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The Challenging Triad: Microbiota, Immune System and Anticancer Drugs

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Abstract

Gut microbiota is essential for the development of the intestinal immune system, protecting the host against pathogens and harmful inflammatory processes. Germ-free animals have smaller Peyer's patches, fewer immune cells and impaired immunoglobulin A (IgA) secretion, fewer intraepithelial lymphocytes, as well as compromised production of antimicrobial peptides. Mucositis (mucosal barrier injury) is a major oncological problem caused by chemotherapeutic agents. Intestinal mucositis translates into a broad spectra of clinical symptoms (diarrhea, vomiting) and can be worsened by neutropenia and antibiotics. Since IECs do not regulate intestinal homeostasis by themselves, but require symbiotic coordination with commensal bacteria and local gut leukocytic cells, the role of intestinal microbiota in the development and severity of mucositis induced by chemotherapeutic products became an issue. The present chapter reviews the interplay between microbiota, immune system, and anticancer therapy. The published researches in this field showed that microbiota has immunomodulatory effect on the anticancer immune response, both in the presence and in the absence of chemotherapy. Animal and human studies evoked that the anticancer response depends on microbiota variability.

Keywords: microbiota, immune system, anticancer therapy, efficacy, toxicity

1. Introduction

The relationship between cancer and microbiota was recognized and challenged since the nineteenth century when William Coley, a surgical oncologist, developed a mixture consisting of killed bacteria of species *Streptococcus pyogenes* and *Serratia marcescens*, also known as “Coley's toxin,” as a treatment for cancer.

Ever since, experimental and clinical researchers tried to isolate microbial agents or products to treat malignant disease, such as treatment of superficial bladder cancer based on an attenuated form of *Mycobacterium bovis*, an oncolytic herpes virus for the treatment of melanoma, or the treatment of pancreatic cancer with *Listeria monocytogenes* [1].

The present chapter reviews the interplay between microbiota, immune system, and anticancer therapy. The published researches in this field showed that microbiota has immunomodulatory effect on the anticancer immune response, both in the presence and in the absence of the chemotherapy. Animal and human studies evoked that the anticancer response depends on microbiota variability. In initiating an efficient chemotherapy, the following aspects should be considered:

- The interactions between microbiota and cancer progression.
- The influence of the microbiota on the chemotherapy response.
- The microbiota imbalance influences drugs bioavailability, efficacy and toxicity.

2. Microbiota, health and diseases

Microbiota affects many physiological processes, while its alteration is thought to render a number of pathologies.

The growing evidence regarding the importance of the microbiome for health and disease and the host-microbe symbiosis at the immunological and metabolic levels become highly challenging for a better understanding of immunopathologies such as autoimmune and inflammatory disorders. Microbiome changes were correlated with a variety of diseases such as inflammatory bowel disease, obesity, type 2 diabetes, autism, and allergies.

Crohn's disease (CD) and ulcerative colitis (UC) are the most prevalent forms of inflammatory bowel disease (IBD), characterized by chronic relapsing inflammation affecting the intestinal mucosa. The etiology of these diseases is unknown, but there are increasing scientific evidences that microbiota influences the pathogenesis of IBD [2].

Patients exhibit a decrease in microbial population and functional diversity, with a decrease of *Firmicutes*, an increase in *Bacteroidetes*, and facultative anaerobes such as *Enterobacteriaceae* [3–5].

The intestinal microbiota was also implicated in several other gastrointestinal-related diseases, such as obesity, type 2 diabetes, celiac disease, and colorectal cancer. The last two of these were

associated with changes in microbiota composition, but interestingly, no pattern of alteration was demonstrated [6–10]. Recent studies showed that the expression of the leukocyte antigen DQ2 is a strong risk factor for the development of celiac disease. It seemed that children possessing this haplotype also had an altered microbiota composition (compared to non-HLA DQ2 individuals) prior to clinically apparent disease [11].

On the other hand, there is a bidirectional functional relationship between the intestine and the kidneys, the urinary pH influencing the intestinal microbiota metabolism, while microbial-related metabolites are involved in the development of the kidney pathologies [12].

Several studies focused on the possibility that the intestinal microbiota may influence the hypothalamus-pituitary-adrenal (HPA) axis, and, therefore, the cognitive function and behavior. HPA is a pathway activated in response to infection and perturbed by psychological stressors (the “gut-brain axis”). There are publications that evoke a direct relationship between enteric infections on one hand and anxiety, depression, and cognitive dysfunctions, on the other hand [13–16].

3. Microbiota and cancer

Microbial communities inhabiting human body represent so far unknown environmental factors that seem to have a role in carcinogenesis.

Cancer susceptibility, development, and progression result from a complex interplay between gene regulation and the environment.

For decades, the researches on the interaction of the microbes with human organism were focused almost exclusively on the effects of **the single pathogenic microbial infection**.

Several mechanisms regarding the cancer development were described for some microbial species.

The direct carcinogen class usually comprises viruses which may produce cancer by genetic mechanisms [17, 18].

Researches on molecular mechanisms revealed that most of the oncoproteins encoded by human viruses target generally the tumor suppressor proteins: retinoblastoma RB1 and p53, which play major roles in cellular anticancer protection.

Other targets reported for carcinogenesis induce by viruses involved interaction with complex pathways of interferon signaling, transcription factors like nuclear factor- κ B (NF- κ B), telomerase complex, or cell adhesion molecules.

The Epstein-Barr virus (EBV), hepatitis C virus, and human papilloma virus are only a few examples of the most studied oncogenic viruses.

The Epstein-Barr virus (EBV) or human herpes virus 4 (HHV-4) is one of the most common viruses in humans and also the first discovered to be involved in tumorigenesis. The EBV

infects immune system cells (lymphocyte B) and epithelial cells, and the infections were correlated with some lymphoma, gastric cancer, anogenital and oropharyngeal carcinomas and with certain autoimmune diseases [19].

Hepatitis C virus is one of the major etiologic agents of hepatocellular carcinoma [20]. Researches on HCV-specific proteins revealed that they exert multiple functions during the life cycle of the virus. Due to their ability to adopt different structural conformations, the viral proteins are capable of various interactions with cellular proteins interfering in signaling pathways essential to cell functions. HCV causes genome instability suggesting that cooperation of both viral and host factors plays a role in developing the disease [21, 22].

Human papillomavirus (HPV) belongs to the DNA class viruses and is capable to infect keratinocytes of the skin and the mucosa. There are over 170 types of HPV described, and about dozen types are considered high-risk human carcinogen producing at least six types of cancer: cervix, penis, vulva, vagina, anus, and oropharynx [23].

The E6 and E7 genes of HPV have been identified as oncogenes involved in promoting tumor growth and transformation to malignancy. The E6 protein is involved in ubiquitination of p53, marking this protein for proteasomal degradation, while the protein E7 is involved in competing the retinoblastoma protein for binding and favors the cell cycle to continue.

The E6 and E7 deregulate the host innate immune defense required for the recruitment of the effector immune cells. Both proteins cooperate for the downregulation of the proinflammatory interleukins: IL-18 and IL-8 and of some chemoattractants like MCP-1 and MIP3 α . Also, proteins E6 and E7 interfere in the intracellular signaling pathways NF- κ B and interferon regulatory factors inhibiting the activation of these major antiviral transcription factors [24].

Although molecular mechanism of cancerogenesis has been explained for some pathogenic viruses, it is too simplistic to consider these microbes the only cause of tumorigenesis. Cancer is a complex multistep process which evolves over time and involves many signaling pathways and molecular interactions to generate a particular cellular phenotype.

Indirect carcinogen mechanisms comprise the injury of the epithelial barrier or inflammation associated to some infections produced by bacterial species like *Helicobacter pylori* or *Chlamydia trachomatis*.

Helicobacter pylori is a gram-negative pathogen which infects about half of humans all over the world and represents the main cause for gastric cancer. The *H. pylori* virulence factors, vacuolating cytotoxin (VacA) and CagA protein encoded by cytotoxin-associated gene-pathogenicity island, are identified as major antigens. These microbial proteins interact with several host receptors like toll-like receptor 2 (TLR2), NOD-like receptor family member NLRP3, and caspase-1 promoting the activation of the inflammasome.

The host cellular dysfunctions on secretory system, apoptosis, and immune inhibition were other mechanisms described as consequences of the *H. pylori* infection [25].

Chlamydia trachomatis infects both men and women, but it is commonly found in the reproductive system of women. The chronic infection causes pelvic inflammation with severe consequences like infertility. The incidence of infections is significant among patients with cervical cancer, but no proof exists to demonstrate that *Chlamydia* itself promotes cancer. Research proved that a common association with HPV favors cancer growth. Further studies in this direction are necessary for confirmation.

Other experiments indicate a correlation between some commensals, the production of oxygen-reactive species, and colon cancer. Thus, superoxide-producing *Enterococcus faecalis* was demonstrated to cause colonic epithelial cell DNA damage [26].

Recent years' researches focused on obesity as a risk factor for different types of cancer. Gut microbiota plays an important role in developing obesity. Some *Clostridium* spp. are microorganisms overrepresented in obese intestine and were directly correlated with liver and colorectal cancers. These commensals convert primary bile acids into deoxycholic acid (DCA), a carcinogen that can cause DNA damage via the production of free radicals [27].

For a long time, scientific research describes many other potential microorganisms involved in cancer promoting, but several questions about the main cause of tumorigenesis were raised because of a low incidence of cancer among infected patients with susceptible agents.

Recent researches have changed the perspective on many human diseases. Many scientific publications in the last years sustain the fact that global changes in our microbiome are the main causes of disease and not only a single opportunistic pathogen development.

Increased communities of *Capnocytophaga gingivalis*, *Capnocytophaga ochracea*, *Eubacterium sabureum*, *Leptotrichia buccalis*, and *Streptococcus mitis* present in saliva were observed in patients with oral squamous cell carcinoma.

Human esophageal cancer was associated in some cases with an increased presence of *Streptococcus anginosus*, *Streptococcus mitis*, *Treponema denticola*, or some *Campylobacter* spp.

Salmonella typhi and *S. paratyphi* were increased in some bile samples collected from patients with gall bladder cancer.

Colorectal cancer is one of the most studied regarding the microbial imbalance and molecular mechanisms of the disease.

Cohort studies demonstrated that samples collected from patients with colon cancer presented feces bacterial diversity with increased communities of pro-inflammatory species of *Fusobacterium* and *Porphyromonas* and a decreased presence of *Lactobacillus*, *Microbacterium*, *Anoxybacillus*, and *Akkermansia muciniphila*.

In colon cancer cases induced by a preexisting inflammatory colitis, microbiota played an important role in influencing inflammation or innate immunity, genomic stability of intestinal epithelial cells (IECs), or the release of some metabolites functioning as histone deacetylase

inhibitors. Studies performed in gnotobiotic or in antibiotic-treated mice revealed the implication of microbes in tumorigenesis driven or not by inflammation.

4. Microbiota and immune functions

In the last years, many scientific studies demonstrated that the commensal is an important participant to the host metabolism, inflammatory process, and immune response.

Nowadays, gut microbiota is particularly the most studied, and it has been proven to be essential for the development of the intestinal immune system, protecting the host against pathogens and harmful inflammatory processes. Germ-free animals have smaller Peyer's patches, fewer immune cells and impaired immunoglobulin A (IgA) secretion, fewer intraepithelial lymphocytes, as well as compromised production of antimicrobial peptides [28–30].

Gut microbiota is involved in the immune responses and inflammatory processes both local and systemic. The link between inflammation and cancer is well known raising the questions about the potential interference of microbiota. This area of research is new, and astonishing recent results revealed that microbiota is a key player in the immunomodulatory mechanisms of cancer and impact of the therapeutic responsiveness [31–35].

The present knowledge sustains that the presence and the quality of gut microbiota may induce inflammation and promote cancer or may induce tumor-destructive immune responses and favor anticancer treatment. Most studies involved experimental animal model of transplantable tumors, and only few data are sustained by clinical evidence.

The inflammation induced by microbiota may contribute to cancer by stimulating the release of cytokines involved in the cell proliferation and apoptosis inhibition pathways.

In a study regarding a hepatocellular carcinoma mouse model, the intestinal microbiota was essential for the promotion and initiation of cancer by signaling pathways involving toll-like receptor 4 (TLR4), a surface immune cell receptor, which senses the microbial molecular patterns. The activation of this receptor induced an increased level of a hepatomitogen, which mediates the proliferative and antiapoptotic effects in tumors [36].

The beneficial immunomodulatory effect in cancer regression is supported by the use of some microbial in anticancer therapy. The intravesical *bacillus Calmette-Guerin* (BCG) therapy is one of the standard methods of management of intermediate- and high-risk non-muscle invasive bladder cancer. Also, intratumoral inoculation of heat-killed *Propionibacterium acnes* in subcutaneous melanoma promotes local and systemic Th1 and Tc1 responses associated with tumor regression.

More other evidences are presented and discussed by the scientific literature about the key role of microbiota and the possibility to modulate it. However, the specific mechanisms are far to be elucidated due to the complex composition and the multifactorial interaction between gene and environment.

5. Microbiota and chemotherapy

The intestinal epithelium is a single-cell layer, which functions as the largest barrier of the human body. It is characterized by a selective permeability for the nutrients, electrolytes, and water and has an effective role in defense against toxins and enteric microbiota. Intestinal epithelial cells maintain the local environmental balance by facilitating the interaction between commensal and the host immune cells [37].

In order to obtain the best anticancer drug bioavailability, the formulation must consider besides the physicochemical properties or drug adjuvants, the permeability of the intestinal barrier.

Mucositis (mucosal barrier injury) is a major oncological problem caused by chemotherapeutic agents. Intestinal mucositis translates into a broad spectra of clinical symptoms (diarrhea, vomiting) and can be worsened by neutropenia and antibiotics. Since IECs do not regulate intestinal homeostasis by themselves, but require symbiotic coordination with commensal bacteria and local gut leukocytic cells, the role of intestinal microbiota in the development and severity of mucositis induced by chemotherapeutic products became an issue [38].

5.1. Cyclophosphamide (CTX)

Cyclophosphamide (CTX) is an alkylating agent commonly used in combination with other therapies to target cancer cells.

The importance of gut microbiota in efficacy of the treatment is sustained by studies involving germ-free (GF) mice and specific-pathogen-free (SPF) mice with transplantable MCA205 sarcomas. A significant decrease effect of the CTX treatment was obtained in case of GF animals in comparison with SPF mice [22].

Similar effects comparing to untreated control groups were obtained in case of the animal treatment with vancomycin A, an antibiotic that destroys the gram-positive bacteria. The results indicate that the presence of some bacteria creates an immunologic local environment essential for the therapeutic effect of CTX [39].

5.2. CpG oligodeoxynucleotides

The cytosine phosphodiester-linked guanine (CpG) oligodeoxynucleotides (CpG-ODN) are synthetic compounds with immunostimulatory effect used for enhancing the anticancer treatments. Preclinical and clinical study demonstrated a synergy between these drugs and monoclonal antibody and can be safely administrated together for a better therapeutic response [40–42].

The microbial DNA contains unmethylated cytosine phosphodiester-linked guanine (CpG) motifs which are recognized by specific immune receptors of the host-like human toll-like receptor 9 (TLR9) present on the surface of different immune cell types. Activation of these receptors enhances the expression of proinflammatory cytokines.

Researches on mouse models with transplantable tumors revealed that the intratumoral administration of the CpG-ODN and a monoclonal antibody (anti-interleukin-10 antibodies) induce hemorrhagic necrosis. This stimulatory immune response was mediated by tumor necrosis factor (TNF) and other inflammatory cytokines [40].

A study published in 2013 in *Science* using experimental model of tumor-infiltrating myeloid-derived cells on antibiotic-treated and GF mice remarkably revealed that the animals were refractory to therapy with CpG-ODN and anti-IL-10 antibody and presented low levels of TNF and cytokines required for promoting the hemorrhagic necrosis. A therapeutic response was obtained after the administration of lipopolysaccharides, a ligand for the TLR9 receptors-like. No response was obtained on TLR9-deficient mice [39].

Furthermore, study on the composition of mouse microbiota demonstrated that *Alistipes shahii* is positively correlated with TNF production in the tumor, whereas the abundance of *Lactobacillus fermentum* negatively correlated with it.

Thus, the research sustains the importance of the intact commensal microbiota for an optimal responses to cancer therapy required for the modulation myeloid-derived cell functions in the tumor microenvironment [22, 41].

5.3. Platinum salts

Platinum salts are coordination complexes of platinum used as chemotherapeutic drugs. Cisplatin and oxaliplatin interfere with DNA repair mechanism inducing intrastrand cross-link adducts activating the proapoptotic pathways. The platinum compound effect depends also by the presence of reactive oxygen species (ROS) for an apoptotic response and DNA damage.

Lida et al. presented evidence in the same study involving CpG-ODN that the therapeutic effect of the platinum salts on transplanted subcutaneous tumor depends on the presence of mice microbiota. The authors sustained that the ROS required for the genotoxic effect of these chemotherapies are produced in vivo by inflammatory cells associated to the tumor [41].

GF mice and antibiotic treatment attenuated the pharmacological effect and reduced the expression of ROS-responsive genes.

Moreover, using transgenic mice deficient for the myeloid NADPH oxidase NOX2 (*Cybb*_{-/-}) with a low ROS response, the effect of oxaliplatin was attenuated.

The study highlights the importance of commensal on an efficient therapy by its contribution to tumor reduction.

5.4. Immune checkpoint blockade therapy

The problem of the therapeutic response variability was the starting point of recent researches which deal with the importance of microbiota in case of the patients treated with monoclonal antibodies involved in the immune checkpoint blockade.

Ipilimumab is an immunoglobulin G1 targeting the cytotoxic T-lymphocyte-associated protein 4 (CTLA4), which is a receptor protein involved in the immune checkpoint system and downregulation of the immune response.

The efficacy of the CTLA4 blockade was associated with T-lymphocyte responses induced by *Bacteroides thetaiotaomicron* and *Bacteroides fragilis* in both experimental models and human. No tumoral response was noticed after the treatment with ipilimumab in case of antibiotic treatment and germ-free mice. Exposure to *B. fragilis*, its polysaccharides, or its specific T cells reversed the response and favored the anticancer effect. The author of the study concluded that some *Bacteroides* spp. may play an important role and that the colitis may even antagonize the therapeutic efficacy [42].

Anti-PD-L1 is a monoclonal antibody successfully used for the treatment of several solid tumors, which target the protein programmed death-ligand 1 (PD-L1).

PD-L1 is a transmembrane protein, which acts as suppressor of the immune system and plays a role in escaping the cancer cells to immune system.

Sivan et al. demonstrated in their study that the commensal *Bifidobacterium* may have an unexpected role in enhancing antitumor immunity in vivo [43].

The authors used for research an experimental model of subcutaneous B16.SIY melanoma growth in genetically similar C57BL/6 mice. The animals were provided by two different animal facilities. After the anti-PD-L1 treatment, the results differ according to the animal provider. The *Bifidobacterium* spp. were identified by sequencing of the 16S ribosomal RNA and were correlated with the antitumor response therapy. The oral administration of bacteria improved tumor control to the same degree as anti-PD-L1, and the association of the microorganisms with this drug nearly abolished tumor outgrowth [22–43].

6. Conclusions

Even though there are increasing evidences regarding the close relationship between tumor development, chemotherapy, microbiota, and the immune system, it is still difficult and speculative to consider the microbes when deciding the therapeutic strategy for patients. However, modulating microbiota may enhance drug efficacy or diminish chemotherapy's toxicity.

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