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Omics sciences and precision medicine in colon cancer

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Abstract

Colon cancer presents a complex pathophysiological landscape, which poses a significant challenge to the precise prediction of patient prognosis and treatment response. However, the emergence of omics sciences such as genomics, transcriptomics, proteomics, and metabolomics has provided powerful tools to identify molecular alterations and pathways involved in colon cancer development and progression. To address the lack of literature exploring the intersection of omics sciences, precision medicine, and colon cancer, we conducted a comprehensive search in ScienceDirect and PubMed databases. We included systematic reviews, reviews, case studies, clinical studies, and randomized controlled trials that were published between 2015-2023. To refine our search, we excluded abstracts and non-English studies. This review provides a comprehensive summary of the current understanding of the latest developments in precision medicine and omics sciences in the context of colon cancer. Studies have identified molecular subtypes of colon cancer based on genomic and transcriptomic profiles, which have implications for prognosis and treatment selection. Furthermore, precision medicine (which involves tailoring treatments, based on the unique molecular characteristics of each patient's tumor) has shown promise in improving outcomes for colon cancer patients. Omics sciences and precision medicine hold great promise for identifying new therapeutic targets and developing more effective treatments for colon cancer. Although not strictly designed as a systematic review, this review provides a readily accessible and up-to-date summary of the latest developments in the field, highlighting the challenges and opportunities for future research. ***Clin Ter 2023; 174 Suppl. 2 (6):55-67 doi: 10.7417/CT.2023.2472***

Key words: *Tumor genomics, pharmacogenomics, proteomic biomarkers, metabolomic, germline mutations.*

Background

Colon cancer is a significant contributor to morbidity and mortality across the globe (1). It is a multifaceted disease, caused by the aggregation of numerous genetic and epigenetic changes that arise at the cellular level in the colon. The use of omics disciplines has significantly enhanced our comprehension of the molecular pathways underlying colon cancer (2). These advancements have facilitated the development of more personalized and precise approaches to managing the disease. The various omics sciences—including genomics, transcriptomics, proteomics, and metabolomics—have revolutionized our understanding of cancer biology (3). Although significant evidence has emerged in favor of single omics approach for the detection of genetic and molecular mutations, their capacity to establish causal relationships between molecular signatures and phenotypic expressions of cancer hallmarks is restricted. Compared to single omics, the multi-omics approach can uncover the underlying complexities, such as metastasis and angiogenesis (4). The analysis of vast molecular data using these technologies from cancer cells offers a comprehensive view of genetic, epigenetic, and metabolic changes that drive tumor development and progression.

Gene expression profiling has revealed differentially expressed genes associated with tumor initiation, progression, and metastasis (5). Additionally, transcriptomic analysis has identified different molecular subtypes of colon cancer, each exhibiting unique gene expression profiles and clinical features. Proteomics and metabolomics have also emerged as valuable tools for identifying novel biomarkers and therapeutic targets in colon cancer. Proteomic analysis identifies

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differentially expressed or post-translationally modified proteins in colon cancer, providing insights into the molecular pathways that are dysregulated in the disease (6). Precision medicine, which involves individualizing therapy based on a patient's molecular profile, has emerged as a promising approach to colon cancer treatment (7). Omics-based profiling of colon cancer enables the identification of specific molecular changes that drive tumor growth, thus allowing the selection of targeted therapies likely to be effective in each patient. Furthermore, precision medicine allows to identify patients at high risk of disease recurrence, enabling the development of personalized surveillance strategies and the optimization of adjuvant therapy (8).

Aim of the review

Currently, a dearth of literature exists concerning reviews that comprehensively explore the present understanding of omics sciences and precision medicine in colon cancer. The primary objective of this manuscript is to deliberate on the current body of evidence regarding the latest developments in omics science and precision medicine in the context of colon cancer.

Methodology

To identify the appropriate studies, we comprehensively searched ScienceDirect and PubMed databases using individual terms and Boolean operators ANDs and ORs. The search terms used included "genetic mutations," "germline genetic mutations," "genetic tests," "hereditary," "somatic genetic mutations," "genetic rearrangements," "proteomics biomarkers," "blood proteomics biomarkers," "clinical diagnosis," "therapy," "pharmacogenetics," "metabolomics," "microbiomics," and "colon cancer." We limited our inclusion criteria to specific types of articles, including meta-analyses, multicenter studies, reviews, systematic reviews, observational studies, case-control studies, longitudinal/prospective studies, retrospective studies, and randomized controlled trials. We refined our search by limiting the publication date between 2015-2023 and excluding all non-English studies. Furthermore, texts available only in abstract form were excluded.

Tumor natural history and clinical history

Colon cancer originates from the epithelial cells of the colon. The natural history of colon cancer involves a sequence of genetic, molecular, and cellular events that ultimately lead to disease development and progression (9). The initial step in the natural history of colon cancer involves the transformation of a normal colonic epithelial cell into a neoplastic cell, which is manifested by mutations in specific genes, like the adenomatous polyposis coli gene. Once these neoplastic cells have formed, they begin to proliferate and accumulate genetic alterations that enable them to evade normal cellular control mechanisms—such as apoptosis and immune surveillance. These genetic alterations comprise mutations affecting oncogenes and tumor suppressor genes, alongside alterations in DNA methylation patterns and chromatin conformation (10). Over time, these neoplastic cells may form a polyp. Furthermore, the spread of colon cancer is facilitated by the development of blood and lymphatic vessels within the tumor, which provides a pathway for cancer cells to enter the circulation and establish secondary tumors. The clinical history of colon cancer can vary depending on the stage and location of the tumor. Early-stage colon cancer may not cause any symptoms and the disease may be detected incidentally during routine screening tests, such as colonoscopy. As the tumor grows and invades the surrounding tissue, it can cause symptoms like rectal bleeding, abdominal pain, and weight loss. These symptoms may be nonspecific and can also be caused by other gastrointestinal conditions, such as inflammatory bowel disease and diverticulitis (1).

Genetics of the tumor

The development of colon cancer involves multiple mutations at the genetic level, DNA methylation alterations, and changes in gene expression (Table 1). These genetic alterations can impact certain cellular processes that regulate cell proliferation and apoptosis, leading to the uncontrolled growth of cancer cells (11). The most frequent genetic aberration in colon cancer is chromosomal instability (CIN), which is characterized by extensive chromosomal aberrations and loss of heterozygosity. This subtype is frequently marked by mutations in key genes, including APC, KRAS, TP53, PI3KCA, and SMAD4. According to a study by Kandioler et al., TP53 mutation was observed in 33% of stage 3 colon cancer patients (12). Interestingly, the study also revealed that TP53 wild-type subjects had a significantly better survival rate than those with TP53 mutations (81% vs. 62%) (12). The most frequently observed cytogenetic abnormality in colon cancer is the loss of heterozygosity on chromosome 18q. Li et al. conducted a study where they investigated copy number variations (CNVs) of plasma cell-free DNA (cfDNA) in cancer (n=80), polyps (n=20), and healthy controls (n=35) using sequencing-based copy number analysis (13). Their results revealed that there were frequent CNVs in various chromosomal regions, such as amplifications on 1q, 8q, and 5q, as well as deletions on 1p, 4q, 8p, 17p, 18q, and 22q (13). These findings were consistent with a previous study conducted by Mampaey et al., who also reported frequent gains in chromosomes 1q, 7, 8q, 13, and 20, as well as losses for 1p, 4, 8p, 14, 15, 17p, 18, 21, and 22 (14).

Colon cancer can exhibit genetic alterations such as the CpG Island Methylator Phenotype (CIMP), where abnormal methylation of CpG islands results in the silencing of tumor suppressor genes (15). CIMP-high tumors are a distinct molecular subgroup that exhibit specific genetic characteristics, such as wild-type P53, microsatellite instability (MSI), and mutated BRAF. A phase 2 study, conducted by Watanabe et al., investigated the clinical significance of RAS/BRAF mutations in circulating cell-free DNA (ccfDNA) (16). The study enrolled 54 patients, 17 of which showed RAS/BRAF mutations at the end of the treatment protocol, while 10

patients had RAS/BRAF mutations in their plasma ccfDNA at the baseline of the study (16). Guda and colleagues recently employed whole exome sequencing and targeted sequencing to uncover somatic mutations in 103 patients. Their study revealed 20 previously unidentified genes in African American CRC patients. Notably, two genes, ephrin type A receptor 6 (EPHA6) and folliculin (FLCN), exclusively mutated in African American CRCs, were identified as potential driver genes based on genetic and biological criteria (17). Similarly, Thai patients with stage 2 and 3 colon cancer exhibited a mutation frequency of 47.2%, 1.9%, 1.9%, 12%, and 14.8% in KRAS, NRAS, BRAF, PIK3CA, and FBXW7, respectively (18).

Genetic testing

The integration of genetic testing in healthcare has been guided by accumulating evidence and established guidelines (19). Initially, patients were evaluated based on observable characteristics or "phenotypes," such as family history, individual risk factors, and tumor characteristics. The use of next-generation sequencing resulted in a shift towards multigene panel testing, which enables the identification of germline mutations that might not have been discovered based on observable characteristics and family history (20). This method has several advantages, including improving the identification of germline mutations for syndromes with genetic heterogeneity and overlapping characteristics (21). Limiting germline testing based on observable characteristics may cause the omission of certain cancer susceptibility genes.

Another diagnostic approach to emerge in colon cancer is stool DNA screening (22). A recent study evaluated the effectiveness of the novel stool DNA test of methylated SDC2 for colon cancer detection, which revealed high sensitivity for detecting colon cancer and advanced adenomas

Table 1. Summary of some of the genes involved in colon cancer, their associated pathologies and OMIM numbers, the inheritance patterns, and the effects of the mutations.

Gene	OMIM	Pathology	OMIM	Inheritance	Pathways/Functions	Effects of mutations
APC	611731	Familial adenomatous polyposis	175100	Autosomal dominant	Wnt signaling pathway; Regulation of cell growth and differentiation	Loss of function mutations lead to the formation of multiple colorectal polyps, which have a high probability of becoming malignant tumors.
MLH1	120436	Lynch syndrome 2	609310	Autosomal dominant	DNA mismatch repair pathway	Mutations increase the risk of colorectal, endometrial, and other cancers by causing genomic instability and accumulation of mutations.
MSH2	609309	Lynch syndrome	120435	Autosomal dominant	DNA mismatch repair pathway	Mutations increase the risk of colorectal, endometrial, and other cancers by causing genomic instability and accumulation of mutations.
MSH6	600678	Lynch syndrome 5	614350	Autosomal dominant	DNA mismatch repair pathway	Mutations increase the risk of colorectal, endometrial, and other cancers by causing genomic instability and accumulation of mutations.
PMS2	600259	Lynch syndrome 4	614337	Autosomal dominant	DNA mismatch repair pathway	Mutations increase the risk of colorectal, endometrial, and other cancers by causing genomic instability and accumulation of mutations.
KRAS	190070	Colorectal cancer	114500	Somatic	MAPK signaling pathway	Gain-of-function mutations activate KRAS, leading to uncontrolled cell proliferation and tumor growth.
TP53	191170	Li-Fraumeni syndrome	151623	Autosomal dominant	Regulation of cell cycle and apoptosis	Mutations impair the tumor suppressor function of TP53, leading to an increased risk of cancer.
BRAF	164757	Colorectal cancer	114500	Somatic	MAPK signaling Pathway	Oncogene, stimulates cell growth and division.
SMAD4	600993	Juvenile Polyposis Syndrome	175050	Autosomal Dominant	TGF-beta signaling Pathway	Tumor suppressor, regulates cell division.
PIK3CA	171834	Colorectal cancer	114500	Somatic mutations	PI3K/AKT signaling pathway	Oncogene, promotes cell growth and survival.

(23). Colon cancer is linked with dysregulated expression of microRNAs (miRNAs), and the expression patterns of these small non-coding RNAs have been linked to the detection and prognosis of colon cancer. A recent review demonstrated the effectiveness of using circulating serum miRNA and fecal miRNA expression as non-invasive biomarkers for early detection of colon cancer (24).

Predisposition

The pathogenesis of colon cancer is multifactorial, involving both genetic predisposition and various environmental factors. Genome-wide linkage analyses have revealed significant correlations between susceptibility loci located on chromosome 8p23 and colon cancer (25). Genetic susceptibility to colon cancer involves modifications in gene expression and DNA methylation, with specific genes being identified as markers for different subtypes of cancer. Additionally, the inactivation of microRNA through DNA methylation can also contribute to the development of colon cancer (26). Furthermore, the epigenetic inactivation of genes responsible for regulating the cell cycle, angiogenesis, repairing DNA, and promoting cellular differentiation are also contributors to colon cancer (27). Although the role of innate immunity genes in the progression of colon cancer is unclear, a weaker immune response is usually manifested in different cancers. Toll-like receptors (TLRs) play a vital role in identifying pathogen-associated molecular patterns, which trigger the innate immune response. Upon activation, TLRs activate NF-κB, which further initiates the transcription of various pro-inflammatory cytokines, and human beta-defensins (hBDs) (28). hBDs are antimicrobial peptides that aid innate immune defense, with hBD-1 being produced by various epithelial tissues, and their expression can be induced. Additionally, upon encountering microorganisms or cytokine stimulation, hBD-2 is highly expressed in normal epithelial cells. Semlali et al. conducted a study that explored the genetic variations and expression of hBDs (hBD-1, hBD-2, hBD-3, and hBD-4) and their potential association with colon cancer. Their findings revealed a significant association between hBDs and the deregulation of innate immunity [29]. These results suggest that hBDs play a critical role in maintaining innate immunity and that their disruption may contribute to the pathogenesis of colon cancer (29).

Correlated syndromes

In addition to sporadic colon cancer, also several colon cancer syndromes have been identified. These syndromes are characterized by a genetic predisposition to colon cancer, often with a specific pattern of inheritance. One of the most well-known colon cancer syndromes is hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome. HNPCC is an autosomal dominant disorder caused by mutations in one of several DNA mismatch repair genes (30). Individuals with HNPCC have a significantly increased risk of developing colon cancer, as well as other cancers such as endometrial, ovarian, and gastric cancer. The identification of HNPCC in families is important, because it can guide screening and surveillance protocols, such as colonoscopies starting at an earlier age or more frequent intervals. Another colon cancer syndrome is familial adenomatous polyposis (FAP), which is also an autosomal dominant disorder. FAP is characterized by the development of hundreds to thousands of adenomatous polyps in the colon, which can progress to cancer if left untreated (31). FAP is caused by mutations in the APC gene, which regulates cell proliferation and differentiation. Individuals with FAP require regular colonoscopies and often undergo prophylactic surgery to remove the colon, to prevent the development of colon cancer. In addition to HNPCC and FAP, there are several other colon cancer syndromes, such as MUTYH-associated polyposis (32), Peutz-Jeghers syndrome (33), and juvenile polyposis syndrome (34). These syndromes are less common than HNPCC and FAP, but still have important implications for patient management and surveillance. The identification of these syndromes can guide appropriate screening and surveillance protocols and help to prevent the development of colon cancer in at-risk individuals.

Genomics of the tumor

Recent advancements in genomic technologies have provided a comprehensive understanding of the genetic changes underlying the development and progression of colon cancer (Table 2). Among the most frequently observed genomic alterations in colon cancer is the mutation of the adenomatous polyposis coli (APC) gene (35). The APC gene is a tumor suppressor that plays a crucial role in regulating the Wnt signaling pathway, which is responsible for controlling cell proliferation and differentiation. APC mutations are identified in up to 80% of colon cancer cases, and they are thought to be an early event in the pathogenesis of the disease (36, 37). In addition to APC mutations, colon cancer is characterized by the accumulation of additional genomic alterations, including mutations in oncogenes such as KRAS, NRAS, and BRAF (38), as well as in other tumor suppressor genes such as TP53, SMAD4, and PTEN (39). Recent studies have also highlighted the importance of epigenetic alterations in colon cancer (40, 41). Epigenetic alterations including DNA methylation and histone modifications affect gene expression without altering the underlying DNA sequence. In colon cancer, aberrant DNA methylation patterns have been found including the MLH1, MGMT, and CDKN2A genes (42). These genetic modifications can result in the loss of function of tumor suppressor genes and the gain of function of oncogenes which consequently contribute to tumor progression (43).

Rearrangements

Multiple genetic alterations, including gene rearrangements, have emerged as a hallmark of colon cancer. Gene rearrangements occur when two or more regions of DNA from different chromosomes are broken and then rejoined in a new order. These rearrangements can lead to changes in gene expression and protein function, ultimately contributing to the development and progression of colon cancer (54).

Table 2. The potential genomics biomarkers in colon cancer.

Author, Year	Biomarker	Methodology	Change	Results	Conclusion
Song et al. (2018) (44)	CBX8, CD96	Gene and isoform expression datasets from The Cancer Genome Atlas	Downregulated	2301 genes and 4241 isoforms were differentially expressed	CBX8 and CD96 are viable prognostic biomarkers
Zhu and Dong (2018) (45)	TUSC3	Oncomine and COEXPEDIA databases	Upregulated	TUSC3 mRNA expression was overexpressed in CRC tissues compared to the control ones	TUSC3 is a potential therapeutic target in CRC
Luo et al. (2020) (46)	MTMR7, GSTM5, GPX2, PDE6B, CDS1, SGPP2, GSTM2, ALDOB, CPT1C, PDE1B, AGMAT, FTCD, HDC, DGKB, ACADL, MAT1A, PLCG2	The Cancer Genome Atlas (TCGA), Genotype-Tissue Expression (GTEx) database, and Gene Expression Omnibus (GEO)	43 mRNAs were upregulated, whereas 104 mRNAs were downregulated	A seventeen-gene metabolic signature emerged as prognostic biomarker. The high-risk patient group had a poor prognosis when compared to low risk (HR: 1.174, P < 0.001)	Seventeen-gene metabolic signature is a potential prognostic biomarker for colon cancer
Cheng et al. (2022) (47)	MTUS1	Tumor tissues were analyzed by qPCR for MTUS1 expression	Downregulated	MTUS1 exhibited lower levels in tumor tissues as compared to normal tissues	MTUS1 can serve as a prognostic and diagnostic biomarker for colon cancer
Chen et al. (2019) (48)	SEPT9, SDC2, NDRG4	Stool samples from cancerous and non-cancerous patients	Upregulated	DNA methylation of SEPT9, NDRG4, and SDC2 showed efficacy for diagnosis of colon cancer, but not BMP3	Potential screening biomarkers for colon cancer
Zhang et al. (2022) (49)	SDC2, TFPI2	Stool samples	Upregulated	Methylation levels of SDC2 and TFPI2 were higher in tumor samples as compared to normal samples	In CRC, SDC2 and TFPI2 were hypermethylated
Moradi et al. (2020) (50)	SOX21	The MethyLight method was utilized to determine methylation levels in the stool	Upregulated	The methylation rates of SOX21 were significantly higher in tumor tissues compared to normal tissues (P < 0.0001)	SOX21 gene promoter methylation is a potential diagnostic biomarker for colon cancer
Alizadeh-Sedigh et al. (2022) (51)	PIK3CA, KRAS, BRAF	PCR-direct sequencing for PIK3CA mutations	-	PIK3CA exon 9 (47.1%) in cancerous tissues	PIK3CA, KRAS, BRAF, and APC hotspot mutations have diagnostic potential in colon cancer
Ghatak et al. (2022) (52)	BDNF, PTGS2, GSK3B and CTNNB1, HPGD	Tissue samples	Upregulated	BDNF, PTGS2, GSK3B, and CTNNB1 were upregulated, whereas HPGD was significantly downregulated	Prognostic and diagnostic biomarkers
Ahluwalia et al. (2019) (53)	YWHAB, MCM4, and FBXO46	The Cancer Genome Atlas, COAD, and READ datasets	Upregulated	DPP7/2, YWHAB, MCM4, and FBXO46 were found to be significant predictors of poor prognosis in CRC patients (HR: 3.42, 95%, p < 0.001)	Potential prognostic biomarkers

One well-studied gene rearrangement in colon cancer involves the fusion of the EML4 (echinoderm microtubule-associated protein-like 4) gene and the ALK (anaplastic lymphoma kinase) gene. This rearrangement results in the constitutive activation of the ALK tyrosine kinase, which promotes cell proliferation and survival. The EML4-ALK fusion has been identified in a small subset of CRC patients, and its presence is associated with poor prognosis (55, 56). Another common gene rearrangement in CRC involves the fusion of the BRAF (v-raf murine sarcoma viral oncogene homolog B) gene and the KIAA1549 gene (57). This rearrangement results in the overexpression of the BRAF protein, which is involved in the RAS/RAF/MEK/ERK signaling pathways. The BRAF-KIAA1549 fusion has been identified in a significant proportion of CRC patients with microsatellite instability (MSI), which is a hallmark of defective DNA mismatch repair. The presence of this fusion is associated with a better prognosis in MSI CRC patients (58).

In addition to these specific gene rearrangements, chromosomal instability (CIN) is a hallmark of CRC, and it can result in a variety of gene copy number alterations, including deletions, amplifications, and translocations. For example, the loss of the tumor suppressor genes APC (adenomatous polyposis coli) and TP53 (tumor protein p53) is a common event in CRC that can result from chromosomal deletions. On the other hand, amplifications of the oncogene MYC (MYC proto-oncogene, bHLH transcription factor) have also been observed in CRC, and these amplifications can lead to increased MYC expression and tumor cell proliferation (59). A study by Créancier et al. reported 2 colon cancer cases (out of 408) with NTRK1 chromosomal rearrangements, with one manifested as TPM3–NTRK1 fusion and other as TPR–NTRK1 fusion (60).

Fusion genes

One important mechanism of genetic alteration in colon cancer is the formation of fusion genes. Fusion genes are created when two previously separate genes become linked together through a chromosomal rearrangement, such as a translocation or inversion (61). This results in a new gene that encodes a fusion protein, which can have altered or novel functional properties compared to the original proteins. Several fusion genes have been identified in colon cancer, with the most common involving the genes encoding the transcription factor ETS-related gene (ERG) and the receptor tyrosine kinase Ret (62, 63). The ERG gene is normally involved in regulating gene expression during development and differentiation, while Ret is involved in cell growth and survival signaling. When these two genes are fused together, the resulting ERG-Ret fusion protein has constitutive tyrosine kinase activity, leading to uncontrolled cell growth and proliferation. Other fusion genes identified in colon cancer include those involving the BRAF gene, which is frequently mutated in colon cancer, and the neurotrophic receptor tyrosine kinase 2 (NTRK2) gene. The BRAF fusion gene results in the activation of the MAPK signaling pathway, which promotes cell growth and survival (64). The NTRK2 fusion gene produces a fusion protein with constitutive kinase activity, leading to increased cell proliferation and survival (65). The detection of fusion genes in colon cancer has important implications for diagnosis, prognosis, and treatment. Fusion genes can serve as biomarkers for the identification of colon cancer subtypes with different clinical outcomes and responses to therapy.

Somatic mutations

Somatic mutations, which occur in non-germline cells, are a critical driver of colon cancer pathogenesis. These mutations affect various genes that participate in diverse cellular pathways, including those regulating cell cycle progression, DNA damage response, and cellular signaling. The adenomatous polyposis coli (APC) gene, which is a tumor suppressor gene that controls cell proliferation and differentiation, is one of the most commonly mutated genes in colon cancer. APC mutations are present in 80% of sporadic colon cancer cases, and loss of APC function results in the accumulation of κcatenin, a transcriptional co-activator that stimulates cell proliferation and survival (35). Colon cancer is characterized by the presence of mutations in several key genes, including APC, KRAS, and TP53. KRAS mutations are particularly prevalent, occurring in around 40% of cases (66). These mutations activate the RAS/MAPK-signaling pathway, which plays a critical role in promoting cell proliferation and survival. In addition, TP53 mutations are also common, occurring in approximately 50% of cases (67). Loss of TP53 function results in the loss of its tumor suppressor activity, which normally regulates cell cycle arrest and apoptosis in response to DNA damage. Furthermore, colon cancer involves somatic mutations in various genes that regulate critical cellular processes, such as DNA repair. For example, the MutS homolog 2 (MSH2) and MutL homolog 1 (MLH1) genes, which play a crucial role in mismatch repair, are often affected by somatic mutations in colon cancer (68). Such mutations can lead to a genetic condition called microsatellite instability, which causes the accumulation of errors in repetitive DNA sequences.

With the advent of modern sequencing technology, it has become possible to identify additional somatic mutations that contribute to the development of colon cancer. For instance, mutations have been detected in genes that regulate chromatin remodeling, such as the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex and the Polycomb repressive complex 2 (PRC2) (69). Rosic et al. conducted a genetic analysis on a cohort of 80 colon cancer patients, which uncovered a novel somatic variation in the form of an imbalance in alleles of single nucleotide variants (SNVs) (70).

Circulating tumor DNA

Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for the diagnosis, prognosis, and treatment of colon cancer, which is a prevalent type of cancer worldwide. ctDNA comprises DNA fragments that are released by tumor cells into the bloodstream and can provide valuable information about the genetic characteristics of the tumor. Studies have revealed that ctDNA is present in nearly all patients with advanced colon cancer, and its levels are associated with the stage and burden of the disease (71, 72).

ctDNA can also be detected in patients with early-stage colon cancer, albeit at lower levels. The detection of ctDNA in the peripheral blood of colon cancer patients is a sensitive and specific method for detecting residual disease after surgery or monitoring the response to treatment. ctDNA analysis offers significant benefits beyond its diagnostic and prognostic value. For example, ctDNA can detect mutations in genes such as KRAS and TP53 that are commonly mutated in colon cancer. ctDNA analysis can also provide information about other genetic alterations—such as microsatellite instability (MSI) or BRAF mutations—that are associated with poor prognosis in colon cancer (73).

Pharmacogenomics

Pharmacogenomics is a discipline that investigates the influence of an individual's genetic variations on drug efficacy and toxicity (74). Colon cancer is a major public health concern, and its treatment involves the use of various chemotherapy drugs. However, the efficacy of these drugs can vary significantly among individuals, due to differences in their genetic profiles (75). Therefore, understanding the pharmacogenomics of colon cancer is crucial for developing personalized treatment plans. One of the most well-known pharmacogenomic biomarkers for colon cancer is the presence of KRAS mutations. The KRAS gene is frequently mutated in colorectal cancer, which has been associated with resistance to EGFR inhibitors like cetuximab and panitumumab (76). These drugs are commonly used to treat metastatic colorectal cancer, and their efficacy is significantly reduced in patients with KRAS mutations. Therefore, testing for the presence of this mutation has become an essential step in selecting the appropriate therapy for colon cancer patients. Another important pharmacogenomic biomarker for colon cancer is the dihydropyrimidine dehydrogenase (DPD) enzyme. DPD is responsible for the metabolism of 5-fluorouracil (5-FU), which is a commonly used chemotherapy drug for colon cancer. Patients with decreased DPD activity are at a higher risk of developing severe toxicities when treated with 5-FU. Therefore, testing for DPD deficiency is recommended before starting 5-FU therapy (77). In addition to KRAS and DPD, several other genetic variants have been associated with the efficacy and toxicity of chemotherapy drugs used in colon cancer. For example, the UGT1A1*28 allele has been linked to an increased risk of severe toxicities when treated with irinotecan (78). Similarly, the TPMT gene variants have been associated with a higher risk of myelosuppression when treated with thiopurine drugs, such as azathioprine and mercaptopurine (79).

Plasma and tissue proteomic biomarkers

Several plasma and tissue proteomic biomarkers have shown promise in early detection and diagnosis of colon cancer (Table 3). Carcinoembryonic antigen (CEA) and epithelial cell adhesion molecule (EpCAM), have shown promise in early detection and diagnosis of colon cancer (80, 81). Elevated levels of CEA have been associated with advanced stages of colon cancer and poor prognosis. EpCAM has been shown to be a potential target for cancer therapy, and its expression levels have been used to predict patient outcomes. Other potential tissue biomarkers for colon cancer include heat shock protein 27 (HSP27), guanine nucleotide-binding protein subunit beta-2-like 1 (GNB2L1), and peroxiredoxin-1 (PRDX1) (82, 83). Tryptophan metabolism dysregulation has been linked to colorectal tumorigenesis, and altered levels of tryptophan metabolites and indole derivatives contribute to the promotion of tumorigenesis by altering the immune response, inducing inflammation, and affecting the balance of gut microbiota. Studies have shown that tryptophan is inversely associated with colon cancer risk (84, 85). According to a study conducted by Vasaikar and colleagues, the use of proteomics has revealed a correlation between reduced infiltration of CD8 T cells and heightened glycolytic activity in microsatellite instability-high (MSIH) tumors. This finding indicates that targeting glycolysis may serve as a potential strategy to overcome the resistance of MSI-H tumors to immune checkpoint blockade (86). A proteomics study by Tang et al. showed that proteins like TFR1, SAHH, and HV307 were differently expressed in colon cancer patients (87). Several studies have demonstrated that tryptophan and indole metabolism pathways are dysregulated in colon cancer, leading to altered levels of tryptophan metabolites and indole derivatives. These metabolic changes contribute to the promotion of tumorigenesis by altering the immune response, inducing inflammation, and affecting the balance of gut microbiota (88). Zhong et al. showed that extracellular vesicles containing SPARC and LRG1 were differentially expressed in colon cancer patients as compared to healthy subjects, and differed by tumor location (89).

Plasma and tissue metabolomics and microbiomics

Recent advancements in molecular profiling techniques, such as metabolomics and microbiomics, have provided new insights into the pathogenesis and progression of colon cancer (Table 4). Metabolomics and microbiomics focus on the comprehensive analysis of small molecules and microbial communities, respectively, in biological samples. Metabolomics analysis can provide a comprehensive understanding of the metabolic alterations that occur during colon cancer development and progression. The analysis of plasma metabolites in colon cancer patients has shown alterations in amino acid, lipid, and carbohydrate metabolism. These metabolic alterations are related to cancer cell proliferation, invasion, and metastasis. In addition, metabolomics analysis of colon tumor tissue has revealed significant differences in metabolic pathways, including glycolysis, tricarboxylic acid cycle, and pentose phosphate (105). A study by Deng et al. reported that plasma metabolomic profiling can be helpful in distinguishing left-sided colon cancer from right-sided colon cancer (106). Microbiomics is the study of the microbial communities that reside within a host. The one residing in the intestine, the so-called gut microbiome, is composed of trillions of microorganisms, including bacteria, viruses, fungi, and archaea. Recent studies have shown that the gut microbiome plays a critical role in colon cancer development and progression. The gut microbiome can influence the host's

Table 3. Summary of protein biomarkers in colon cancer, their type, technique used, and sample.

References	Protein Biomarker	Up-/down-regulated	Type of Biomarker	Technique	Sample
Zhang et al. (90)	Transgelin-2 (TAGLN2)	Upregulated	Diagnostic biomarker	Fourier transform mass spectrometry (FTMS)	CRC tissue
Ghazanfar et al. (91)	ACTBL2	Upregulated	Diagnostic biomarker	Two-dimensional gel electrophoresis coupled to mass spectrometry (2DE-MS)	CRC tissue
Hao et al. (92)	DPEP1	Upregulated	Diagnostic biomarker	FTMS	CRC tissue
Jonsson et al. (93)	MMP-9	Upregulated	Diagnostic biomarker	ELISA	CRC tissue
Quesada-Calvo et al. (94)	OLFM4, KNG1, Sec-24	Upregulated	Diagnostic biomarker	Liquid chromatography-mass spectrometry (LC-MS)	FFPE CRC tissue
Guo et al. (95)	PCBP1	Upregulated	Predictive biomarker	2D gel electrophoresis	Cell lines and tumoral tissue
Yamamoto et al. (96)	Cyclophilin A, Annexin A2, Aldolase A	Upregulated	Diagnostic biomarker	LC-MS	FFPE CRC tissue
Zhang et al. (97)	LRG1	Upregulated	Diagnostic biomarker	Quantitative real-time PCR and ELISA	CRC tissue and plasma
Katsila et al. (98)	pEGFR	Upregulated	Predictive biomarker	Quantitative proteomic analysis	Plasma
Ivancic et al. (99)	LRG1, EGFR, ITIH4, SOD3	Upregulated	Diagnostic biomarker	Targeted liquid chromatography-tandem mass spectrometry	Serum
Bhardwaj et al. (100)	MASP1, Osteopontin, PON3, TFRC1, Amphiregulin	Upregulated	Diagnostic biomarker	Liquid chromatography	Plasma
Langers et al. (101)	MMP-2, MMP-9	Upregulated	Predictive biomarker	ELISA	CRC tissue
Yu et al. (102)	STK4 or MST1	Downregulated	Diagnostic biomarker	Mass spectrometry (MS/MS), ELISA	Serum
Martin et al. (103)	APOE, AGT, DBP	Upregulated	Predictive biomarker	Gel electrophoresis (2D-DIGE) followed by LC-MS/MS	Serum
Yang et al. (104)	PSMA1, LAP3, ANXA3, serpin B5	Upregulated	Predictive biomarker	Mass spectrometry	Serum and CRC tissue

immune system, metabolism, and gut barrier function, all of which are critical factors in colon cancer pathogenesis. In colon cancer patients, there is a significant dysbiosis in the gut microbiome, with a reduction in beneficial bacteria and an increase in harmful bacteria. Moreover, certain bacterial species have been implicated in colon cancer development and progression, such as *Fusobacterium nucleatum, Streptococcus bovis,* and *Escherichia coli* (107, 108). These bacteria can promote tumorigenesis by inducing inflammation, altering the gut microenvironment, and producing genotoxic metabolites.

Tailored therapy

Despite advances in diagnosis and treatment, a significant proportion of patients with colon cancer continues to experience disease recurrence and treatment resistance. Tailored therapy, which involves individualizing treatment based on a patient's unique characteristics, has emerged as a promising approach to improving outcomes in colon cancer. Tailored therapy in colon cancer involves the use of biomarkers, which are molecular or cellular indicators that can predict disease behavior or response to therapy (116). These biomarkers can be used to identify subgroups of patients who are likely to respond to specific treatments or who have a higher risk of disease recurrence. Some of the most commonly used biomarkers in colon cancer include microsatellite instability (MSI), KRAS mutation status, and BRAF mutation status. Patients with MSI-high colon cancer are more likely to respond to immune checkpoint inhibitors, which activate the immune system to attack cancer cells (117). In contrast, patients with MSI-low or microsatellite-stable (MSS) colon cancer may benefit from conventional chemotherapy regimens. KRAS and BRAF mutations are associated with resistance to certain chemotherapy drugs, and patients with these mutations may benefit from alternative treatment approaches. For example, patients with KRAS mutations may benefit from targeted therapies that inhibit downstream signaling pathways, such as EGFR inhibitors (118). Similarly, patients with BRAF mutations may benefit from combination therapies that target multiple signaling pathways (119).

Table 4. Summary of metabolomics and microbiomics biomarkers for early diagnosis of colon cancer.

Author	Metabolite(s)/Pathway (s)	Up-/Down-regulated	Specimen	Findings
Cross et al. (109)	Glycochenodeoxycholate	Upregulated	Serum	Positive association was observed in CRC among women
Long et al. (110)	Xanthine, hypoxanthine, D-mannose	Downregulated	Serum	Lower levels observed in CRC compared to control. Hypoxanthine to xanthine levels indicative of CRC progression
Sinha et al. (111)	Clostridia Lachnospiraceae p-aminobenzoate and conjugated linoleate	Downregulated	Feces	A strong correlation was observed in fecal samples of CRC patients. Metabolites predominated by Enterobacteriaceae and Actinobacteria.
	Fusobacterium Porphyromonas p-hydroxy-benzaldehyde palmitoyl-sphingomyelin	Upregulated		
Gao et al. (112)	Methionine Tyrosine Valine Isoleucine	Upregulated	Tissue	Tissue amino acid profile has good sensitivity and specificity for diagnosis of CRC ($p<0.001$)
Ning et al. (113)	Glycolysis and amino acid metabolism	Upregulated	Urine	GC-TOF/MS-based metabolomics as diagnostic biomarkers for CRC
	Lipid metabolism	Downregulated		
Wang et al. (114)	Choline Phenylalanine Asparagine Isocitrate Cysteine Hippurate Dimethyl sulfone Creatinine Alanine Methylamine	Downregulated	Urine	NMR-based urinary metabolomics has potential for early diagnosis of CRC
	Homocysteine Glutamine cis-Aconitate Acetoacetate trans-Aconitate Guanidoacetate	Upregulated		
Yang et al. (115)	Proline and Glutamine	Upregulated	Feces	Microbe-associated metabolites have diagnostic potential for CRC
	Glycerol Linoleic acid Oleic acid	Decreased		
	Proteobacteria Fusobacteria Firmicutes	Upregulated		

Conclusions

Colon cancer is a complex and heterogeneous disease that requires a multi-omics approach for its proper diagnosis, prognosis, and treatment. The integration of omics sciences and precision medicine has revolutionized our understanding of colon cancer and the way we approach diagnosis and treatment. The identification of specific genetic mutations and genomic rearrangements, as well as the development of new biomarkers have allowed for more accurate diagnoses and personalized treatment plans. This information can guide the selection of tailored therapies, which can improve patient outcomes and reduce treatment-related toxicities. Precision medicine based on omics technologies is rapidly advancing in the field of colon cancer, and its potential to revolutionize cancer care treatment cannot be overstated. By identifying the specific molecular abnormalities driving cancer growth and progression, precision medicine can offer targeted therapies that can block or inhibit those abnormalities. The ability to tailor therapy based on each patient's characteristics has led to improved patient outcomes and better overall survival rates. However, there is still much to be learned in this field, and continued research is necessary to identify new biomarkers and therapeutic targets. Furthermore, access to these cutting-edge technologies must be expanded, to ensure that all patients can benefit from personalized treatment plans.

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Conflicts of interest statement

Authors declare no conflict of interest.

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