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How Knowledge on Microbiota may be Helpful to Establish an Optimal Diet for Health Maintenance

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Abstract

In the last few years, gut microbiota has been identified to be an essential mediator in health and disease. In fact, it interacts with various organs and systems in the body, including brain, lung, liver, bone, cardiovascular system, and others. Microbiota-derived metabolites such as the short chain fatty acid (SCFA) butyrate are primary signals, which link the gut microbiota and physiology. Then, the findings on the roles of microbiota profoundly change not only the key concepts of biology and medicine, but also of nutrition. In fact, it is currently evident how the main task of nutrition is not to nourish us, but to maintain a comfortable environment for the intestinal microbiota. In this way, it works in symbiosis with us, correctly controlling the functioning of the organs, the physiological parameters and the cellular regenerative processes. It is also evident that the strength of reparative processes correlates with the ability of digestive system to process complex foods, which increases during weaning, a period of time in which the diversity of bacterial strains increases. Therefore, a task of food is to keep trained the digestive system, to which it corresponds an high microbiota diversity. Elderly leads to reduced microbiota diversity to which corresponds an intestinal frailty, responsible for the frailty of the elderly. In conclusion, a correct diet may not only keep us in good health but may also guarantee us longer longevity.

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Introduction

On the basis of recent acquisitions, the human body consists of two entities: one cellular, the other microbial. The last is numerically ten times the first and give us 4 million of genic units versus the 24,000 from our cells. The microbial body contains countless anaerobic bacterial strains living in the anaerobic lumen space. Surprisingly, each of us can be better identified through our gut microbes's DNA than the one from our own cells. This bacterial genome is able to compensate our genetic damage, repair our DNA and modify our genetic expression.

There is still a lot to discloser on this microbial body, of which, recently, a large new branch has been discovered, composed by symbiont extremophile bacteria: many of their roles in physiological functions are known, i.e. blood pressure, plasma levels of cholesterol, metabolism and in their control of kidney, heart, neuroendocrine system and brain functions. Nowadays over 4500 articles support the role of microbioma as moderator in health and diseases, [1,2,3] and an altered gut microbiota composition, dysbiosis, has been reported in several neurological, neurodegenerative and neurobehavioral diseases as Parkinson's, Alzheimer's, epilepsy, and autism. [4,5,6] Studies comparing germ-free animals and animals exposed to pathogenic bacterial infections, probiotics or antibiotics suggest the participation of the microbiota in the pathogenesis of such diseases, a pivotal role in host defense, regulation of immunity and the development of autoimmune disease. Accordingly, once inoculated into germ-free mice in experimental models of Parkinson's disease, the microbiota of Parkinson's patients worsened the outcomes. Again, different intestinal dysbiosis, producing different chronic inflammatory responses, can lead to different neurological disease, i.e. Parkinson's or Alzheimer's. [7]

The gastrointestinal tract could represent a vulnerable area through which pathogens may influence all aspects of physiology, even inducing central nervous system neuroinflammation. The transitory clinical outcomes reported by fecal transplantation on epilepsy, movement disorders and autism confirm the importance of restoring a good microbiota in these conditions. [8] Furthermore, they suggest how a stable change in microbiota may produce stable clinical outcome. A stable modification of microbiota may be obtained acting on the intestinal environment, as reported on ketogenic diet, a rich in fats and poor in carbohydrates diet. [9] Its ability to produce a stable modification of microbiota, and not the production of ketosis, [10] may be responsible of its anticonvulsive effect, lasting years after its administration for only few months.

The Role of Taste Receptors

The discovery of taste receptors (TRs) not only on the tongue but also in all digestive system, makes us understand how the main task of the digestive system is to protect the intestinal ecosystem, not only to nourish us. In fact, TRs recognises and memorise the food to produce anticipatory response aimed to demolish potentially aggressive one. This concept completely changes our approach to nutrition.

TRs recognize six basic tastes: salty, sweet, bitter, sour, umami and fats. Sweet, salty and umami taste receptors trigger frenetic brain activity that profoundly affects moods, emotions and memories (emotional regions of the brain]. In addition, responding to specific taste, they regulate the production of ghrelin and insulin, resulting in control of appetite and satiety. Bitter taste receptors represent a powerful safeguard against the consumption of potentially dangerous foods. TRs are part of interoception system where the signals for foods and sex are very strong, since they are key to ensuring the survival of the species. For these reasons the food dependence may be very strong, like a drug addiction.

Microbiota influences host-eating behaviour and food preference by altering TRs expression or transduction. Germ-free mice have altered TRs for fat on tongues and on intestine, [11] and preferred more sweets, having higher amount of sweet TRs in gut than wild mice. [12]

All in all, microbiota imposes the host to eat the food it likes, sometimes at the expense of host fitness, [13] i.e. Prevotella likes diets rich in carbohydrates, Bifidobacteria rich in fibers. [14] In this way, a dysbiosis may strongly affect the food preferences. A gastric bypass surgery modifies TR, too,

changes microbiota and alters satiety and food preferences. [15]

Microbiota controls metabolic processes, too. Metabolic phenotypes link to specific dietary preferences, i.e. urinary chocolate metabolites are different in indifferent or in desiring chocolate. [16] An intestinal dysbiosis modifies essential amino acid metabolism, for example that of tryptophan and tyrosine, which are the precursors of important brain neurotransmitters, such as serotonin, dopamine, noradrenaline, and adrenaline, [17] thus resulting in an imbalance of brain functions.

Microbiota Development

At birth, there is only a small sample of strains acquired during prenatal life. However, soon after (within the first 1000 days of life), the newborn arrives to have a microbiota like the mother had at the moment of conception. After birth, microbiota grows and the strains diversity increases. The Firmicutes/Bacteroidetes ratio increases until adults, then return to decrease in the elderly. [18] The frailty in older people, defined as poor resolution of homeostasis following a stress, is reported to be linked to a frail gut, that is characterised by a low-grade chronic mucosal inflammation, impaired immune response, increased permeability, and reduced microbiota diversity. Reduced microbiota diversity carry out to chronic inflammation: a type of inflammation unable to repair tissues continually damaged by stressor. In fact, our health depends from the reliability of inflammatory processes to repair our tissues and regenerate them following a programmed dead: apoptosis. Two types of cytokines carry out these processes: the pro-inflammatory that produce necrosis, and the anti-inflammatory, that rebuild tissues. In chronic inflammation different anti-inflammatory cytokines are produced, unable to rebuild.

At the brain level, chronic inflammation impairs the synaptogenesis and neurogenesis, tools of neuroplasticity, through which a not chronic inflammation repair neuronal circuits. Chronic inflammation in the brain has been reported to be the common pathogenic cause of different neurological [19, 20] and behavioural conditions.[21] In autism-like behaviours this inflammation has been reported to produce neuroanatomical damages. [22] Chronic inflammation damages all organs: in sexual organs causes sexual pathological conditions, [23, 24] and allow the development of amyloid [25] or atherosclerotic plaques, [26] as well as tumours. [27] Moreover, cytokines are involved in apoptosis cellular dead, and in neurodevelopment, too. The inappropriate cytokines, produced in chronic inflammation, may produce different symptoms. In fact, chronic inflammation has been defined "the mother of disease". [28]

As the frailty in elder, also the first 1000 days of life of newborns is reported to be a high vulnerability period of time, and also this period of time is characterized by a reduced microbiota diversity. Then, there is a high risk to fall in chronic inflammation. Mainly during weaning, digestive system learns to processes complex foods, in gradual and progressive way. It learns to recognize and memorize foods to produce adequate response and make it harmless. It is equivalent to bring the digestive system to the gym: training has to be gradual and progressive. Microbiota has to be perturbed by stressful agents, but the strength of stress must be comparable with the force of microbiota. If properly carried on, these perturbations increase microbiota diversity; increase its strength to process food and to orchestrate corrected inflammatory processes. The food must be considered the best coach of the gut, and only a strong digestive system allows a confortable environmental to microbiota, allowing the microbiota to literary takes care of us. In fact, our health doesn't depend on the health of our cells but to the force of reparative processes carry out by our bacteria.

Human colostrum contains a high quantity of alpha-lactalbumin (ALAC). At birth, the gut is completely immature and ALAC starts the postnatal maturation program, which occurs mostly during weaning, but lasts up to 7 years, enhancing all the functions of the gut, included the pivotal function of self-repair. Weaning mimics evolution, starting from simple to more complex food intake, and has to be gradual and progressive to allow the digestive system to gain its maximum strength, in terms of both complex food processing and reparative processes. Once obtained, this strength has

to be maintained by training the intestine with a varied diet. Weaning increases the tolerance of the intestine for complex food. This concept highlights the misguided perception that long-term deprivation diets are beneficial for health, since, with such diets, the stimulant function of food exposure is lost or impaired . [29].

Strategies for the modulation of gut microbiota are therefore expected to give a relevant contribution in the management of disorders associated with its impairment.

The 'Optimal' Diet

There is no doubt that the diet is the easier and powerful way to act on intestinal ecosystem, confirming how the food may be considered a medicine. Through food, communication with the microbiota is possible. The recent acquisition on microbiota put in evidence that the main function of the diet is not to nourish our body, but to communicate with and modulate bacterial populations hosted in the human gut. Previous studies clearly show how food consumption is directly responsible for microbial strains density perturbation. [30]

Through diet, a comfortable environment to intestinal ecosystem can be maintained, which avoid bacteria to close themselves into spore, allowing for high biodiversity degree among microbial populations.

Considering that low microbial diversity corresponds to low grade chronic inflammation, in our opinion, an optimal diet has to keep the intestine as able as possible to produce a high-grade inflammatory response when exposed to complex food, as reported by ref.7. Under normal physiological conditions, however, the intestine has to be able to return to a very low-grade inflammatory state in a relatively short time. A weakened intestine is unable to do this, and remains in a permanent, intermediate-grade inflammatory state.

If weak in its digestive function, food allergies and intolerances may arise, which, we suggest, should be considered warning signs for a decreased ability in reparative processes. Eliminating or reducing these foods reduces the symptoms, without triggering the physiological healing capacity of the body. The increased incidence of food intolerances shows a continuous trend of intestinal weakening, which is in part due to a sub optimal diet. [31] Prolonged deprivation diets can also have helpful or dangerous implications for our health. Other than training the digestive system, a correct diet has to nourish its cells. Among all the enteric metabolic processes, SCFAs synthesis, through fibers fermentation by bacteria, is pivotal considering their specific nutritive function on digestive tract cells. These intestinal cells are mostly fed by short chain fatty acids (SCFAs), which, other than being nutrients, are reported to have specific anti-inflammatory properties, being histone de-acetylase inhibitors. [32] In fact, a class of nonsteroidal anti-inflammatory drugs, synthesized from acetic and propionic acids, probably has a double anti-inflammatory effect, through the inhibition of both cyclooxygenase and histone de-acetylase. [33]

In the human gut, SCFAs may be obtained by bacteria fermentation of fibres in the colon, as in frugivorous, or directly by demolition of fats, as in carnivorous. In fact, along evolutionary ages, humans shorten intestine, allowing more energy available to the brain, but mainly shortened colon, decreasing it from 60% of the length of digestive system to actual 15%, only a 5% more than those of carnivorous. This was possible since human learned to obtain SCFAs from saturated fats, as it is in the predators' diet. It is necessary to distinguish between different molecules of fats, the unsaturated, the saturated and the short chain ones: they have very diverse health impact. In a correct diet, saturated fats have to be introduced and/or, at least, butter, as source of butyric acid, the most nutritive of gut cells among SCFAs. Based on these data, it might be that the recent 'war' against fats, mistakenly promoted to avoid an increase in blood cholesterol, has decreased the capacity to keep gut cells well fed. Despite substantial evidence that high cholesterol is not necessarily a cardiovascular risk factor, the war against fats goes on. Such evidence includes a recent meta-analysis of 69,000 patients, which demonstrates an inverse correlation between cholesterol levels and the incidence of cardiovascular diseases. [34]

A corrected diet introduces complex food to stimulate and maintain an active digestive system, which had developed in an 'omnivorous direction'. Diets lacking in complex food weaken the intestine and, as a consequence, the self-reparative processes it controls.

Mimicking its original function, in adults, supplementation of ALAC is useful in reinforcing the intestine and decreasing chronic inflammatory conditions. A highly inflamed intestine may need a short period of rest (i.e. decreased complex food intake), to allow ALAC to work in an environment similar to that found at birth, and to allow recovery prior to repetition of the 'weaning process', when food must be gradually re-introduced following a progressive degree of complexity. As for fats, we have to distinguish among proteins and carbohydrates on the basis of their complexity to be digested. No food have to be avoided or excluded, but its complexity has to be evaluated as the weights of a barbell in a training table.

Consistent decrease in number of epileptic seizure have been reported following ALAC supplementation in epilepsy, both in experimental models [35, 36] and in clinical studies. [37, 38, 39] In the treatment of migraine, preliminary results show a positive correlation between the ability of ALAC to decrease intestinal inflammation and a decrease in the number of headache attacks. [40] However, an accompanying diet protocol, mimicking the nursing and weaning time period, may be very helpful in optimizing clinical outcomes (as demonstrated in preliminary trials). During the 'nursing period' (at least 30–40 days), complex foods must be avoided. The diet should only include fruits, or fruits and large-leaf vegetables with a lot of butter, olive oil and vinegar, to nourish the digestive system well and decrease inflammation. Later on, other more complex vegetables can be included, and then carbohydrates, starting with low glycemic index carbohydrates and gradually introducing higher glycemic index carbohydrates. Subsequently, meat protein can be introduced, starting with fish, then white meat, and finally red meat (preferably fatty meat, as eaten by carnivores). In this way, this protocol is able to reinforce the digestive system and its reparative processes. Also, longevity studies show that a correct diet is able to increase the duration of 'good health', by strengthening the healing processes that decrease with aging as the intestine becomes increasingly worn. [41] Being a chronic inflammation due to decreased microbiota diversity, only a diet able to keep high microbiota diversity guarantees us the longevity. A similar protocol has been reported to be able to decrease autoimmunity and to improve multiple sclerosis symptoms. [42]

Conclusion

The intestinal microbiota has important functions in health and disease and research in this area is a frontier in medicine. Microbial colonization runs in parallel with immune system maturation and transforms at every life stage (weaning, growing, ageing), playing a role in intestinal physiology and regulation. Increased understanding of the pathogenic role of inflammation in disease brings us back to the past, when the role of the intestine in diseases was well known. The diet is the oldest form of therapy. However, only a diet based on evidence for the impact of food on the digestive system, taking into account evolutionary history and the physiology of the human digestive system, may be helpful to human health.

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