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Potential role of microbiota in oncology and palliative care

Abstract

Gut microbiota and intratumoural microbiota emerge as an important and, until now, completely ignored factor in treating cancer and cancer pain. Changes in gut microbiota can explain symptoms like the onset of cancer cachexia, inflammation, neuropathic pain and cancer pain. This knowledge offers perspectives of discovery of new therapeutic possibilities which may form a non-toxic complementary treatment of cancer with the potential of improving the quality of life of patients. This paper analyses current knowledge and future perspectives on this subject.

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Keywords: microbiota, gut bacteria, cancer pain, neuropathic pain, intratumoural bacteria

Introduction

The human organism is inhabited by more than 100 billion microorganisms (10^{14}). They form a specific ecosystem. Most are bacteria but there are also viruses, archeons, yeasts, one-cell eukaryotes and parasites [1, 2]. This means there are ten times more microorganisms than somatic cells in the human body [3, 4]. *Bacteroides* and *Firmicutes* account for more than 90% of gastrointestinal bacteria [5]. Analyses of the bacterial DNA revealed more than 1000 different species [6]. Most numerous and metabolically active are the gut bacteria called gut microbiota [4]. Among them most abundant are anaerobic bacteria. The microbiota composition is highly variable and depends on, among others, diet, drugs consumed by the host, and host genetics [7].

Since the first microscope saw them, it has been known that bacteria inhabit the human body. However, only recently have we learned how important they are in health and disease and that they interact bidirectionally with the host [8]. For example, microbiota influences the host's immune system, and in return, the immune system influences microbiota composition [9]. This interaction is the basis of the evolution of our adaptive immune system in the past millions of years.

This paper suggests the relevance of microbiota for the well-being of oncological and palliative care patients. How important is caring for the balanced and healthy microbiome for our patients?

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Investigating human microbiota

Most of the gut bacteria cannot be grown in cultures [10] and were inaccessible to scientists for decennia. One of the techniques is to infect sterile mice colons with those bacteria and investigate their influence on the rodents [11]. These experiments revealed invaluable data on such diseases as inflammatory bowel disease, diabetes, and cancer but also neurodevelopmental disorders like autism [11] and many others. However, these data should be viewed cautiously because of the difference between mice and human colon.

Until recently, those bacteria were called simply commensals, which meant a long-term biological interaction (symbiosis) in which members of one species (bacteria) gain benefits while those of the other species (human host) neither benefit nor are harmed [12]. However, this symbiotic definition evolved recently because of microbiota's physiological role and enormous benefits and threats to human beings.

This change was brought up by the development of low-cost, high-throughput sequencing of the bacterial genome (hence called the microbiome) has only recently given scientists the experimental tools to investigate the breadth of the ins and outs of the human microbiome [13]. It resulted in an explosion of interest in the human genome and provided us with a better understanding of the importance of the microbiome to human health and disease, including those (dying) with cancer.

Brain–gut-microbiome

Methods how to influence human microbiota

The oldest method to influence microbiota is the consumption of fermented food [14]. This technology has been known for thousands of years. To the food that should be fermented, salt is added, which kills all the bacteria and fungi except *Lactobacillus*, milk bacteria. These live bacteria which are beneficial to humans are called probiotics. Fermented food could be stored for a time, especially in the winter, without refrigerators. Most probiotics are from the genus *Lactobacillus* or *Bifidobacillus*. The number of probiotic bacteria in food needs to exceed 10^8 because most, but not all, are killed in contact with gastric juice [15]. Frustratingly, in the most commercially available probiotic preparations, there are not enough bacteria to influence the gut microbiome [16], or one needs to eat a lot of them continuously. Not unimportant for the health of our microbiota is that modern sales-driven food technologies usually kill bacteria and fungi after fermentation to prolong their shelf life [17]. In that way, we keep the taste and get rid of a few potentially harmful and pathogenic bacterial species but also lose contact with the sources of thousands of bacterial species, which are beneficial and essential to our health. Well-balanced microbiota prevent the growth of pathogenic bacteria and thus prevent infection [2].

Together with live bacteria, consumed food can be enriched with prebiotics. These are unique molecules needed for the growth of bacteria in the colon but not necessarily needed or even absorbed by humans. For example, oligosaccharides excreted in human milk are not digested or absorbed by newborn babies but serve as food for the growth of the (beneficial) bacteria [18]. Many vegetables contain inulin, a non-digestible and non-absorbable polysaccharide known as dietary fibre or fructan. It has a potent prebiotic effect, and gut bacteria ferment it, producing considerable gasses [19, 20]. This is the reason why some vegetables like Jerusalem artichoke are disliked by some people.

Once scientists could investigate gut microbiome, they started to manipulate it and observe the metabolic consequences for the host. The oldest way to manipulate the microbiome is the use of antibiotics [21]. Furthermore, to our horror, we noticed that a straightforward course of antibiotics causes changes in the microbiome that are still visible after two years [21]. Antibiotics in humans are rarely selective and are not suitable for the investigation of positive results of their use. However, in mice, antibiotics can change the microbiome so that they experience less neuropathic pain (see further) [22]. It is thus theoretically possible to produce specific and narrow-spectrum antibiotics that will not harm the host but decrease pain sensations.

Another tool to investigate the effects of genome manipulation is faecal transplantation. Specially prepared bacteria isolated from healthy donors' faeces can be administered as odourless suspension by the naso-duodenal tube [23] or directly to the colon through rectal applications [24]. Patients with abundant growth of *Clostridium difficile* bacteria after the use of antibiotics benefited from faecal transplantation from healthy donors [23, 24].

The gut–brain axis

Once better tools to investigate microbiomes became available, it was evident that bacteria exercise a profound effect on many, if not all (some may remain unknown) physiological processes in the human body. This interaction was called the gut–brain axis (GBA) [25, 26]. There are three angles of this system. The first is the microbiome and microbiome-derived neuroactive molecules directly affecting the brain [26]. The

brain (second angle) responds through the autonomic nervous system. Furthermore, gut-derived molecules of neuronal, immune and endocrine character still affect the brain. The gut microbiome and the brain communicate with gut cells (the third angle), including endocrine cells [25, 26]. Some molecules are released into the circulation and act as hormones at a distance; some interact with peripheral and central receptors in the brain [25]. All communication is bidirectional. Dysbiosis leads to the appearance of proinflammatory cells (*i.e.*, lymphocytes Th1, Th17). Probiotics, by lowering the concentration of proinflammatory cytokines (*i.e.* IL-1b, IL-2, IL-6, IL-12, IFN-γ and TNF-α) and increasing the concentration of anti-inflammatory cytokines such as IL-10 or TGF-β, can inhibit systemic inflammatory responses [27]. Until recently, we knew only fragments of this system. The puzzle is almost complete.

Systemic inflammation and the role of intestinal epithelial integrity

The mucosal barrier consists mainly of intestinal epithelium separating the inner and outside world. It spatially segregates gut microbiota and the host's innate immune system, preventing the host's immune reaction toward nonspecific bacteria in the gut and dietary antigens. The epithelial surfaces consist of a columnar epithelium covered with mucus containing secretory IgA globulins and polymeric immunoglobulin receptors (pIgR) [28]. The gastrointestinal tract and the gut-associated lymphoid tissue (GALT) are constantly challenged by the antigens and bacteria trying to pass the barrier and invade the host. The barrier cannot be impermeable as food intake, digestion, absorption of food-derived nutrients, exchange of water and electrolytes, and endocrine and paracrine hormone production are vital to the host. It must rapidly discriminate between "friend and foe", for example, invasive pathogens, harmless food antigens, and gut bacteria. Entero-invasive pathogens evoke rapid immune responses associated frequently with diarrhoea and rapid clearance of pathogens [29]. In the course of maturation in childhood, the GI system develops tolerance to normal or healthy gut microbiota [30]. A sophisticated network of receptors serves, among them pattern recognition receptors (PRR) and toll-like receptors (TLRs), of which many different types exist [31, 32]. Sensing and differentiation between commensal and pathogenic bacteria and harmful antigens is critical to the integrity of the protective barrier but also for signalling, which subsequently will lead to the stimulation of a defensive immune response [31, 33]. The cross-talk between this system's elements is essential [34]. All of this needs energy, and processes that limit the energy to the system, like injury or inflammation, or processes associated with cachexia and undernutrition, may disrupt this barrier and, in this way, initiate disease [34]. Many of these diseases begin with chronic inflammation of the intestinal barrier and migration of bacteria and their antigens through the barrier to blood. In health, microbiota and products synthesized by the Paneth cells control the growth of bacteria in the intestinal lumen [34]. Disrupted and low mucosal barrier will be permeable to the pathogen.

The role of microbiota in undernourished and cachectic patients

Cancer cachexia is a syndrome of progressive weight loss, loss of appetite, weakness and muscle wasting and inability to synthesize new proteins [35]. This syndrome is responsible for many failures in oncology and is not amenable to simply providing more calories in the consumed food [36]. Dysbiosis has been shown to influence cancer cachexia, among others, through reduced integrity of the gut epithelial barrier and induction of systemic inflammation [34].

This systemic inflammation probably responds to systemic non-steroid anti-inflammatory drugs (NSAIDs) like ibuprofen. In a systematic review of thirteen studies, all but two showed either improvement or stabilization in weight or lean body mass after treatment with NSAIDs [37]. Above was the rationale for designing a new study where NSAIDS were incorporated into a total treatment program for cancer cachexia [38]. The results of this study are not yet available.

Cancer cachexia has been associated with decreased levels of *Lactobacilli* and increased levels of *Enterobacteriaceae* and *Parabacteroides*. Theoretically, it is possible to manipulate the microbiota. Different routes and treatments have been investigated in laboratory animals. Faecal microbiota transplant appeared to be promising in the treatment of cancer cachexia [39]. It will take time before we shall see controlled human studies.

Microbiota and cancer pain

Cancer patients often struggle with chronic pain [40], the severity of which most probably also depends on the condition of the intestinal microbiota [2, 39]. Pain in cancer is closely related to inflammation [41]. In one study analysing retrospective data from two clinical trials, there was a statistically significant correlation between cancer pain reported by the patients and the CRP [42]. Corticosteroids are anti-inflammatory in cancer pain but also have detrimental adverse effects

[43]. On the other hand, inflammatory pain can alter the intestinal microbiota, and this results in disturbances in the metabolism of amino acids by intestinal microorganisms [44]. This influence is bidirectional, as pain causes changes in the microbiota, but changes in the composition of the microbiota cause an increase in the perception of pain [44]. Also, morphine, most often used to control pain, may change the microbiota and make the host more vulnerable to pain (see further) [45]. The alteration of gut microbiota is related to disruption of the intestinal barrier and systemic inflammatory response that is generally complemented by the release of proinflammatory mediators by immune and glial cells. Pathogen-associated molecular patterns (PAMPs) derived from gut microbiota [46], as well as pattern recognition receptors (PRRs) and toll-like receptors (TLRs), play a key role in this process [47, 48].

In laboratory animals, nonspecific commensal bacterial flora appears to increase pain perception in inflammatory conditions, and microbial-free mice had reduced nociception compared to mice with unchanged microbiota [49].

If these data, primarily obtained in laboratory animals, will be confirmed in humans with cancer, this may open new avenues for the complementary treatment of pain. Moreover, recognized complementary therapies for pain may work in that way.

Changes in the microbiota after chemotherapy

Until now, chemotherapy was rarely related to pain. We knew that chemotherapy could induce damage to the intestinal epithelium, which often results in transient diarrhoea in as much as 10% of the chemotherapy-treated patients [50]. Some light on this subject was shed by experiments in mice by Wardill et al. [51]. They hypothesized that the TLR4 receptors in the gastrointestinal tract, known to be involved in innate immune signalling, are involved in gastrointestinal toxicity and induction of hyperalgesia. In this experiment, gastrointestinal toxicity of a single dose of irinotecan was compared between TLR4-deleted and wild-type mice. The TLR4-deleted animals suffered much less diarrhoea and weight loss. This notion was confirmed by much less mucositis, gut permeability, and inflammatory markers in TLR4 deficient mice. Interestingly these mice showed less pain-like behaviour supported by less induction of glial activation in the lumbar spinal cord. TLR4 could be a unique factor for irinotecan-induced gut toxicity and pain [51]. Similarly, gut microbiota promotes the development of oxaliplatin-induced mechanical hyperalgesia (OIMH) [52]. OIMH was significantly reduced in germ-free and antibiotic-pretreated mice. Restoration of microbiota revoked this process. This effect strongly relates to the TLR4 expression on the gastrointestinal tract macrophages. Lipopolysaccharides (LPS), known to induce neuroinflammation when administered to mice, abrogated this protective effect [53]. A mutation of the LPS binding site on TLR4 protected mice from allodynia and chemotherapy-induced nerve damage [53]. Procedures blocking TLR4 have shown pronounced effects on pain behaviour in models of chronic inflammation and nerve injury [54].

Microbiota, morphine tolerance and metabolism

Morphine is the most commonly prescribed analgesic to cancer patients. After administration, morphine is metabolized in the gut and liver to morphine-3-glucuronide (M3G) and morphine-6-glucuronides (M6G) in the proportion of 9:1 (for the recent review. Please read [55]). M6G binds to the opioid receptor [56] and exercises a more potent analgesic effect than morphine [57]. M3G does not bind to opioid receptors but interacts with TLR4 and is probably responsible for opioid-induced hyperalgesia [55]. Both glucuronides are excreted with bile in the gut, where microbiota reconvert them to morphine, which is reabsorbed into the circulation and provides analgesia [58]. This process is responsible for the prolongation of morphine analgesic activity.

It was shown in a murine model that immediately after morphine administration, the drug induces gut microbial dysbiosis, including a significant increase in pathogenic bacterial species. A decrease in communities associated with stress tolerance and impairment in bile acids metabolism and M3G to morphine de-glucuronidation in the gut is observed [45]. Morphine induces the growth of *Enterococcus faecalis*, and this bacterium was a marker of augmented tolerance to morphine [45]. Treatment with morphine also induced gut inflammation, increased gut permeability and bacterial translocation into circulation [45, 59]. Tolerance development was attenuated by the treatment with antibiotics or in germ-free mice, and probiotics reversed this process [60]. Dysbiosis in humans is associated with pain in different diseases [59]. In summary, the long-term effects of morphine on the gut microbiota are analgesia-unfriendly and are responsible for more inflammation, tolerance and hyperalgesia. Most of these phenomena are described in murine models, but some human observations suggest they are also valid in the clinic. Some indirect observations were made when probiotics were administered directly after chemotherapy. Restoration of the gut microbiota through

probiotics could prevent or reverse the psycho-physiological deficits often found in young survivors following chemotherapy, ultimately leading to reduced symptom burden and improved health [61].

Microbiota and neuropathic pain

Damage to the neural system may provoke neuropathic pain, which may be experienced until the end of the patient's life. This damage can be done by chemotherapy, which damages fine skin fibres and the repair mechanisms of the nerves. Dysbiosis may disturb adaptive microbiota responses, directly promoting sensory neuron regeneration [62]. Neuropathic pain emerging after chemotherapy may be related to the release of inflammatory cytokines and oxidative stress [63].

It is confirmed that in the experimental nerve constriction injury in rodents, *Clostridiales* become more abundant, while other producing butyrates like *Escherichia*, *Corynebacterium*, *Ignatzschineria* and *Butyricimonas* become sparser [64]. The paklitaxel-induced neuropathic pain is caused by the changes in microbiota, especially by the decrease of *Akkermansia mucinophilia*, which correlates with inflammatory diseases [65].

Faecal transplantation from patients with severe postoperative pain to germ-free mice induced pain-related behaviour suggesting neuropathic pain [66]. Faecal transplantation from patients with mild or absent postoperative pain to germ-free mice did not cause this reaction [66]. So, this suggests that the microbiota mediates the sensation of neuropathic pain by modulation of pro- and anti-inflammatory lymphocytes. Feeding mice for 14 days with sodium butyrate, the most crucial metabolite of *Lactobacillus* bacteria, significantly decreased pain behaviour and levels of TNF-α in a nerve constriction model [67].

Potential role of intratumoural bacteria in the origin of pain

Intratumoural bacteria are still *Terra incognita* in pain research. We know that bacteria are there, and each type of tumour has a distinct bacterial population [68]. We also know that they influence the results of cancer therapy, and we know that a low dose of radiotherapy, which may sterilize tumours, is beneficial in case of pain caused by bone metastasis [69]. At the moment one can only speculate that intratumoural microbiota is important in the onset and experience of cancer pain too [70].

Conclusions

New research tools enabling gene sequencing of large populations of bacteria, wherever they are, opened a new area of research. And they immediately showed how important and, until now, completely ignored gut bacteria are. They participate in many, if not all, physiological processes of the body and are essential factors in the experience of health and disease. Currently, most of the data is obtained from experimental animals, but clinical data is slowly emerging. It also looks that gut microbiota and possibly intratumoural bacteria are essential for the experience and treatment of cancer pain. Modern methods of influencing gut microbiota, in addition to the diet of probiotics and prebiotics, as well as by manipulation of the gut microbiota by antibiotics and faecal transplantation, promise soon breakthrough in the treatment of pain and possibly other symptoms in cancer. These methods may help to treat cancer cachexia and overcome tolerance to morphine and the development of neuropathic pain after chemotherapy. The complementary or alternative methods used in oncology and palliative care may exert their effect through modification of gut microbiota.

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KP (a medical student) — analysed a large number of articles on the subject and wrote a first draft of the article. ZŻ — after reviewing the draft, edited it and, in consultation with the first author, produced the final text.

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