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Host, its microbiota and their interactions

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Abstract

The development of sequencing technologies has advanced the field of host-associated microbiology by showing the huge diversity and functionality of the omnipresent microbes of all multicellular life. With these advances, new interesting questions have been raised with regards to microbial community composition, pollutants that can interact with the host microbial community, the factors that can affect the host microbial community and the processes that determine the enormous variety of the microbiota among hosts of the same species or genotype. However, conceptual disagreement regarding the ecology, genetics and evolutionary concepts regulating microbial diversity are frequently occurring in this field. Concepts such as symbiont, holobiont, and hologenome are generating discordances in the scientific community regarding microbial host associations and microbial communities. Then it is important to take into account the definitions and clarify the bases of these concepts: the holobiont refers to the host and their symbiotic microbes. Therefore, the hologenome are the genes of host plus the genes of their symbionts. However, the symbiont definition is wide open and when we use it at the holobiont level it can be misinterpreted as all microbes in a host. To separate symbionts from non-symbionts, it is necessary to search at the functional level for the emergence or enhancement of traits at the holobiont level. For that reason, not all of the microbiota are symbionts and, therefore the holobiont should only include the host and all the microbial symbionts that inhabit it. Consequently, host-associated microbes are part of the amalgam in the complex organisation of an organism and can also be explained by ecological associations. Understanding these complex interactions between host and its microbiota can, for instance, give us insight into how this community can influence the host's regulatation of pollutants as stress factors. More important, to understand synergistic effects of pollutants such as microplastics and metals on the host and their microorganisms, constitute one of the new frontiers in toxicology. Finally, it is important to take into account how stress factors such as competition, environmental changes, pollution, and diet can influence the fitness, genome dynamics and diversification between organisms.

Introduction

One of the most fundamental dimensions of a multicellular organism is their associated microbial community. Since birth, organisms get colonized by a wide range of different microorganism mainly composed of bacteria but also fungi, viruses and protozoa (Sommer and Bäckhed 2013). Microorganisms cover all the mucosal surface of their hosts: digestive, respiratory tissues and urogenital tracts, but it is the gastro intestinal tract (GIT) that has received most attention because its important role in many aspects of the host function (Bendtsen et al. 2012; Hanning and Diaz-Sanchez 2015). The coexistence between multicellular life and its associated microbiota and its importance in host evolution is unmistakable (Brucker and Bordenstein 2012; Moran and Sloan 2015). Microbes allow the host to perform functions that would not have evolved without them, such as providing vitamins and nutrients to the host as well as other functions related with diet such as fermentation and proteolytic activities (Mackie 2002; Ley et al. 2008a; Hanning and Diaz-Sanchez 2015). The gut microbiota community can by its interactions; for example, protect their host against intestinal parasites (Koch and Schmid-Hempel 2011), ferment carbohydrate polymers of plant cell walls in the GIT (Mackie 2002), and activate the adaptive immune system related to the early microbial colonization of the skin, digestive, respiratory and urogenital tracts in vertebrates (Maynard et al. 2012). The dynamic and complex interactions between the microbiota and its host have been formed through evolution in all multicellular organisms (Maynard et al. 2012; Moran and Sloan 2015).

Our view on the gut microbiota over the last two decades is mostly bacteria-centered; only a handful of papers focus on viruses or microbial eukaryotes (protozoa and fungi) (Macfall-Ngai et al. 2013; Marchesi et al 2015; Marchesi et al. 2015). Although microbial eukaryotes and the viral components are important (Breitbart et al. 2003; Nam et al. 2008), bacterial gut microbiota receive more attention because of its high abundance and the fact that GIT is colonized by diverse and functional bacteria (Scanlan et al 2008; Cénit et al. 2014; Marchesi et al. 2015). In humans, the GIT is mainly colonized by anaerobic bacteria followed by aerobic and facultative anaerobic bacteria and archaea (Clemente et al. 2012; Sommer and Bäckhed 2013). The complex human gut microbial communities consist of about 500-1000 species. The majority of these bacteria are members of the Bacteroidetes and Firmicutes phyla that dominate the gut microbiota. Other bacterial phyla such as Proteobacteria,

Verrumicrobia, Actinobacteria, Fusobacteria and Cyanobacteria are also found (Qin et al. 2010; human microbiome project 2012; Sommer and Bäckhed 2013; Cresci and Bawden 2015). Microbial community composition depends on the location in the gut as microbial density and diversity increase from the proximal to the distal gut (Ley et al. 2008a; Sekirov et al. 2010; Sommer and Bäckhed 2013).

It is commonly assumed that the host and their associated bacteria represent millions of years of coevolution (Mackie 2002; Wang et al. 2015; Pitta et al. 2016). Recently, sequencing technologies and new studies have revolutionized our way of understanding how these ubiquitous unicellular organisms affect their host's fitness in different ways, in terms of nutrition, immunity, development, physiology, behavior, and reproduction (Werren et al. 2008; McCutcheon et al. 2009; Brucker and Bordenstein 2013; Stilling et al. 2014; Sullam et al. 2015; Sommer et al. 2016). Across species the structure and diversity of gut microbiota is correlated with diet and even with phylogeny and geographical location of the host (Ley et al. 2008a, Brucker and Bordenstein 2012; Bolnick et al. 2014a; Gajardo et al. 2016). This agrees with empirical studies in which gut microbiota as symbionts perform functions and have specific roles (McFall-Ngai et al. 2013). Moreover, some of these functions are dependent on specific host-microbe combinations to be sustained even though these microbial communities mostly are taxonomically diverse and dynamic (Ley et al. 2008b; Medina and Sachs 2010; Brucker and Bordenstein 2012; Yano et al. 2015, Pitta et al. 2016, Adair and Douglas 2017).

The actual number

In the last 4 decades an assumption, based on false premises, has grown strong in the microbiome field and has been perceived as a "fact". Based on imprecise number estimates it was assumed that a human body contains ten times more microbial cells than the human cells (Savage 1977; Kurokawa et al. 2007; Quin et al. 2010; Rosner 2014; Hanning and Diaz-Sanchez 2015; Sender et al. 2016a; Sender et al. 2016b). In my opinion, the microbial cells in the GIT and in the human body were overestimated to highlight the importance of the microbiome in complex organisms and their properties (Rosner 2014).

Even if the number of microbiota is variable and the number of human cells has been difficult to determine, there are now better and consistent estimates for both bacterial and human cell numbers (Suau et al. 1999; Bianconi et al. 2013; Pritchard et al. 2014). Though it is still frequently reported that the proportion of cells in human microbiota outnumber human body cells by a factor of ten to one, we now know that in hosts such as humans, microorganisms are roughly in equal abundance as host cells (Sender et al. 2016b). Estimates around 3.9×10^{13} bacteria and 3.0×10^{13} human cells in a 70 Kg "reference man" have been found to suggest ratio around 1:1 (Sender et al. 2016a; Sender et al. 2016b). This ratio is also attributed to all bacterial cells associated to an animal host (Colston and Jackson 2016; Sender et al. 2016a; Sender et al. 2016b). However, there is a lack of information regarding non-human hosts. Furthermore, it is important to clarify that if you only take the number of nucleated cells it is possible to get a ratio 1 to 10 (Sender et al. 2016a). By exaggerating the amount of microbes in a host, the value conveys the idea of humans as a diverse ecosystem and microbes having wide-ranging impacts on host physiology, however, a ratio closer to 1:1 should not change the importance and the attention to this topic (Sender et al. 2016b).

From symbiont to holobiont

New approaches base on sequencing technologies to study gut microbiota have shown how this symbiotic system is an important dimension of every single organism (Eckburg et al. 2007; Cullen et al. 2015; Stothart et al. 2016; Schwartzman and Ruby 2016, Pitta et al. 2016). It is suggested that the gut microbiota and its host cannot be viewed as autonomous entities and instead needs to be observed as a biomolecular network integrating both the host and its associated microbiota (Brucker and Bordenstein 2012; Brucker and Bordenstein 2013; Bordenstein and Theis 2015). This view combines the host and associated microbiota to a concept called the holobiont, which goes further than the association between a host and its microbiota. The combination of the host genome and the microbiome genome as a hologenome argues for the existence of complex assemblages of organisms that are the unit of natural selection and have similar properties as an individual organism (Rosenberg et al. 2007; Rosenberg and Zilber-Rosenberg 2014; Bordenstein and theis 2015 ; Moran and Sloan 2015; Douglas and Werren 2016). This approach has many parallels with the controversial group selection theory in which natural selection acts on groups of individuals within species/populations (Wilson 1975; Peck 1992; Wilson et al. 2008; Veelen 2009; Moran and

Sloan 2015). In this view on the host and its microbiota, selection occurs at the hologenome level as the primary unit of selection (Rosenberg et al. 2007; Rosenberg and Zilber-Rosenberg 2014; Bordenstein and Theis 2015). In light of this, new approaches need to be considered to separate the environment from the host genotype, and their symbiotic microbes as co-adapted genome (Brucker and Bordenstein 2013). However, even if some gut microbes are transferred vertically from mother to offspring and horizontally between social interactions (Koch and Schmid-Hempel 2011; Cénit et al. 2014), this inheritance is affected by several factors such as anthropogenic interactions and environmental stress factors.

In many cases the gut microbes are promiscuous and vary among host and habitats. Because of this promiscuity, it is very difficult to determine the evolutionary impact of the selection at the hologenome level and if and where it is important (Moran and Sloan 2015). Considering the host microbiome as an ecological community could be a more effective framework compared to the holobiont concept when describing host-microbe systems (Robinson et al. 2010; Moran and Sloan 2015; Douglas and Werren 2016; Adair and Douglas 2017). In an ecological community, there are more than one level of selection resulting in microbial traits that allow them to survive and grow in the host. Under an island biogeography framework (Fenchel and Finlay 2005), every single microbe can be clustered by habitats i.e. host, and fidelity of this association is maintain depending of the strength of the following fundamental ecological processes: dispersal, local diversification, selection pressures, and ecological drift (Costello et al. 2012; Douglas and Werren 2016; Adair and Douglas 2017). Even if the concept of holobiont is debated, one thing is clear; host microbes have a strong influence on the host fitness and health and host microbes are at the same time affected by many factors (Moran and Sloan 2015; Douglas and Werren 2016).

The new sequencing achievements in the understanding of host microbe interactions call the scientific community to analyze the concepts used more deeply. There are discordances in the use of concepts such as symbiont and hologenome in the field of the GIT microbiome, and the general use of these concepts in different scientific frameworks are obscuring the tenets of the evolutionary theory to understand the host evolutionary biology. In the fields of ecology and evolution, there are different concepts that are in focus for the investigations of gut microbiota. For example, “symbiosis” has multiple definitions that depends on the field and

the biological questions. Other example is the concept that the hologenome perspective contrasts with the fields of ecology, genetics and evolution (Douglas and Werren 2016). Much worst is the regular misconception that the holobiont concept implies the selection on the whole microbiome in a host (Moran and Sloan 2015), not only the microbe-symbionts. It is necessary to clarify the use of these terms in describing host-microorganism associations in order to compare and advance in this field of science.

The use of the symbiont concept in gut microbial studies have been used in multiple ways to describe host-microbiota associations, for example: i) *"An obligate or transient microorganism that forms a parasitic, mutualistic or commensal interaction with a host"*. (Brucker and Bordenstein 2012), ii) *"Two or more species living closely together in a long-term relationship"* (Bordenstein and Theis 2015), iii) *"microorganism that colonize a host in an intimate and characteristic manner, and have major impact on host fitness*" (Moran and Sloan 2015), and with notions that symbiosis is the same as mutualism or a sub class of a mutualistic interactions (Chow et al 2010; Martin and Schwab 2013). The problem with these definitions is that everything can be a symbiont from *Escherichia coli* to fibrocystic Pseudomonas or The human immunodeficiency virus (HIV) (Suarez in-prep.). The lack of definitions is unsatisfying and leaves a trail of misunderstandings and unclarity about the features of symbiont relationships. Therefore, the following definition of symbiosis has been put forward: *"subclass of biological association among individuals of different species whose association is ontogenetically constant and intimate and that phylogenetically has resulted in the emergence of new traits at the level of the holobiont"* (Zook 2015; Suarez *in*-prep.). To this definition it would be interesting to add the enhancement, the decrease and the remove of a trait to the concept of emergence of new traits at the holobiont level: *"Subclass of biological association among individuals of different species whose association is ontogenetically constant and intimate and that phylogenetically has resulted in the emergence of new traits,* enhancement, decrease or loss *of traits at the level of the holobiont"*.

The holobiont approach has mainly been descriptive, characterizing the diversity of gut microbial communities (Adair and Douglas 2017). We need to include analysis about specific and multiple traits interactions between the host and its associated microbiota to understand the impact on fitness of these interactions and the impact of selection at the hologenome level.

Also, what is a holobiont has not been clarified. The research that takes the microbiome as an ecological community does not contradict the hologenome view. Actually, as the holobiont refers to the microbial symbionts, the remaining non-symbiotic microorganisms in our body are "merely" ecological entities. The controversy is the proposal of hologenomes as the principal units of selection (Zilber-Rosenberg and Rosenberg 2008; Brucker and Bordenstein 2013). However, this problem is based in that whole associated microorganism and the microbiome are part of the holobiont and in the supposition that all these microorganisms have a tendency to avoid mechanism to evolve selfish traits in pro to the fitness of the holobiont (Moran and Sloan 2015). With a more precise definition of symbiosis, confusion about what constitutes a holobiont can thus be avoided. Therefore, I argue that not all the microorganism should be part of the holobiont-hologenome, only the ones that are microbial symbionts that inhabit the host.

Host - microbe selection

In host associated microbiota, the host genotype, diet and the environment play an important role in influencing the microbial composition (Douglas 1998; Muegge et al. 2011; Bolnick et al. 2014a; Bolnick et al. 2014b). The complex interactions between the host and its microbiota are under continuous selection. Note that not only the pathogenic, parasitic or antagonistic microorganism make this selection pressure (Ley et al. 2008b). Beneficial and opportunistic microbes are constantly changing, revealing new phylo-types that are not necessarily recognized by the host and can become a 'pathogen-like entity' (Zhang et al. 2010). On the other hand, the services provided by the microorganism such as nutrition, immune system and developmental regulation (Lee and Mazmanian 2010; Lathrop et al. 2011; Koch and Schmid-Hempel 2011; Bolnick et al. 2014), does not mean that the microbes, microbes-symbionts or the host evolved to be "altruistic" or to avoid the tendency to be selfish (Rosenberg and Zilber-Rosenberg 2014). However, in symbionts and holobionts the fitness of the host is in some way dependent on the microbiota and vice-versa because their heritable history (Rosenberg and Zilber-Rosenberg 2014), but not as obligate such as mitochondria and eukaryotes in endosymbionts, that are stable and transmitted from generation to generation vertically (Brucker and Bordenstein 2012). Therefore, if the host environment is compromised the microbiota could start to compete against the host for resources (Wasielewski et al. 2016), and the symbiont microbes will also perish with its host. The environment plays an important

role in selection for both the host and its microbiota. Environmental stress factors such as pollution and environmental disturbances can change the diversity and promote traits or activities of microbiota in the environment, gut, and whole host. (Breton et al. 2013; Merrifield et al. 2013; Wu et al. 2014; Ninkov et al. 2015; Vargas and Dussán 2016; Rothenberg et al. 2016; Varg and Dussán 2017).

Stress

Many of the microorganisms that live in association in the GIT may be involved in various processes related to the regulation of intestinal maturation, nutrient absorption, infection risk mitigation and more (Hooper et al 2001; Maynard et al. 2012; Hanning and Diaz-Sanchez 2015). Moreover, recent investigations (Cryan and Dinan 2012; Chen et al. 2013; Farmer et al. 2014; Yano et al. 2015; Hoffman et al. 2016) have shown that the gut microbiota impact is beyond the intestinal tract. External triggers may affect the host, which may then change the gut environment. Such an external trigger could be exposure to predators which in fish may release stress hormones in the host. Fig. 1 illustrates how this could be investigated in the crucian carp (Varg et al. in prep.). Actually, evidence about the complexity of this host-microbes interactions has been found, including direct cell-to-cell communication, metabolic regulation during the intake of xenobiotic compounds, signaling between organs and organ systems (Cryan and Dinan 2012; Stilling et al. 2014; Kan et al. 2015). Furthermore, different stress factors, both natural and anthropogenic have a stunning influence on the abundance and composition of the microbiota in the gastro-intestinal tract in all organisms (Wu et al. 2014; Bolnick et al. 2014a; Bolnick et al. 2014b; Ninkov et al. 2015). Previous studies have demonstrated that environmental chemicals and other resources of stress can induce vast changes in the gut microbiota and in the whole microbiome composition of animals (Kan et al. 2015; Stothart et al. 2016).

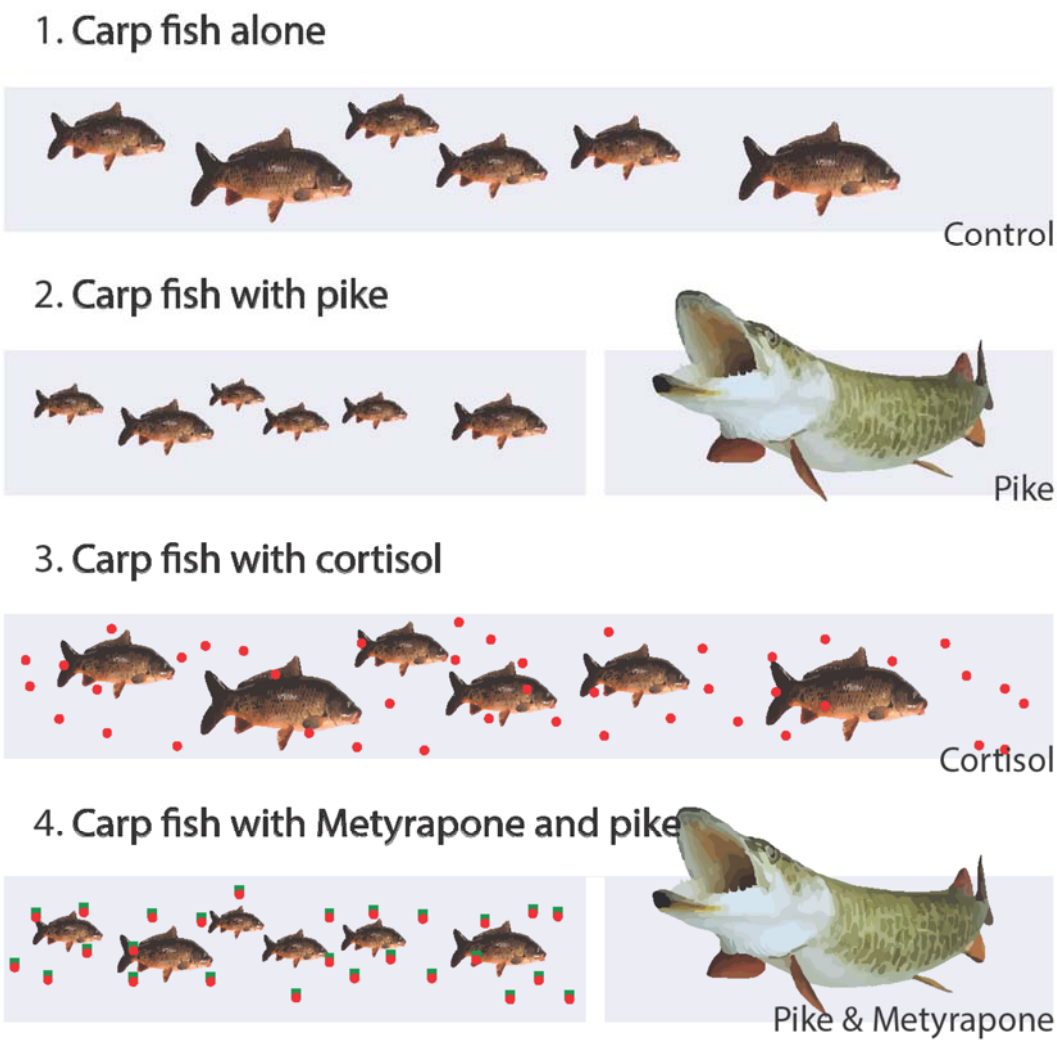

Figure 1.

Project 1.The role of the host responses and host metabolism changes are important in the regulation of the bacterial gut colonization and in the impact that the gut microbiota might have. The goal of the study is to investigate how the increment of glucocorticoids levels released by predation stress can affect the gut microbiota diversity and abundance in crucian carp fish (*Carassius carassius*). Glucocorticoids levels might potentially influence the colonization of beneficial and non-beneficial microbiota.

Microplastics as stress factor

Small plastic fragments, beads, granules and fibers below 1 mm in diameter are called microplastics (Santos et al. 2009; Cole et al. 2015). They can be specifically manufactured (Napper et al. 2015; Cole et al. 2016) or they are the consequence of mechanical, biological or photodegradation and subsequent fragmentation of large plastic items (Andrady 2015; Cole et al. 2016). Although the presence of microplastics in marine ecosystems is receiving increasing attention (Coe and Rogers 1997; Thompson et al. 2004; Ivar do Sul and Costa 2007; Moore 2008; UNEP 2009; Costa et al. 2009; Cole et al. 2015), there is a gap in our knowledge regarding their presence in freshwater ecosystems, which act as a recipient and a mode of transportation to marine ecosystems. One of the major concerns about microplastics is that they can enter food webs via direct ingestion because of their bioavailability in water environments and terrestrial ecosystems (Cole et al. 2013; Tanaka 2013). There are also indirect ways to be exposed to microplastics such as ingestion via predation of organisms that contain microplastics, i.e. microplastics can be transported in the food chains (Nowack et al. 2007; Zhu et al. 2008; Ferry et al. 2009; Mattsson et al. 2015). The presence of more than 100 000 microplastic particles per m^3 of debris is considered to be an environmental hazard (UNEP, 2005; Eerkes-Medrano et al. 2015). In fact, a large variety of organisms have been reported to ingest and accumulate microplastics, from zooplankton to fish (Mattsson et al. 2015; Cole et al. 2015).

Ingesting microplastics instead of food can have stressful effects at the holobiont level, i.e., a host and its associated microorganisms (Lozupone et al. 2012; Cénit et al. 2014; Farmer et al. 2014; Pietroiusti et al. 2015; Stothart et al. 2016). In terms of toxicity, microplastics and sub-micrometer plastics can cause anything from subtle effects, cytotoxicity, genotoxicity to mortality by chemical leaching and physical interactions (Wagner and Lambert 2018). For example, microbiota has a role on the host immune response, development and function of vital organs (e.g. the brain) and production of key elements (e.g. vitamin B12) (Koch and Schmid-Hempel 2011; Farmer et al. 2014; Bennett et al. 2015; Marchesi et al. 2015). The presence of ingested microplastics and their possible effects involve stress in the gut microbiota, affecting bacterial gut colonization. Therefore, the effects on the host responses and host metabolism changes due to external stress factors on the microbiota cannot be ignored and should be investigated.

Metals as stress Factors

In water systems and in the environment, xenobiotics such as toxic metals are widely distributed in low concentrations. However, in some areas of the world its concentration increases due to anthropogenic release and natural sources (Ozsoy and Krumbur 2006; Ting et al. 2013; Vargas and Dussán 2016). Toxic metals such as chromium (VI) (hereafter, Cr (VI)) are released in natural aquatic system due metal alloying, the manufacture of dyes and pigments, as well as for leather and wood preservation (Kotaś and Stasicka, 2000; Zeng et al. 2016; Varg and Dussán 2017). Although, Cr(VI) damages several organs and tissues (DoH 1991), the bioavailability and further damage is determined by the efficiency of uptake from the gut into the blood and also from the retained metal in the GIT mucosa (Miller 1996, Mutuma et al. 1999, Ninkov et al. 2015). Cr (VI) and other toxic metals such as cadmium (Cd) and lead (Pb) can produce moderate, to severe health disorders by inhaling air, eating food and drinking water that has been contaminated with the metal (Kotaś and Stasicka, 2000; Zeng et al. 2016). The entrance of these pollutants to the GIT and its impact on the gut ecology can provide insight in the understanding of mechanism of toxicity, immunological stress response, and structure and balance of the microbiota (Wu et al. 2014; Ninkov et al. 2015). In order to understand how the gut microbiota can mediate the bioavailability and the toxicity of environmental pollutants it is necessary to consider the absorption, distribution, metabolism, and excretion of xenobiotics as complex environmental factors (Nicholson et al. 2005). In this way, the gut microbiota is capable to interact with metals since many metals have been recognized as an essential or trace elements (Mutuma et al. 1999; Wu et al. 2014). Moreover, studies focused on metal bioremediation have shown how gut microbes such as lactic acid bacteria or *Lysinibacillus sphaericus* can remove toxic metals *in* vitro by uptake, adsorption or absorption (Halttunen et al. 2007; Vargas and Dussán 2016; Varg and Dussán 2017). However, metals have an overall negative effect on gut microbiota, with a high detriment of diversity and changes between beneficial to pathogenic bacteria (Fazeli et al. 2011; Ninkov et al. 2015). Finally, microbe-host interactions also play an important role in the integrity of the intestinal barrier involving epithelial junctions and physical impediments of the mucous layer (Breton et al. 2013). The changes in the gut environment such as pH, oxidative balance, detoxification enzymes, transporting host proteins and xenobiotic metabolization by the gut microbiota and its metabolites will also impact the bioavailability of chemicals in the gut lumen (Claus et al. 2011; Breton et al. 2013).

Synergistic stress

The effects of microplastic ingestion can either be physical damage or toxic via chemical activity. There are many compounds associated with plastic materials that may be toxic, such as antimicrobial agents and nanomaterials that can affect the environment and organisms in the ecosystem (Wagner and Lambert 2018). This may eventually compromise individual fitness by reducing feeding, energetic reserves, growth rate, fecundity and survival (Cole et al. 2016). Moreover, the bioavailability of microplastics and their possible interactions with different pollutants in the environment (Tanaka et al. 2013; Rochman et al. 2014; Wagner and Lambert 2018) open the possibility of synergic toxic action of microplastics with other pollutants like toxics metals such as Cr (VI)**.** Unfortunately, the joint synergistic effects of microplastics and pollutants on organisms remain unexplored, constituting one of the new frontiers in toxicology. Studying microplastics and toxic metals may also help to understand the reported pathological and physiological consequences of nanomaterials with biological activity. For example, some nanopolymers agglomerated with silver and copper can damage healthy microbiota due to their antimicrobial activity (Echegoyen and Nerin, 2013; Cushen et al. 2014). Moreover, studying microplastics may also help to discover new unknown biological effects cause by this particles (Pietroiusti et al. 2015). Furthermore, it is important to understand the interaction between the gut microbiota and the microplastics as a selection pressure, which can help us to know which microorganisms are capable of ab-adsorbing or degrading microplastics and other pollutants as a beneficial trait, while the microbiota is interacting with a host (Pietroiusti et al. 2015; Vargas and Dussán 2016).

Concluding remarks

New sequencing technologies now provide us with data and means to analyze the functions of the amazing microbial world. Moreover, the study of micro-organisms in the context of animal associations is essential to understand the host biology. Not all of the microbiome are part of a holobiont and hologenome. The holobiont only includes the host and all the microbial symbionts that inhabit the host. This means that not all the microbes of the host are symbiont organisms; *"Subclass of biological association among individuals of different species whose association is ontogenetically constant and intimate and that phylogenetically has resulted in the emergence of new traits,* enhancement, decrease or loss *of traits at the*

level of the holobiont". The rest of the organism can be only pathogenic, opportunistic, beneficial, mutualistic, parasitic, commensalism, etc., but not necessarily symbionts. To understand the effect of the associated microorganisms to the host and vice versa it is necessary to also understand how the pollution, environment and other stress factors are affecting both host and its microbiota

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