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Review Article

The human gut fungiome: Role in physiology and detoxification

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Abstract

The intestinal microbiota is an ecosystem where bacteria, archaea, viruses, and protists, are entangled, but not alone. We take microbiota as the bacterial community because, in many historical papers, the probes to detect other organisms in the intestine were rarely used. But in addition, unicellular fungi or yeasts do exist in microbiota, their assembly is called the mycome or fungiome, and it can reach the size and number of our human cells. The bacteria are far more numerous. For a long time, the whole was taken for a nest of pathogens, but in fact, yeasts adapted and evolved as symbiotic cells helping not only our digestion, but also angiogenesis, tissue growth, vitamin synthesis, and our nervous, endocrine, immune systems and even our detoxification system. Much of what we swallow is or will become fermented, like bread, cheese, or wine. Since the beginning of agriculture, our food is eaten lightly by microbiota including yeasts first in plants not treated by pesticides. Natural yeasts still unknown are in hundreds of types or species at the very least, bringing in particular during their work of fermentation a multiplicity of aromas that play a role in the famous detoxification; but the usual diet only provides a few strains of these yeasts. In yeasts like in all cells, ubiquitous cytochrome P450 detoxifying enzymes form a vast family also involved in cell respiration, which is stimulated to some extent by the aromas and other signals secreted. Yeasts could attract and coordinate bacteria to eliminate in part chemical pollutants.

Introduction

The intestinal or gut microbiota is an ecosystem where bacteria, archaea resembling them, all microscopic and nucleus-less cells, but also non-cellular viruses, multicellular protists, are entangled, and however, they are not alone. We take microbiota as the bacterial community because, in many historical papers, the probes to detect other organisms in the intestine were rarely used. But in addition, unicellular fungi or yeasts do exist in microbiota, their assembly is called mycome or fungiome, and it can reach the size and number of our human cells.

It is, in fact, the external environment comparable to what is in the soil, in our digestive system, but also over our skin, in our mucosa in the respiratory system, etc., with far fewer insects, but inside our body also. For a long time, it was taken for a nest of pathogens, experience shows that they are essentially and often essential symbiotic organisms when we are quite healthy because they help us to live and digest. A lot of pathologies develop when we are lacking them. In addition, on these microorganisms, we are learning more nowadays, and they play other important functions by having adapted apart from digestion, for example for our so-called defense immune system, but also the hormonal, and nervous, and we see it unexpectedly, for our detoxification system. We have continually and mutually adapted to our microbiota for several hundred thousand years; living organisms have a microbiota, and more particularly it was developed since the beginnings of humanity and agriculture. This review will more specifically defend the role of yeasts in the gut microbiota.

The microorganisms contained in our microbiota are much more numerous than our human cells; in particular, they eat

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before we do and simplify the food bolus in an essential way to therefore offer us simpler molecules, sometimes less toxic, to absorb.

Much of what we swallow is, in fact, fermented: that is, pre-digested by these microscopic organisms. Yeasts thus play for instance an important and irreplaceable role in the production of bread, wine, drinks, and cheese. But also, this has been highlighted more recently, and it has been used for a long time in history, on vegetables: the role of fermentation, or of the very beginning of it, and not with just any microbiota, is often positive if the product is edible and yeasts are precisely on vegetables and fruits before the natural harvest, as long as it has not been treated with fungicides, precisely killers of these fungi. Fungicides are in fact from the family of pesticides, they are toxic petroleum-based products, which we have discovered very recently to be used for a long time, and then well characterized [1,2].

Natural yeasts are in millions of copies and hundreds of types or species at the very least, bringing in particular during their work of fermentation a multiplicity of aromas, and among them, we appreciate some very much, which play a role as we will see in the famous detoxification or detoxication. The yeasts usually make them, but the usual diet with the so-called baker's yeast only provides one strain of these yeasts, which gradually impoverishes our microbiota if alone or in the majority. They are very numerous different strains as is seen. Some make a little alcohol during fermentation and are therefore said to be alcoholic. These have been selected by life because they also favor antiseptic properties and first the relative storage of food.

The fungiome and its different roles

There are about a hundred times more genes in the human microbiota than in the human genome [3], which may be less for some researchers [4], but the fungiome is anyway much smaller than the microbiota, without however being precisely evaluated yet. This is still a new and evolving subject. However, it seems about a hundred times smaller than the microbiota, and it is therefore comparable to human cells [5]. For the record, there are about 200 different types of human cells.

There is not only the fungiome and the microbiome at the intestinal level. We work more frequently today on other levels of the digestive system, oral or stomach for example. However, it does seem that the gut microbiota is the most important in the body. This in no way excludes the cutaneous, pulmonary, or vaginal microbiota, for example, in fact in all the tissues in contact with the external environment. But we now know that symbiotic intestinal bacteria have co-evolved with humans for at least 200,000 years [6], and recently we even learned that the microbiota co-evolves more with our family and social relationships [7]. It is therefore very likely that the same is true for yeasts, because they are very useful in our diet anyway, and they eat before us, thus it is really a symbiosis.

The antitoxin and immune role of certain intestinal yeasts

While studies of the microbiota had focused on bacteria, Ianiro et al. [8] show that there is an essential role of fungiome in disease and human health, by achieving a beneficial focus for yeast Saccharomyces boulardii for instance which acts as an antitoxin. But this is much less known. Hudson et al. [9] show that genomic sequencing and morphological analysis of S. boulardii reveal changes in cell wall components compared to non-probiotic S. cerevisiae, which may partly explain the probiotic functions of S. boulardii. This research strongly suggests that the interaction between S. boulardii and the mucosal immune system in the healthy gut is limited but with important implications for future work examining S. boulardii as a disease prophylactic agent and vehicle for disease therapy.

For information, there are food probiotics (living cells) and prebiotics (nutrients, not necessarily directly digestible, including micronutrients, which are helping probiotics too). These compounds greatly aid digestion [10]. Everything is not always the same, some microorganisms are not permanent; it varies with the digested contents of the stomach, and what we are used to consuming, in what we call the food bolus.

Cordonnier et al. [11] show that the addition of yeast of a certain Saccharomyces cerevisiae species greatly reduces the effect of Escherichia Coli toxins in the context of diarrhea or even intestinal bleeding. The authors note that these toxins negatively affect the Peyer's patches, which are 5 to 200 lymphoid follicles located at regular intervals in the ileum, which precedes the large intestine. We also know that with antibiotic treatment we must reconstitute the intestinal flora thanks to yeasts, but for the moment, we mainly recommend in drugstores a main single strain, from Saccharomyces cerevisiae.

Perez [12] establishes a list of commensal yeasts, which we carry, and that is first known. Many are Candida, some are believed to be pathogens, and others are symbionts. There are therefore fewer known of them than the bacterial part of the microbiota, but we still know very little about them. The fungal part begins to be deciphered thanks to its interactions with the immune and bacterial systems. The case of Candida albicans in the context of dysbiosis, or dysregulation, is studied.

Maccaferri et al. [13] demonstrate the effects of Kluyveromyces marxianus B0399 on adherence, immune function, and colonic microbiota. They explain that this strain has several beneficial and specific properties for a fungal microorganism, so it is being considered for application as a commercial probiotic. Kluyveromyces marxianus B0399 has been shown to induce a decrease in cytotoxic potential.

Possemiers et al. [14] show that the administration of EpiCor (a product derived from natural strains patented by Cargill), derived from Saccharomyces cerevisiae, has been shown to have immunomodulatory properties in human and in vitro clinical trials. However, the underlying mechanisms of immune protection via the gut remain largely unknown. The team studied that low doses of EpiCor have a prebiotic-like modulating effect on the microbiota, associated with the lumen and the mucosa of the colon. A significant decrease in pro-inflammatory cytokines was observed at the end of the treatment period.

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Zhaxi et al. [15] demonstrate that yeast(s) improve the development of intestinal structures and immune lymphoid tissues and promote intestinal health in weaned piglets.

Role of yeasts in the synthesis of vitamins (K, B12) and other molecules

It seems that the synthesis of certain vitamins, such as from the group K in particular, is provided by the food bolus, plants, and at the intestinal level, by the microbiota itself and by its own work, even if receptors and specific transporters are needed in human cells. Among the cells of the microbiota responsible for the synthesis of vitamins, there are bacteria, but the role of yeasts which are responsible for this and for fermentation, including lactic acid, has long been specified [16]. The production of vitamin D at the medical level by yeasts, again derived from the Saccharomyces cerevisae type, could even be exploited in the event of a deficiency, and this is promising [17]. Moreover, it is a mixture of probiotics that seems the most effective at the intestinal level for certain vitamins, for example, B12.

In February 2023, the role of butyrate, a short-chain fatty acid, and many other compounds, is highlighted in the role of chronic fatigue in humans, which affects 17 to 24 million people, by Guo et al. [18] in the team of Brent Williams in New York, and this is obtained by an original genomic technology, in the disruption of the network of intestinal bacteria, which are identified, and correlatively there are less numerous pathologic and anti-inflammatory strains.

Role in angiogenesis, especially intestinal

We increasingly emphasize the role of yeasts and bacteria in angiogenesis, the formation of new vessels, and, this involves similar mechanisms in the modulation or in the control of inflammation, but also in digestive pathologies, health in general, and various rheumatoid arthritis for example. It is also the case in longevity, today. In budding (dividing) yeast there are highly conserved markers that stimulate angiogenesis, in particular [19]. The boulardii variety of Saccharomyces cerevisae seems to play an important role at this level [20], but yeasts that are poorly characterized to date could also be involved.

Consecutive growth

Tekce et al. [21] study different doses of dietary probiotics, yeasts, and probiotic-yeast combinations, on agronomic performance parameters, and visceral organ weights. This improves meat quality in merinos, which are Anatolian lambs. These cell uptakes have a positive effect on the general growth of the visceral mass of these animals. Thorsteinsson et al. [22] also show that supplementation of the yeast/lactobacillus products in milk replacers during the first month of life had a positive effect on calf growth, this is established. Yeasts are not just poisonous mushrooms, of course.

Role of yeasts at the level of the brain or neural signals, or intestinal neurons

Much more surprising: there is remarkable conservation in the evolution of signals from yeast to the mammalian brain, as noted by many authors reviewed [23]; particularly in the glucose-lowering pathway, or for increasing longevity. Detoxification even in the brain seems to use pathways comparable to those of yeasts, for the transport and elimination of excess copper or zinc, for example. Thus, the intestinal microbiota could send signals to the brain to stimulate satiety [24], and in this case, it would be the role of certain well-balanced intestinal yeasts in different varieties. Research is increasing at this level.

We must explain that at about the same period, we scientifically knew that around the intestine existed a kind of second brain, a very developed nervous system called enteric and autonomous, which plays a role that has begun to be known since the end of the 1990s, of course, to suppress contractions, but also to ensure important transmissions at the rather unconscious level, and secretions and vascularization [25]. It is therefore quite possible that the signals to modulate angiogenesis also join this enteric nervous system. Recently, pesticides, particularly glyphosate-based, have been shown to alter this whole system [26]. Our team's research shows that long-term toxic pesticides, again based on glyphosate but not alone and only, alter the gut microbiota in rats [27], a phenomenon that appears to be gender-dependent.

In summary

The role of non-pathogenic commensal intestinal yeasts is positive on digestion of course, and health; it is a balance. It's modular. But yeasts undoubtedly play an important role in the immune system, and many others described here, by promoting defenses. These defenses also act through detoxification apparently also have signals to the most numerous and smallest bacteria. Having defined the most unexpected roles of fungiome, the next paragraph addresses these questions.

Fungiome and the microbiota in detoxification

The gut microbiota plays a role in human detoxification, this has been found especially in insects [28], and for digestion as known. In any case, different aromas, notably released during chewing, influence digestion [29], and we will see that they play a role in that respect.

There are indeed many enzymes involved in the regulation of nutrition and metabolism [30], but also detoxification, after food intake, and this from the beginning of smell, saliva, stomach, liver, intestine, and its microbiota. In every cell of the body, in microbes and thus yeasts, these enzymes exist, in fact. They form a family also involved in cell respiration, therefore an essential activity. This is the vast family known as cytochrome P450 enzymes. There are at least 18 major families of that, 44 subfamilies, and 57 functional enzymes in humans [31]; they have been extensively described before [32].

The body metabolizes, eliminates, or even takes charge with them, but in some instances in an incomplete manner, or 95% of the drugs that have been ingested, but also polluting chemicals, or even our hormones after use, and in particular "aromatic" substances, to so-called aromatic carbon cycles.

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Therefore these are involved in the structures of hormones and the recognition of all the cells of our body, as soon as and before entering the mouth [33], there are cytochrome P450 enzymes in the cells of the microbiota, in particular in bacteria and yeasts, which also bring their tribute. These enzymes are classically regulated by signals involving hormones... and aromas, the simplest form of hormones. There are also hormones that can be felt from outside the body, called pheromones.

Cytochromes P450 are like an immune system, but much smaller because at the molecular level. Cytochromes P450 constitute thus an intra-and extracellular system, which contributes with other known families of enzymes, to the elimination of troublesome substances from the body. Some are insoluble, so we can write like sand or spam. Cellular communications can have a hormonal or nervous origin [34] because it is a complex mixture of chemical and electrical signals, and these are very hampered by interferences. However, most chronic diseases precisely involve a disruption of cellular signals and communications, with inhibitions as if everything were gradually being silted up or "spammed" [35].

Intestinal yeasts coordinate bacteria

Mu et al. [36] showed in an exciting way that the so-called BR14 yeast (a strain of Saccharomyces boulardii that we have already cited), very resistant to stress, prevents colitis, restores the intestinal barrier, and quite specifically rebalances the bacterial flora. Zebrafish larvae (Danio rerio) exposed to these yeasts see the colonies of their beneficiary intestinal bacteria increase [37]. Similarly [38] show again very recently in the freshwater fish of a fairly common mountain lake, the largemouth bass, a salmonid, that the culture of yeasts in their diet (3%) increases symbiotic bacteria and not pathogens. There are comparable results even with yeast prebiotics in chicken [39]. In humans, it would even seem that it is a mechanism of adhesion to the walls of the Saccharomyces but not always cerevisiae yeasts that regulate and avoids pathogenic bacteria because they are recognized and stick to them [40]. This is true in one of its many strains in any case, which is not baker's yeast. A receptor called Nod2 would play a role, to simplify [41]. Many articles underline the regulating role of kefir besides, for a long time; it is a fermented product at this level and more generally [42].

Kefir is rather of artisanal origin but cannot be easily reproduced. The yeasts it contains (there are several origins of kefir) have not all been characterized. To give an idea, there are at least 34 strains in 3 genera, including 15 from Saccharomyces cerevisiae and others including 9 from marxianus [43]. And of course, there may be others in the gut regulating bacteria, and not everyone consumes kefir! However, today there are very few yeast strains on the market that help digestion (those fighting against bacterial antibiotics), but most of them exist naturally on fruits and vegetables not treated with fungicides, but which are probably a myriad.

If there are very toxic fungi secondary metabolites that damage health in several ways in the fetus and adult [44] such as aflatoxin B1, the progression of several diseases including cancer has been by contrast reduced by beneficial microbial gut target metabolites recently [44]. Butyrate is often cited as a mediator for pathogenic bacterial control. Amyotrophic lateral sclerosis or neurologic disorders like attention deficit hyperactivity disorder can be at least partially improved by gut microbiota metabolites [45]. There is a network of different signals in which yeasts are involved, in particular, compounds of yeast cell walls [46], to maintain health at different levels. Golisch et al. [47] underlined the role of β-glucans and polysaccharides in the human gut microbiota and particularly in yeasts to influence gut microbiota community and bacterial taxa and thus physiology. Some fungi could be at least a good marker of physiology for detoxification.

This has been recently demonstrated for symbiotic bacteria, allowing the resistance to an insecticide, bringing thus enzyme possibilities of degradation of the neonicotinoid imidacloprid, through insect gut [48]. But it is clear that yeasts symbionts in insects among other animal kingdoms play an interesting role in the detoxification of secondary plant metabolites degrading plant cell walls [49] and allows to better their nutrition.

In humans, the gut microbiome appears similarly more and more important for nutrition. There are even now really potential therapeutic applications. The gut-derived signals reach the brain and may promote detoxification, and in the context of certain pathologies like obesity there is an involvement in the development of neuroinflammation and its regulation, if this appears altered; it can subsequently alter behaviors [50]. It is certain that the human colonic microflora influences the alterations of xenobiotic-metabolizing enzymes by catechins, for instance. The detoxication system in the liver and other human cells, but also the gut microflora is obviously involved in the regulation of the xenobiotic-metabolizing enzymes [51]. Microbiota may have been adapted to us for a long time. In the whole database, comparative functional genome analysis reveals the habitat adaptation and biocontrol characteristics of plant growth-promoting bacteria, for instance [52].

It thus appears crucial for detoxification among other roles that the body possesses an equilibrated microbiota for which we became symbionts at least a thousand years ago. Microbiota can be remodeled after natural detoxification [53], especially during fasting [54]. In particular, it is important that we acquire back several beneficial yeasts in it, that have been killed or suppressed by excessive use of fungicides in the recent intensive agricultural era. The actually commercialized probiotics may be insufficient from this point of view because there are only a few strains available. In appreciable natural wine fermented with natural yeasts, for instance, (because raisin is one of the very ancient fermented fruit) we genetically identified at least five still poorly characterized species, including ascomycetes and basidiomycetes (personal unpublished data), that could have become human symbionts since ancient times.

Conclusion

Intestinal yeasts are numerous, and very different in kind, even if they are much less than bacteria, they can coordinate these at least in part. They form the fungiome, which is

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still mostly unknown, yet we can identify some of these organisms, and we can begin to observe their roles. They have been symbiotic with us for millennia. They undoubtedly play to help our immune system, sometimes they present an anti-inflammatory role, and this could be also crucial in the detoxification of pollutants. They have all the enzymatic equipment to detoxify us, namely cytochrome P450 enzymes. Thus they produce aromas which also, through their structure, stimulate this phenomenon, and thus the synthesis of these enzymes themselves.

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