REVIEW ARTICLE

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Gut microbiota – new insight in colorectal cancer pathogenesis

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Abstract: *Gut microbiota is a superorganism involved in homeostasis and in pathogenesis. Microbiota composition is influenced by several factors such as: type of birth (cesarean or natural), role of age, role of diet. Pathological consequences of certain type of diet (especially western type of diet) may, in fact, be mediated by gut microbiota alteration. Also few studies have investigated the issue of gut microbiota composition in patients suffering of colorectal cancer, several reports notice relevant differences. Certain pathogenic bacteria in gut microbiota have been extensively studied in relation to their role in colorectal cancer. Thus, Fusobacterium nucleatum, which is abundant in colorectal cancer patient's colon, may initiate the progression from adenoma to adenocarcinoma. A suggested pattern of oncogenesis in colorectal cancer may be represented by this: dysbiosis-inflammation-oncogenesis. A metanalysis that has been published in 2006 concluded a protective role of probiotics in colorectal cancer and in colonic adenoma.*

Keywords: *colorectal cancer, gut microbiota, probiotics*

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Human gut harbors a complex and abundant microbial community which is symbiotically linked with host organism and plays a major role in maintaining the homeostasis by the way of fulfilling various functions such as: limiting the number of intraluminal pathogens, functionnal optimization of immunity system, and important contribution to maintaining energy balance.

It is estimated that there are around 1,014 microorganisms in the colon (mostly bacteria) which is 10 fold above the number of eukaryote cell of human body and that contains a 100 fold richer genome than human genome [1]. As a matter of fact we may acknowledge the existence of a true superorganism whose implications in physiology and pathology of human body are continuously revealed by a great pool of scientific data.

Microbiota composition is influenced by several factors such as: type of birth (cesarean or natural), role of age, role of diet.

Pathological consequences of certain type of diet (especially western type of diet) may, in fact, be mediated by gut microbiota changing [2].

It has been noticed that there are significant differrences between European children that eat a western diet and African children that eat rural diet rich in vegetal fibers and poor in meat, as concerning the

composition of gut microbiota.

Firmicutes genera is prevalent in European children and Bacteroidetes genera is depleted as opposed to African children in whom the ratio is reversed [3]. The real significance of those changes is to be better defined in the near future. Medical literature is abundant in information on this topic, especially about the composition of microbiota in various pathological situations, but the studies published are mostly animal studies and the implications in understanding of pathological mechanisms and in medical practice are ill defined.

The role of gut microbiota played in certain inflammatory ailments (such as inflammatory bowel diseases – IBD) is well known [1]. Important practical consequences may be derived from these data: stool transplant and probiotics treatment [4]. Chronic local inflammation is a risk factor for colorectal cancer (CRC). As a matter of fact patients suffering from IBD have a yearly risk of CRC of 1% after 10 years from the onset of inflammatory disease [4]. It is an answered question as to what extent the composition of gut microbiota is implicated in CRC susceptibility.

Also a few studies have investigated the issue of gut microbiota composition in patients suffering of CRC [1], several reports notice relevant differences. For instance, a study indicated an increased prevalence of Bacteroidetes and Prevotella genera than in general population [5]. Another study which investigated bacterial populations on the surface of colonic mucosa as opposed to luminal bacteria showed that there was an abundance of Faecalibacterium and Dorea species in patients suffering of adenomatous colonic polyps as opposed to those without polyps [6].

Certain pathogenic bacteria in gut microbiota have been extensively studied in relation to their role in CRC. Thus, Fusobacterium nucleatum, which is abundant in CRC patients' colon, may initiate the progression from adenoma to adenocarcinoma [7]. Rubinstein showed that the species of Fusobacterium which produced the virulence factor FadA stimulated epithelial cell proliferation, promoted inflammation and initiated oncogenesis [8]. Similar studies have been published about other components of gut microbiota such as: E. Coli, B. fragilis, S. Gallolyticus (former S. bovis particularly associated with CRC) [8,9,10,11]

Also it is obvious that there is a change in CRC patients gut microbiota composition, it is not clear if those changes are already present before the diagnosis of CRC suggesting a role of risk factor or those changes reflect the consequences of the disease.

From another point of view, the CRC risk factors modify gut microbiota and may elicit the oncogenic process by this route. Several studies have indicated that a meat diet, by the way of microbiota composition alteration, may play an important role in oncogenesis [12,13].

Obesity is a major risk factor in CRC. Many studies showed a certain pattern of gut microbiota change in obese subjects, in animal as well as in human studies [14,15]. Gut bacteria have an impact on peripheral resistance to insulin, systemic inflammatory status and on systemic adiposity by the way of interaction with intestinal epithelial cells. Those interactions are very complex and mutually beneficial. Thus, gut bacteria metabolize various nutrients such as digest-resistant carbohydrates which results in production of short chain fatty acids (mainly butyrate). Gut epithelial cells uses as a main source of energy those fatty acids. Moreover, butyrate may be involved in anti-oncologic effects [16]. Backend noticed, in a mice study, that germ-free subjects experienced a 60% increase in adiposity and a significant increase in peripheral resistance to insulin after 14 days from stool transplant performed from lean mice, in spite of a restrictive diet. Stool transplant from obese mice elicits an even greater increase in total fat mass, which may render a reasonable demonstration about the role played by microbiota in obesity and this may further suggest a role in colonic oncogenesis [15].

A suggested pattern of oncogenesis in CRC may be represented by this: dysbiosis – inflammation – oncogenesis. Alteration of gut microbiota (dysbiosis), as a response to an unidentified trigger, has been studied in animal experimental models with regard to collective or individual role of bacteria in development of inflammation and CRC [17]. The pathogenic

mechanism is still unclear but we may appreciate an involvement of certain receptors of innate immune system responsible for microbial detection [18].

Indirect data on the topic of gut microbiota in CRC are derived from the acknowledged protective role of probiotics. The term of probiotics has been used for several decades but World Health Organization has issued a definition only in 2001: „ live microorganisms that render health benefits when they are administered in proper doses" [19]. Lactic bacteria and Bifidobacteria are among the most known types of probiotics. A metanalysis that has been published in 2006 concluded a protective role of probiotics in CRC and in colonic adenoma [20]. The authors of this metanalysis suggested a cautious use of these data as the interventional type of studies were still not enough to render an unequivoque positive answer.

Recently, Faecalibacterium prausnitzii, a commensal bacterium in gut microbiota that has anti-inflammatory properties, has also been indicated as a probiotic to decrease the risk of CRC [21].

Mechanisms engaged by probiotics in the process of oncogenesis are multiple: cell cycle influences, oxygen reactive species, apoptosis, specific bacterial enzymes, influences on human host metabolome [1]. Probiotics have an important contribution to the development of mucosal associated immune system as it modulates unspecific inflammatory response and it dampens down mucosal inflammation. Probiotics exert also certain effects on dendritic cell, colonic epithelial cells, lamina propria T cells, thus having an impact on adaptive immune system. Perdigon noticed in a mice study, that joghurt (rich in lactic bacteria) hampered the growth of colonic tumors which had been previously induced by mice exposure to 1,2 dimetilhidralazine [22]. Urbanska reached a similar conclusion in another mice study. He showed that yoghurt might reduce the volume of the tumor. Induction of apoptosis may be credited as a major mechanism that mediates the beneficial effects of probiotics against oncogenesis of colonic tumors. Hence, the induction of apoptosis could be seen as a phenomenon of oncologic screening [23].

In spite of all these experimental data from animal models that indicate the fact that probiotics have the potential to stop the development of CRC, systematic studies to show the same benefits in humans are very limited. In a human study about the prophylactic effect of Lactobacillus casei in CRC the conclusion was that two years of continuous administration significantly reduced the incidence of CRC as compared to control group [24]. Recently, in a cohort study that included 45000 subjects over a period of 12 years it has been noticed that large daily amounts of yoghurt reduced the incidence of CRC, suggesting a major prophylactic benefit from long term administration of joghurt [25,26]. Future clinical studies should consider, also, the standardization of probiotics composition, as well as the control of diet, time and frequency of probiotics administration. They should identify the proper biomarkers that may allow monitor of long term effects.

In conclusion, a large and significant pool of data indicates a major role of gut microbiota in CRC oncogenesis as well as in CRC prophylaxis. The majority of studies are, still, animal studies. Those and the few human studies are, never the less, highly suggestive. Unfortunately, we do not know the definition of „normal" composition of gut microbiota, yet. The mechanisms that link dysbiosis and CRC are complex and are related to local and systemic chronic inflammation. Some of the modifiable risk factors in CRC (obesity, diabetes mellitus, and western type of diet) may act, also, through alteration of gut microbiota. The prophylactic role of probiotics may render a powerful mean to significantly reduce the incidence of CRC in the future.

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