Host Genetics and Microbiota Interactions in Colorectal Cancer

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The role of microbiota in colorectal cancer has been studied since alterations in its composition were observed. In addition, there are more and more pieces of evidence that microbiota could be implicated in colorectal cancer progression. Thus, the components of the microbiota could be biomarkers for the diagnosis and prognosis of colorectal cancer. In addition, it is important to address how the microbiota interacts with the host and how the host shapes the microbiota, in order to understand the biological pathways and mechanisms involved in their relationship and the consequences of their interactions in colorectal cancer.

colorectal cancer genetics genomics microbiota

1. Microbiota Involvement in CRC

1.1. Microbiota Composition

When microbiota is analyzed, bacterial composition is usually analyzed. The studies about the role of archaea, viruses, fungi, and parasites are scarcer, and their effect on the rest of the microbiota is less known. However, there are valuable studies that have contributed to the understanding of the diversity in the composition of the microbiota and the complex interactions between the different members of the microbiota.

1.2. Pathways and Biological Functions of the Microbiota

One of the most remarkable features of bacteria is the plasticity of their genomes. Thus, it is not enough to know what taxa are present in colorectal cancer (CRC), and it is necessary to know the biological functions that they can carry out. There have been technical limitations to studying the gene content of microbiota, but its study is increasingly feasible.

However, it must pointed out that microbiota is functionally redundant in healthy persons[1][2]. Although a lot of taxa carrying diverse genes can be found in the microbiota, those genes have similar functions[1][2]. That is, the composition of microbiota varies between individuals, but the biological functions present in the microbiota are conserved. Thus, it is necessary to elucidate if this functional redundancy is perturbed in CRC, and how. To study the bacterial genes present, they can either be indirectly inferred using the microbiota composition, or directly by whole-genome sequencing of bacterial content.

In a study where stools from adenoma, CRC, and healthy patients were analyzed, based on the bacterial content, the biological functions were inferred[3]. In this case, the pathways related to amino acids biosynthesis, fermentation (isobutanol, acetate, and lactate), glucose metabolism (gluconeogenesis, glycolysis, and glycogen biosynthesis and degradation), saturated fatty acids, reductive incomplete TCA, nitrate degradation and methanogenesis were different in CRC samples[3].

Moreover, when the left and right colon cancer were compared, since the microbiota had a different composition, the microbial pathways present were different[4]. In the case of left colon cancer, “L-lysine fermentation” and “cob(II)yrinate a,c-diamide biosynthesis I” pathways were predominant, while there was no significantly enriched function in right colon cancer[4].

One study analyzed the bacterial gene content of CRC and healthy stools[5]. There were no significant differences in KEGG pathways between the genes present in CRC and healthy stools, but two KEGG modules (leucine degradation and guanine nucleotide biosynthesis) were significantly enriched[5]. In addition, 12 orthologous gene groups were more abundant in CRC (e.g., “Glycine reductase”, “N-acetylornithine carbamoyltransferase”, and “Rrf2 family transcriptional regulator”), while 7 were less abundant (e.g., “Type IV pilus assembly protein PilF”, “Protein-serine/threonine kinase” and “Phosphatidylglycerophosphatase B”)[5].

In another work, the gene content from whole-genome sequencing data was assigned to protein families or domains, and some differences were found between CRC and healthy samples[6]. In the case of protein domains, 7 were more abundant in CRC samples, and those domains were related to bacterial invasion and adhesins; while 5 were reduced domains related to antibiotic resistance, bacteriophage maturation, and threonine biosynthesis[6]. In the case of protein families, one family was more abundant in CRC (associated with proline iminopeptidase) and the other less abundant (associated with threonine biosynthesis)[6].

Moreover, novel methods have been developed to cluster bacterial genes using their co-abundance and, therefore, to find consistently disturbed genes in CRC[7]. That approach was used to analyze publicly available datasets and in healthy samples, the largest co-abundant gene group was from *Clostridia*, while in CRC the origin of those genes was taxonomically more diverse[7]. In addition, the largest co-abundant genes cluster in CRC had genes involved in the “metabolism of glycine/sarcosine/betaine”, “protection from the biochemical damage induced by reactive oxygen species”, “uptake of p-aminobenzoyl-glutamate”, and “transporters responsible for importing iron”, biological functions that are related to cancer progression[7].

To sum up, the studies where the biological capabilities of bacteria are analyzed are fewer than the ones analyzing the content, and few pathways or biological functions have been detected to be different in CRC. In accordance with the functional redundancy of microbiota, although the taxa present can change, the main functions of microbiota seem to be conserved and few pathways related to cancer progression can be detected.

2. Interactions between Host Genetics and Microbiota in CRC

The researchers have recapitulated some of the changes that have been observed, both in composition and biological functions in microbiota. However, is the host somewhat driving those changes, or does the microbiota change the host cells?

How host genetics shapes microbiota composition and microbiota the biological functions of the host have been intriguing questions. Over the years, their study has evolved, and it has not been until recently that the researchers have had a more precise picture of the genetic mechanisms that shape the host–microbiota interactions. The development of *omics* approaches has facilitated the analysis and inference of correlations and interactions between the host genetics (and its different layers) and microbiota. Although the number of such studies is scarce, the results of those studies have highlighted that there are some mechanisms shared by host genetics and microbiota, and other mechanisms that are independent.

2.1. Shared Risk Components

2.1.1. Genetic Variation

The study of the genetic variants of the host that affect the abundance of bacterial taxa has been a valuable asset to get genetic signatures related to microbiota composition[8]. Based on those genetic signatures of microbiota composition, it has been analyzed the contribution of various phyla to CRC risk using Mendelian Randomization analyses[9]. Although it is an indirect method, it gives information to determine if there are shared genetic mechanisms to CRC risk and the abundance of a given phylum. Although the results were weak, the genetic variants associated with the abundance of Firmicutes and Cyanobacteria phyla were also associated with the genetic risk of CRC, specifically with the genetic risk of left colon cancer[9]. It must pointed out that in the study in question, the genetic variants involved in total cholesterol levels were determined to be a risk factor in left colon cancer[9]. Thus, it cannot be ruled out that modifiable risk factors such as cholesterol levels could shape the risk of CRC through the host genetic and/or microbiota composition.

As mentioned previously, strains of *E. coli*$^{pks+}$ have been involved in CRC risk. The pks pathogenic island carries genes involved in colibactin, a genotoxic that could cause mutations in host cells[10]. The long-term exposure of *E. coli*$^{pks+}$ causes a distinct mutational signature in organoids, showing a bias towards T to N substitution and a single T deletion at T homopolymers[10]. In fact, these two mutational signatures were enriched in CRC samples[10]. In addition, a study showed that the transplant of the microbiota of CRC patients to a mice model altered the DNA of the cells of the gut of the mice[11]. Thus, the microbiota could cause somatic mutations in host cells.

2.1.2. Transcription

Moreover, the effect of the genes expressed by the colonic mucosa and the composition of the microbiota in CRC patients have been analyzed, among other gastrointestinal diseases[12]. In that study, they observed in CRC a correspondence between the variability of gene expression of gut tissue and microbiota composition[12]. In addition, they detected three pathways that affected the composition of the gut microbiota in the three gastrointestinal diseases that were analyzed (CRC, inflammatory bowel disease, and irritable bowel syndrome), namely “Oxidative

phosphorylation", "*RAC1* pathway" and "*ERBB1* downstream pathway"; and 52 pathways specific to CRC[12]. For example, among those specific pathways, there was the Syndecan-1 pathway[12], a pathway previously associated with tumorigenic activity and that affects the abundance of *Parvimonas* and *Bacteroides fragilis* in CRC[12], bacterial taxa that are biomarkers of CRC due to their role in the carcinogenesis. Regarding gene expression and taxa associations, the effect of the expression of 745 genes in the abundance of 120 microbes was found and those genes of the host were involved in tumor growth, progression, and metastasis[12].

Previously, the researchers have discussed the higher presence of *Fusobacteria* in certain subtypes of CRC[13]. When the expression of genes of the host tissue was analyzed to compare the expression pattern in the presence or absence of *Fusobacteria*, pathways of the host related to inflammatory-related signaling (e.g., "IL-8 signaling" or "Th17 activation"), "aryl hydrocarbon receptor (AhR) signaling", cellular organization, movement and invasion pathways, and metabolic pathways (e.g., cholesterol and proteoglycan metabolism) were affected[13]. In that study, the role of *Fusobacteria* in CRC was experimentally analyzed and it was observed that *Fusobacteria* has protumorigenic effects[13]. The formate produced by *Fusobacteria* activates AhR signaling, which can lead to tumor invasion, activating proinflammatory profiles[13]. That is, a bacterial metabolite affects the expression of host cells and affects CRC progression.

Moreover, a study analyzed publicly available data to determine if the composition of microbiota affected host gene expression in early-stage CRC and advanced-stage CRC[14]. The bacterial taxa with more connections with the expression of host genes in early-stage CRC were *Ilumatobacter*, *Rhodospirillum*, and *Nitrosospira*, while in advanced-stage CRC they were *Desulfurella*, *Nitriliruptor*, and *Jeotgalicoccus*[14]. Indeed, these taxa are not the usual taxa associated with CRC. Thus, this kind of novel approach is useful to unveil hidden biological mechanisms. In addition, the connected genes with these bacteria belonged to biological functions related to proliferation, biogenesis, and cell cycles in early-stage CRC, and related to migration and angiogenesis in advanced-stage CRC[14].

2.1.3. Methylation

Another study analyzed the role of the microbiota in the methylation patterns of tumor suppressor genes[15], since their deregulation is one of the characteristics of CRC progression. The abundance of *Hungatella hathewayi* showed a correlation with the methylation level of tumor suppressor genes such as *SOX11*, *THBD*, *SFRP2*, *GATA5*, and *ESR1*; and *Fusobacterium nucleatum* with the methylation levels of *MTSS1*, *RBM38*, *PKD1*, and *PTPRT*[15]. In the case of the well-known tumor suppressor genes in CRC, *MLH1*, *APC*, *PTEN*, and *CDX2* showed correlations with bacterial taxa[15]. Specifically, *H. hathewayi* abundance was correlated with *CDX2*, *Streptococcus* spp. with *MLH1*, and both taxa with *APC*[15]. In addition, using an experimental approach, the upregulation of DNA methyltransferase in host cells by *F. nucleatum* and *H. hathewayi* was observed[15].

Moreover, the transplant of the microbiota of CRC patients to a mice model showed that the methylation patterns in the mice cells change and those changes were enriched in genes involved in cell growth, signal transduction, nucleic acid binding, protein synthesis, channels, and carrier proteins[11]. Then, the methylation status of several

genes in samples of the original CRC patients was analyzed, and the combination of some of them was able to discriminate between CRC patients and healthy controls[11]. In addition, the samples with higher methylation changes showed a higher abundance of *Parvimonas*[11].

2.1.4. Metabolites

In the case of the relationship between fecal microbiota and the metabolome, both layers were able to discriminate CRC samples from adenoma and healthy controls[3]. In addition, several genera were correlated with metabolites from the fecal microbiota[3]: Cholesteryl esters and sphingomyelins metabolites were positively correlated with the abundance of *Fusobacterium*, *Gemella*, *Parvimonas*, *Peptrostreptococcus*, and Erysipelotrichaceae, while negatively with *Coprococcus*, *Dorea* and *Blautia*. In the case of diacylphosphatidylcholines, they were negatively associated with *Coprococcus*, *Dorea*, and *Blautia*; and triacylglycerol metabolites were negatively correlated with *Desulfovibrio* and *Synergistes* genera[3]. Based on those results, a model to discriminate between adenomas, CRC, and healthy patients was developed[3].

It must be pointed out that the metabolites of the microbiota could interact with host cells' through cell receptors. One study analyzed the metabolites present in the murine gut, and some of them were further investigated. It was observed that some metabolites derived from microbiota were able to activate pathways in human cell models[16]. This kind of interaction should be further studied in CRC, to determine if the microbiota interacts with host cells in this way and leads to the development of CRC.

2.1.5. Multilevel

Although the effect of the microbiota in the fecal metabolome in adenomas and CRC was established[3], the effect of host genetics was further studied[17]. In the case of the shared risk component, it was detected that the genetic variants associated with the abundance of Bacteroidetes and Firmicutes were also involved in adenoma or CRC genetic risk[17]. In addition, genetic variants associated with cholesterol, triglycerides, phosphatidylethanolamine, and phingomyelin metabolites were associated with adenoma or CRC genetic risk[17]. There were also detected interactions between host genes of pathways related to cholesterol metabolism and the effect of genetic variants related to HDL cholesterol in adenoma and CRC risk[17]. As previously mentioned[9], the interplay between host genetic factors, host lifestyle, and microbiota could shape the risk to develop adenomas and CRC.

2.2. Independent Risk Components

One study analyzed the role of bacterial toxins in pre-tumorous and tumorous tissue and the effect of host genetics in CRC[18]. The results showed that the *cif* toxin gene was more present in pre-cancerous polyps or adenomas, toxins of *Escherichia coli* were more abundant in adenocarcinomas, and *E. coli*$^{pks+}$ strains were a risk factor for CRC[18]. Interestingly, polygenic risk scores were used to measure the genetic risk of developing CRC in those patients, and there was not any significant difference between patients with pre-tumorous and tumorous lesions, and healthy individuals[18]. Thus, the host genetics did not influence the bacterial toxins and their role in the development of the lesions[18].

Previously, the researchers have discussed some examples of shared risk components of host genetics, the fecal metabolome, and microbiota[17]. However, when the three layers were analyzed altogether using multi-*omic* integration procedures, the variance of risk to adenoma and CRC explained by each layer was different[17]: microbiota had more weight in the variance, metabolome had less weight, and the contribution of host genetics was limited. Except for the factors that explained more variance, where microbiota and metabolome showed covariance, covariance was not detected in the rest of the factors[17]. Thus, when all the information of *omic* layers is used to analyze their involvement in adenoma and CRC risk, their contribution to adenoma or CRC risk was independent[17]. In fact, the models built to predict adenoma and CRC risk based on microbiota and the metabolome[17] were more robust when information from the three layers (host genetics, microbiota, and metabolome) was used, a fact which strengthens the idea that each layer captures part of the risk to CRC. That is to say, the information is not redundant[17] (**Table 1**).

Table 1. Summary of the findings about host–microbiota interactions in colorectal cancer.

Level	Host Affects Microbiota	Microbiota Affects Host
Genetic variation	Host variants associated with CRC could shape microbiota composition[9]	*E. coli*$^{pks+}$ could cause somatic mutations in host cells[10]
Transcription	Host gene expression shape microbiota composition in CRC[19]	*Fusobacteria* disrupts host gene expression[13] Microbiota composition shapes host gene expression in CRC stages[14]
Methylation		*Hungatella hathewayi* and *Fusobacterium nucleatum* disrupt the methylation of tumor suppressor genes[15] Parvimonas abundance is higher in CRC patients with altered methylation[11]
Metabolites	Correlation between certain metabolites and abundance of microbiota[3]	Bacterial toxins and host genetic risk are not linked[18]
Multilevel	Host variation shapes some microbial taxa and metabolites but each layer explains part of the risk[17]	

As the researchers have reviewed, there are biological mechanisms that are involved in both genetic CRC risk and microbiota composition, but not all the role of microbiota in CRC is influenced by the genetics of the host. It must pointed out that the composition of the microbiota is influenced by diet[20] or lifestyle[21]. Therefore, the host could shape the composition of the microbiota by modifiable risk factors rather than genetic factors and that could partially explain that there are shared and independent risk factors. For example, the metabolism of cholesterol is one consistent pathway altered, an alteration that could partially be due to the host genetic component and another part of the diet. In addition, bacteria can shape the function of the host cell, by changing the expression and methylation patterns of key genes in CRC development.

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