two daughter cells: one that retains stem cell identity and another that becomes a progenitor cell with the capacity to differentiate. These progenitor cells migrate upward along the crypt–villus axis, ultimately giving rise to fully differentiated intestinal epithelial cells (*Figure 1*). Under certain conditions, such as mechanical injury, disease, or tumorigenesis, stem cells may undergo symmetric division, resulting in the expansion of the stem

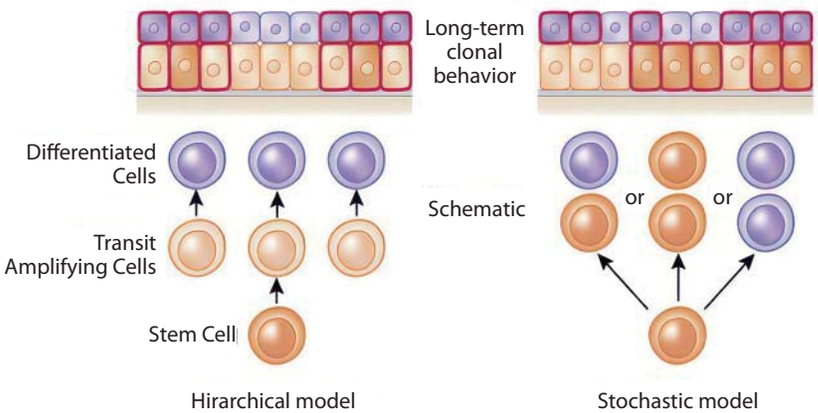

Fig. 1.
Hierarchical organization of normal colon crypts – comparison between the stochastic model and the CSC model
Hierarchical vs. stochastic stem cell model. The classical SC model consisting of stem and transit amplifying cells (left panel) would lead to an invariant asymmetry with similar and invariant clone sizes. In contrast, a progenitor population with stochastic fate leads to population asymmetry involving different sized clones over time (right panel).

cell pool. The intestinal crypt is estimated to contain approximately 16 stem cells, which can be categorized into two putative stem cell lineages based on their position and functional characteristics. [7].

Stem Cell Identification and Models in the Intestinal Crypt

The identification and isolation of intestinal stem cells remain subjects of ongoing debate. Early studies utilizing DNA labeling and lineage–tracing techniques proposed two distinct models for stem cell localization within the crypt. In the "+4 position" model, stem cells are thought to reside at the fourth cell position above the crypt base, immediately following the Paneth cells that occupy the bottom of the crypt. These stem cells give rise to progenitor cells, which migrate upward along the crypt–villus axis to differentiate into mature epithelial cell types, while Paneth cells migrate downward toward the crypt base [8]. Subsequently, the "crypt base columnar (CBC) or zone model" emerged following the detection of small, actively cycling immature cells located interspersed between Paneth cells at the crypt base. These cells, referred to as cryptic primary colon cells, are marked by expression of the Wnt target gene Lgr5, highlighting their stem–like potential. Several molecular markers have been implicated in regulating the critical processes of proliferation and differentiation within these stem cells, including Musashi–1 (Msi–1), CD29, Bmi–1, Lgr5, aldehyde dehydrogenase–1 (ALDH1), Tert, and Achaete–scute family BHLH transcription factor 2 (Ascl2). Together, these models reflect the dynamic and heterogeneous nature of stem cell populations in the intestinal crypt and underscore the complexity of stem cell hierarchy and lineage commitment in normal intestinal homeostasis [9].

Stem Cells and Models of Colorectal Carcinogenesis

Colorectal carcinogenesis results from the cumulative effects of genetic and epigenetic alterations, interactions with the microenvironment, and dysregulation of stem cell signaling, ultimately transforming normal intestinal mucosa into an aberrant phenotype. Within this process, the tumor–initiating stem cell harbors the critical oncogenic mutations and gives rise to the first malignant cell. Importantly, these stem cells are distinct from progenitor cells that sustain tissue proliferation but do not initiate tumors [10]. Following malignant transformation, two conceptual models have been proposed to describe tumor development and progression: the stochastic model and the cancer stem cell (CSC) model (*Figure 1*). In the stochastic model, every tumor cell has the potential to both initiate and propagate the tumor. Each transformed cell may acquire additional mutations, and migrating clones can give rise to distinct metastatic lesions, resulting in tumor heterogeneity. In contrast, the CSC model posits that only a small subset of tumor cells the cancer stem cells possess true tumor–initiating capacity. Similar to normal tissue organization, tumors are hierarchically structured under this model. CSCs give rise to multipotent progenitors, which are moderately proliferative, and differentiated tumor cells, which are largely non–proliferative. CSCs are defined by self–renewal, multipotency, limited proliferation, angiogenic capacity, and immune evasion. They exhibit relative resistance to conventional therapies due to efficient DNA repair mechanisms, detoxifying enzymes, and drug efflux transporters, making them key drivers of tumor relapse. Through symmetric division (expansion of CSCs) or asymmetric division (production of heterogeneous progeny), mutated stem cells and their descendants can colonize the entire crypt. Subsequent genetic and epigenetic changes may further enhance tumor aggressiveness and metastatic potential [11].

Molecular basis of colorectal cancer
Genomic instability

The loss of genomic stability may lead to formation of colorectal cancer through accelerated acquiring of multiple tumor associated mutations. As far as this disease is concerned, the genomic instability has several forms, each of which has a different cause [12].

Chromosomal instability

The most common type of genomic instability when colorectal cancer is in question is chromosomal instability that has a great number of changes of the structure and the number of chromosomal units. Chromosomal instability is an efficient mechanism for causing physical loss of wild–type copy of tumor suppressor gene, such as APC, P53 and SMAD4, the normal function of which is an opponent to the malignant phenotype [13].

Impairment of Physiological DNA–Repair Mechanisms in Colorectal Cancer

In a subset of colorectal cancer patients, inactivation of genes responsible for DNA mismatch repair (MMR) leads to a distinct type of tumor known as mismatch repair–deficient colorectal cancer, or microsatellite instability (MSI)–high cancer. This inactivation can be either hereditary, as in hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome), or acquired, for example through epigenetic silencing such as promoter methylation of MMR genes.Patients with HNPCC carry germline mutations in key MMR genes, primarily MLH1 and MSH2, conferring a lifetime colorectal cancer risk of up to 80%, with disease often manifesting by the age of 40 [14]. In individuals with acquired MMR defects, tumors typically develop within approximately 36 months after a preceding colonoscopy. Given this high

risk, annual colonoscopic surveillance is recommended for patients with known germline MMR defects. Additionally, preventive surgical interventions, such as colectomy, may be advised in patients presenting with advanced lesions or high–risk features [15].

Aberration and methylation

Epigenetic gene silencing, primarily driven by aberrant DNA methylation, represents one of the key mechanisms of genetic inactivation in colorectal cancer (CRC). Unlike this locus–specific hypermethylation, colorectal cancer cells also exhibit a modest but global hypomethylation of cytosine residues across the genome. However, a significant gain of aberrant promoter methylation, particularly in regions rich in CpG islands, leads to transcriptional repression of tumor–suppressor genes. In sporadic colorectal cancers exhibiting microsatellite instability (MSI), somatic epigenetic silencing of the MLH1 gene is a critical event responsible for the loss of mismatch repair function. Although the precise molecular basis of the CpG island methylator phenotype (CIMP) remains unclear, this epigenetic subtype is observed in approximately 15% of all CRC cases, frequently associated with widespread promoter hypermethylation [16].

Mutational Inactivation of Tumor Suppressor Genes – APC

Colorectal cancer arises through the progressive accumulation of multiple genetic and epigenetic alterations that disrupt the normal regulatory mechanisms of cell proliferation and differentiation. Among the earliest and most critical events in this process is the aberrant activation of the Wnt/β–catenin signaling pathway. Under physiological conditions, cytoplasmic β–catenin levels are tightly controlled by a multiprotein β–catenin destruction complex, which mediates its phosphorylation and subsequent proteasomal degradation. A pivotal component of this complex is the adenomatous polyposis coli (APC) protein, a tumor suppressor that not only facilitates β–catenin degradation but also prevents its nuclear translocation and transcriptional activation of oncogenic target genes. Mutations in the APC gene, located on chromosome 5q21–22, result in the production of truncated, nonfunctional proteins incapable of regulating β–catenin. The consequent accumulation of β–catenin in the nucleus leads to constitutive activation of Wnt target genes such as MYC and CCND1 (cyclin D1), driving uncontrolled cellular proliferation and early adenoma formation. Loss–of–function mutations in APC are among the most frequent genetic alterations in colorectal cancer, occurring in up to 80% of sporadic cases and serving as the initiating event in familial adenomatous polyposis (FAP), an inherited cancer predisposition syndrome [17].

TP53

Inactivation of the p53 pathway through mutations in the TP53 gene represents the second critical step in colorectal cancer development. In most tumors, both TP53 alleles are inactivated, typically through a combination of a missense mutation that abolishes p53's transcriptional activity and a deletion of the 17p chromosomal region, which removes the second TP53 allele [18].

TGF–β tumor – signaling pathway

Mutational inactivation of TGF–β signaling represents the third key step in colorectal cancer development. Somatic mutations in TGFBR2 are observed in approximately one–third of colorectal cancer cases [19].

Activation of oncogenic pathways RAS and BRAF

Several oncogenic mutations in the RAS and BRAF genes, which activate the mitogen–activated protein kinase (MAPK) signaling pathway, occur in approximately 37% and 13% of colorectal cancer cases, respectively. KRAS mutations primarily activate the GTP–binding state of RAS, which transmits proliferative signals downstream. BRAF mutations enhance the serine–threonine kinase activity of BRAF, further triggering the MAPK signaling cascade. Patients with numerous and large hyperplastic lesions a condition known as hyperplastic polyposis syndrome are at high risk of developing colorectal cancer. Histologically, disease progression in these patients often involves intermediate lesions characterized by serrated luminal borders [20].

Phosphatidylinositol 3 – kinase

Approximately one–third of colorectal cancer cases harbor activating somatic mutations in the PIK3CA gene, which encodes the catalytic subunit of phosphatidylinositol 3–kinase (PI3K) [21].

Elaboration of signaling pathways in normal colon vs. CSC

Intestinal homeostasis is continuously regulated by a complex interplay of signaling pathways, including Wnt, Notch, and Hedgehog, which maintain the balance between proliferation, differentiation, migration, and self–renewal. The Wnt pathway is crucial for endoderm formation and plays a central role in the development, maintenance, and proliferation of intestinal crypts. Mutations in APC (present in ~80% of sporadic colorectal cancers), β–catenin, or other regulatory proteins in the Wnt pathway leads to constitutive activation, resulting in uncontrolled proliferation, a shift from asymmetric to symmetric cell division, and increased cell survival. Wnt signaling also contributes to epithelial–to–mesenchymal transition (EMT) and invasion [22,

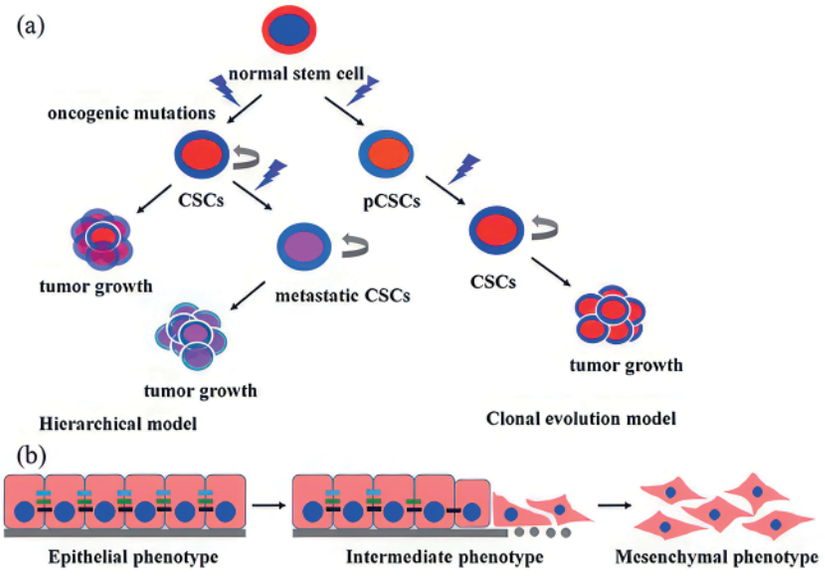

Fig. 2. Stem cell model of metastasis Schematic illustration of cancer stem cell (CSC) models of tumorigenesis and the general features of EMT. (a) CSC models: Hierarchical and clonal evolution prototypes are shown. CSC subpopulations exhibit self-renewal capacity and the potential to differentiate, occupying the apex of the tumorigenesis hierarchy. (b) EMT process: Cancer cells transition from a round, cobblestone-like morphology to an elongated, fibroblast-like morphology, facilitating migration and invasion. Abbreviations: CSC, cancer stem cells; pCSC, precancerous stem cells; EMT, epithelial-mesenchymal transition.

23]. The Notch pathway can promote tumorigenesis by accelerating proliferation while simultaneously inhibiting differentiation. BMP and TGF–β, members of the TGF–β superfamily, signal through Smad proteins. BMPs, primarily expressed in stromal cells, act antagonistically to Wnt and are most active at the top of the crypts, whereas TGF–β inhibits intestinal epithelial proliferation and induces apoptosis. Hedgehog proteins mediate communication between stromal and epithelial cells; they are thought to suppress Wnt signaling, possibly via BMP, and are expressed in +4 stem cells, although their precise role remains unclear [24, 25]. Finally, in colorectal carcinogenesis, activation of the phosphoinositide 3–kinase (PI3K) pathway promotes increased proliferation of intestinal stem cells [21].

Epithelial Mesenchymal Transition (EMT) and development of metastasis

Tumor–propagating cells reside within the cancer stem cell (CSC) population, which is also responsible for metastasis formation. These cells invade from the primary tumor, intravasate into the circulation where they survive, disseminate to distant sites, traverse endothelial barriers, and ultimately establish secondary tumors (*Figure 2*). Epithelial–to–mesenchymal transition (EMT) is a critical step in this metastatic process [26].

Identification of Colorectal CSCs

Several molecules have been identified as markers of cancer stem cells (CSCs), including CD133, CD44, CD24, CD166, Lgr–5, and ALDH–1. CD133, a pentaspan transmembrane glycoprotein involved in plasma membrane organization, was the first CSC marker discovered. This was demonstrated by injecting CD133–positive and CD133–negative (sorted) cells into immunodeficient mice: only a small subset of $CD133^+$ cells were capable of initiating tumor growth, whereas $CD133^-$ cells could not. $CD44^+$ cells exhibit CSC–like features and, as single cells, are able to form spheres in vitro and stem–like xenograft tumors in vivo. Interestingly, CD44 expression is negatively associated with tumor invasion depth, lymph node infiltration, and patient survival outcomes. The combined expression of CD133 and CD44 appears to be particularly informative and represents a promising approach for CSC identification. Additional CSC markers include CD166, epithelial cell adhesion molecule (EpCAM), ALDH–1, CD29, CD24, CD26, Msi–1, Lgr–5, and Wnt/β–catenin signaling activity. Moreover, pluripotency–associated genes such as Oct–4, Sox–2, Nanog, Lin–28, Klf–4, and c–Myc serve as surrogate markers; their expression correlates with poor prognosis, higher likelihood of disease relapse, and resistance to conventional chemotherapy and radiotherapy [27, 28].

Therapeutic challenges

According to the cancer stem cell (CSC) model, tumor growth is driven by a small subpopulation of CSCs that are resistant to conventional therapeutic modalities. Standard therapies primarily eliminate the bulk of differentiated cancer cells, which reduces tumor size and temporarily alleviates disease symptoms. However, because CSCs remain largely unaffected, these therapies do not prevent disease relapse. In contrast, therapies specifically targeting CSCs may not significantly reduce the overall tumor size. Still, they are expected to inhibit tumor regrowth and prevent metastasis formation by eradicating the cells responsible for long–term tumor propagation [29]. Experimental evidence supports the role of cancer stem cells (CSCs) in chemotherapy resistance and disease relapse. Monoclonal antibodies can be employed to directly target CSC–specific surface mark-

ers, such as CD133 and CD44, or drug transporters involved in chemoresistance. Targeting these molecules may reduce tumor size, limit metastatic potential, and help overcome resistance to conventional chemotherapy [30]. Additional rational strategies for CSC–targeted therapy involve inhibition of critical self–renewal signaling pathways, including Wnt, Notch, PTEN, and Hedgehog. Small–molecule inhibitors of Wnt signaling and γ–secretase inhibitors targeting the Notch pathway have been proposed as promising therapeutic agents in colorectal cancer [31]. An alternative approach involves induction of differentiation and disruption of epithelial–mesenchymal transition (EMT). Targeting EMT reduces the generation of new CSCs derived from EMT and can help overcome drug resistance. Strategies in this context include: a) Modulation of signaling pathways, such as BMP4 or PI3K; b) Application of microRNAs to alter gene expression profiles; c) Epigenetic therapy. BMP signaling promotes differentiation and apoptosis in colorectal CSCs by modulating the Wnt pathway. Moreover, combining BMP pathway activation with chemotherapeutic agents such as oxaliplatin and 5–fluorouracil enhances antitumor effects. It can lead to tumor regression in colorectal cancer [32]. Inhibition of the IL–4 pathway using anti–IL–4 antibodies or IL–4 receptor antagonists in $CD133^+$ colorectal CSCs enhances the antitumor effects of conventional chemotherapeutic agents [33].

Conclusion

The lifetime risk of colorectal cancer is estimated to range from 5% to 10% and is closely associated with the aforementioned risk factors. Studies that characterize colorectal cancer at the molecular level are essential for genetic testing of high–risk syndromes, identification of novel predictive biomarkers for therapy response, and development of non–invasive molecular diagnostics for early cancer detection. Recent advances in the cancer stem cell (CSC) model of colorectal cancer have uncovered new biological mechanisms that may serve as rational foundations for the development of targeted therapies. Understanding the signaling pathways that govern the metastatic phenotype provides critical information for designing drugs capable of controlling tumor growth and preventing disease relapse. CSCs represent rational targets for novel therapeutic agents aimed at enhancing the efficacy of conventional treatments, reducing local recurrence, and preventing distant metastasis. Furthermore, histopathological techniques combined with detection of CSC–associated tumor markers can guide personalized therapy selection, monitor disease relapse, and assist in the biological classification of tumor aggressiveness in colorectal cancer.

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