The Human Gut Microbiota in all its States: From Disturbance to Resilience

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Introduction

Gut microbiota has emerged as a promising preventive and therapeutic target and lever for human health. Recent studies of different world populations suggested that adoption of Western lifestyle is associated with functional and structural alteration of the human gut microbiota. Based on studies of populations that have not yet adopted a western lifestyle, those that are in transition and western populations, the observed alterations may lead to aberrant/sub-optimal interactions of the gut microbiota with its host. The concomitant emergence of chronic diseases—metabolic and immune disorders and inflammatory bowel diseases (Durack and Lynch, 2019; Mosca et al., 2016)—has stimulated interest in the design of strategies targeting the restoration of microbiota-host crosstalk (Vieira et al., 2016; Markey et al., 2020).

Large cross-sectional studies based on population-based cohorts have provided unprecedented insight into the inter-subject variability of gut microbiota, in association with host genetics and multiple clinical and environmental factors (Falony et al., 2016; Vandeputte et al., 2017) (**Fig. 1**). Further studies concurred that host genetics plays a minor role in gut microbiota variation and that environmental factors explain less than 20% of gut microbiota variation (Falony et al., 2016; Zhernakova et al., 2016; Manor et al., 2020; Partula et al., 2019; Byrd et al., 2020; Deschasaux et al., 2018; Rothschild et al., 2018), suggesting the importance of other unknown factors. While longitudinal studies have been relatively scarce, we have recently witnessed an increasing number of longitudinal studies that provide additional insight into gut microbiota dynamics following birth (Yassour et al., 2016; Bäckhed et al., 2015), in healthy adults (Mehta et al., 2018; Abu-Ali et al., 2018), or diseased adults (Lloyd-Price et al., 2019). These studies are fundamental in describing and understanding the ecological forces and microbial assemblies behind stability and response to challenges associated with clinical markers. Human gut microbiota, mostly assessed through fecal samples, is globally considered stable over the short- and long-term in healthy adults, despite day-to-day fluctuations in response to diet, ingestion of environmental bacteria (Arumugam et al., 2011) and indoor environment (Lax et al., 2014). The gut microbiota may sometimes be exposed to more acute and/or more pronounced perturbations by way of travel, medication, stress or shift in dietary habits (Karl et al., 2018). One remarkable feature of the gut microbiota is its capacity to bounce back to its initial state following an acute short-term stressor, a recent topic of great interest (Sommer et al., 2017; Costello et al., 2012; Gibson et al., 2014; Fassarella et al., 2021; Shade et al., 2012). Interestingly, the extent of alteration and the speed of recovery of gut microbiota both vary significantly across individuals, types of stressor, their duration and repetition. For example, in the case of antibiotic treatment, the most studied perturbation, recovery of gut microbiota has been reported to vary significantly between subjects and to depend on factors such as the initial state of the

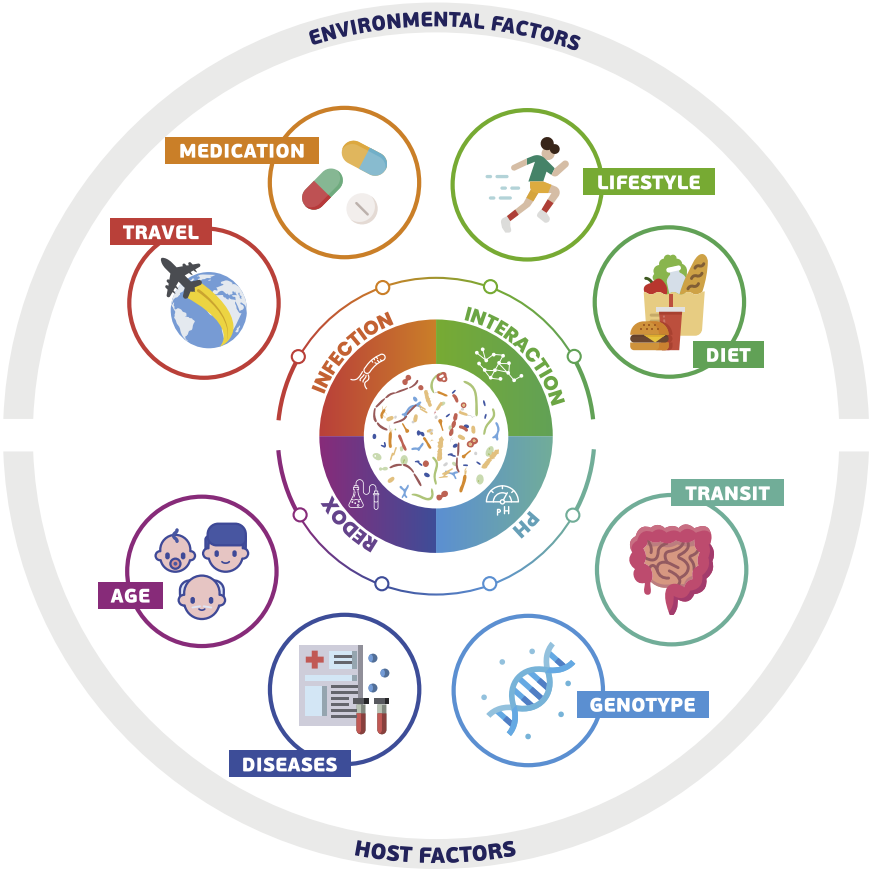

Fig. 1 Overview of host and environmental factors that are associated with gut microbiota variation, in addition to intrinsic factors.

gut microbiota and dietary habits (Cabral et al., 2019; Ng et al., 2019). In some cases, the exposure to repeated and/or cumulative stressors leads to the emergence of new gut microbiota configurations, such as alternative stable states, first described for ecosystems in response to climate change (Scheffer et al., 2001) and recently for gut microbiota (Lahti et al., 2014).

Given the association between gut microbiota alteration and clinical outcomes, the gut microbiota is an attractive target for human health. Understanding its plasticity, variability and response to challenges, from both ecological and host viewpoints, is fundamental to guide the further design of microbiota-based solutions. In this review, we synthesize recent advances in understanding human gut microbiota stability and plasticity in response to short-term acute disturbances. We address some strategies that are aimed to modulate the gut microbiota to alleviate lasting functional and structural alterations.

Approaches to Study Gut Microbiota

Gut microbiota states can be defined according to different variables that characterize microbial composition and function across spatial gradients for different members of the community (Fig. 2). The advent of sequencing approaches followed by their wide use has provided a comprehensive picture of the whole ecosystem and its features, both at the compositional and functional levels. Targeted analysis such as 16S rRNA sequencing allows study of the composition of the gut microbiota (Archaea and Bacteria). Other targets such as Internal Transcribed Spacer gene sequencing provide insight into the fungal community.

The alpha-diversity (intra-sample) and beta-diversity (between-samples) are commonly used to measure differences in ecological states before and after a disturbance. Alpha-diversity metrics may concern the number of species (richness) or both the richness and the evenness, using the Shannon index or the Simpson index (Morris et al., 2014). Common beta-diversity metrics used to evaluate microbiome changes can be phylogenetic-based, such as UniFrac (Lozupone and Knight, 2005), or non-phylogenetic-based, such as Bray-Curtis dissimilarity and Jensen-Shannon Divergence (Arumugam et al., 2011). Recent approaches couple evaluation of the microbial load with sequencing to provide more quantitative data for the microbial ecosystem. Shotgun metagenomic sequencing has provided an unprecedented view of both composition at a higher resolution (down to strain level) and function, ranging from global pathway analysis, with the use of the KEGG database (Tanabe and Kanehisa, 2012), to complementary use of dedicated databases to profile the resistome (Jia et al., 2016; Ruppé et al., 2019) and Carbohydrate-Active Enzymes (CAZymes)

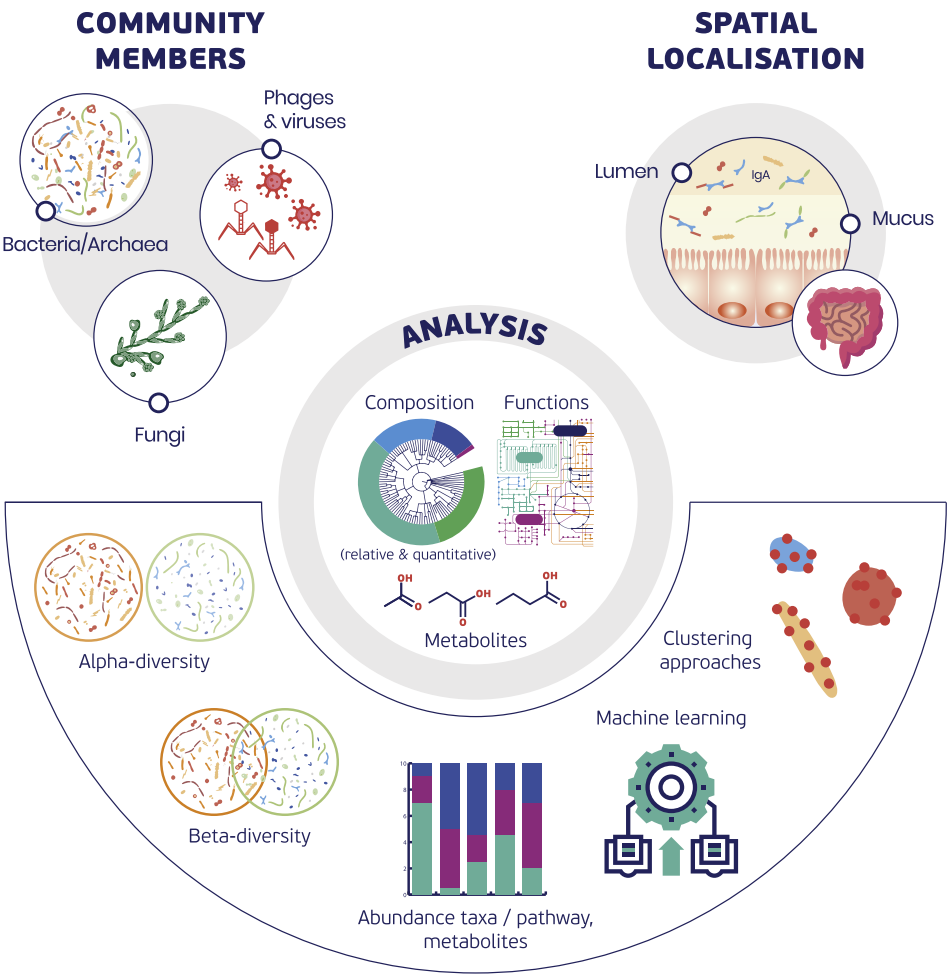

Fig. 2 Overview of the study of gut microbiota, including community members, spatial localization, and analysis.

(Cantarel et al., 2008). Altogether, studies of the gut microbiota with combined approaches allow a detailed assessment of composition and function, which are complementary when studying gut microbiota stability and response to disturbances.

Gut Microbiota Stability in Human

From birth onwards, the gut microbiota coevolves with its human host, and its development is of crucial importance for health in later life. The gut microbiota development is regulated by a complex interplay between the host and environmental factors, including diet and lifestyle (Derrien et al., 2019). While the gut microbiota is highly dynamic during the first years of life and highly responsive to environmental factors, the microbiota becomes more stable in adulthood, despite day-to-day fluctuations in diet and lifestyle and exposure to gastrointestinal infections and antibiotic treatments. In adults, the largest variation in human gut microbiota is inter-subject, typically accounting for up to 70% of gut microbiota variation (Fu et al., 2019). The high inter-subject variability in structure complexifies the identification of factors that are associated with health. The exploration of large population-based cohorts has unveiled multiple novel host and environmental variables associated with gut microbiota variation, such as drugs and bowel movement, clinical factors which are among the largest identified contributors to variation in human adult gut microbiota (Falony et al., 2016; Zhernakova et al., 2016; Manor et al., 2020; Vujkovic-Cvijin et al., 2020; Rothschild et al., 2018; Sun et al., 2020) (**Fig. 1**). However, the commonly captured factors explain no more than 20% of gut microbiota variation, suggesting an additional contribution from unknown factors or stochastic effects. To date, most of the large population-based studies are cross-sectional and provide a snapshot of the current state of gut microbiota. The emergence of well-phenotyped and dense time-series studies allows fine-grained exploration of the gut microbiota dynamics in health and disease. Currently, longitudinal studies are highly variable in sampling density, number of subjects, and techniques to study the gut microbiota. A few studies followed gut microbiota composition for several years, on a limited number of subjects, and showed that human gut microbiota is relatively stable over both short- and long-term in healthy adults (Faith et al., 2013; Rajilić-Stojanović et al., 2013; Poyet et al., 2019) (Martínez et al., 2013;

Flores et al., 2014). Variation in the high intra-subject specificity increases with time (Rajilić-Stojanović et al., 2013; Costello et al., 2009). Notably, 60% of microbial strains remained over the course of 5 years, with Bacteroidetes and Actinobacteria significantly more stable (Faith et al., 2013). Other studies reported that dominant members were stable while members with low abundance and/or prevalence exhibited a more unstable pattern (Fu et al., 2019; Mehta et al., 2018; Byrd et al., 2020; Rajilić-Stojanović et al., 2013). The densest sampled study consisted of two subjects followed for one year on a daily basis, which showed stability over each month, altered mostly by travel and/or infection (David et al., 2014a). When the gut microbiota of 5 individuals were clustered into microbiota states, termed enterotypes, a transition could be observed between enterotypes in over short and long periods (Rajilić-Stojanović et al., 2013). However direct transitions between *Bacteroides*-dominated and *Prevotella*-dominated communities were rare, suggesting the presence of a barrier between these states, as confirmed using a larger cohort over a one year-period (Levy et al., 2020).

Concerning the dynamics of gut microbiota, more diverse and resolutive approaches have allowed a comprehensive view of gut microbiota stability. Shotgun metagenomics down to strain level suggests a higher variation of taxa abundance than strain presence over a year (Schloissnig et al., 2013), and others have shown that metagenomes (functional capacity) and metatranscriptomics (activity) are more stable than taxa abundance (Lloyd-Price et al., 2017; Mehta et al., 2018), with metatranscriptomics being more dynamic than metagenomes (Abu-Ali et al., 2018; Mehta et al., 2018). A limited number of studies examined the stability of metabolites. Both taxa and metabolites were found to be stable between time points over 4-week intervals in healthy subjects, with a lower correlation for metabolites than taxa (Taylor et al., 2020). A more detailed study observed stability of the fecal metabolome over months to years, with fluctuations mostly due to the metabolism of amino-acids (Poyet et al., 2019). While the stability of gut microbiota has been assessed mostly through fecal analysis, a few studies have revealed high temporal dynamics of small intestine microbiota driven by diet (Kastl et al., 2020).

Beyond current focus on bacterial communities, other inhabitants of the gut, including archaea, fungi, protozoa, phages and other viruses make significant contributions to the mass and metabolism of the microbiota (Richard and Sokol, 2019) and directly affect gut microbial communities (Martínez Arbas et al., 2021). Relatively few studies have examined the stability of the gut virome (Minot et al., 2011) or of fungal communities (Raimondi et al., 2019). Gut phageome composition was found to be stable over time for 80%–95% of phage within a subject over 2-year observation periods (Minot et al., 2011). Fungal communities were reported to be highly variable between and within-subjects with no subject specificity, in contrast to bacterial communities (Raimondi et al., 2019). Overall, human gut microbiota is considered relatively stable in healthy adults at community level over short- and long-term, with higher dynamics for individual taxa.

Concepts of Gut Microbiota Response to Disturbance

In this section, we will summarize how a microbiota assemblage could result from some combination of stochastic and deterministic effects. We then explore the conceptual differences between several types of disturbances and, finally, the theoretical mechanisms that lead to multiple microbiota states.

Stochastic and Deterministic Effects on Microbiota Assemblage

A microbial ecosystem is defined by the consortium of microorganisms it contains and is shaped by the surrounding biotic and abiotic factors (Berg et al., 2020; Marchesi and Ravel, 2015). In human gut microbiota, biotic factors may include the host immune system and genetics, and abiotic factors nutrient intake and bowel movement. The assemblage of microbial species into communities results from deterministic processes such as environmental selection and stochastic processes (or ecological drift) (Stegen et al., 2012; Zhou and Ning, 2017). The deterministic processes involve various nonrandom biological interactions, including environmental selection, whereas stochastic processes can be defined as ecological processes that generate community diversity patterns indistinguishable from those generated by random chance alone (Zhou and Ning, 2017). While deterministic factors can be manipulated, stochastic factors such as genetic mutation, gene duplication, interspecies interactions, emigration, immigration, and random drift are difficult to control (de Vrieze et al., 2020).

Types of Disturbance

Several types of disturbance can affect an ecosystem to an extent that depends on their intensity, temporality, and targets (Relman, 2012). The combination of intensity and temporality makes it possible to differentiate between acute (or pulsed) disturbances and chronic (or continuous) disturbances, the repetition of pulsed disturbances yielding chronic effects (Sommer et al., 2017). For example, the intake of antibiotics, which has been the most studied stressor, may be either acute over a short period, while repeated intake can be considered chronic, moreover the intensity of the disturbance may depend on the dose administered and the antibiotic range of activity (referred to as a spectrum). In addition to deterministic disturbances, stochastic disturbances can be described as the microbial community's intrinsic ecological drift (Nemergut et al., 2013). Ecological drift is inherent to various biological processes such as dispersion, biotic interactions within the community, the disappearance/colonization of certain species, and the historical contingency of gut microbiota (Fukami, 2015; Costello et al., 2012).

Resistance, Resilience and Hysteresis

An ecosystem that is exposed to a disturbance will respond by two joint phenomena, the resistance, measured by the stability of the ecosystem, and the recovery capacity, measured by the distance between a state that has drifted and its initial state. Exposed to a stressor, the stability of communities (i.e., resistance) and their ability to return to their initial state (i.e., recovery capacity) define the ecosystem's resilience. The emergence of a stable state presupposes that restricted space, for the configuration of these phenomena, exists. Thus, several unstable states may exist during a disturbance, but disturbed ecosystems can persist in a new microbiome state even under unfavorable conditions (Khazaei et al., 2020). Hence, with constant environmental constraints, emergence of other stable alternative states suggests that hysteresis phenomena are possible, allowing multistability under an identical set of parameters. Hysteresis is defined as the lack of reversibility after a catastrophic bifurcation, meaning that when conditions change in the opposite direction, the ecosystem stays in the alternative state (Dakos et al., 2019; Beisner et al., 2003). In a disturbance context, deterministic and/or stochastic, the unstable state may pass through a tipping point, which may cause it to switch to another alternative stable state. Such tipping elements, associated with age, were described in human gut microbiota using bimodal distribution detection across a thousand samples (Lahti et al., 2014), although bimodality or clustering is insufficient to prove hysteresis (Gonze et al., 2017). When the disturbance level goes beyond the retention level, the ecosystem was unable to return to the previous stable state, even after the end of the perturbation (Fig. 3). The retention phenomenon may arise with a specific change to parameters governing interactions within the

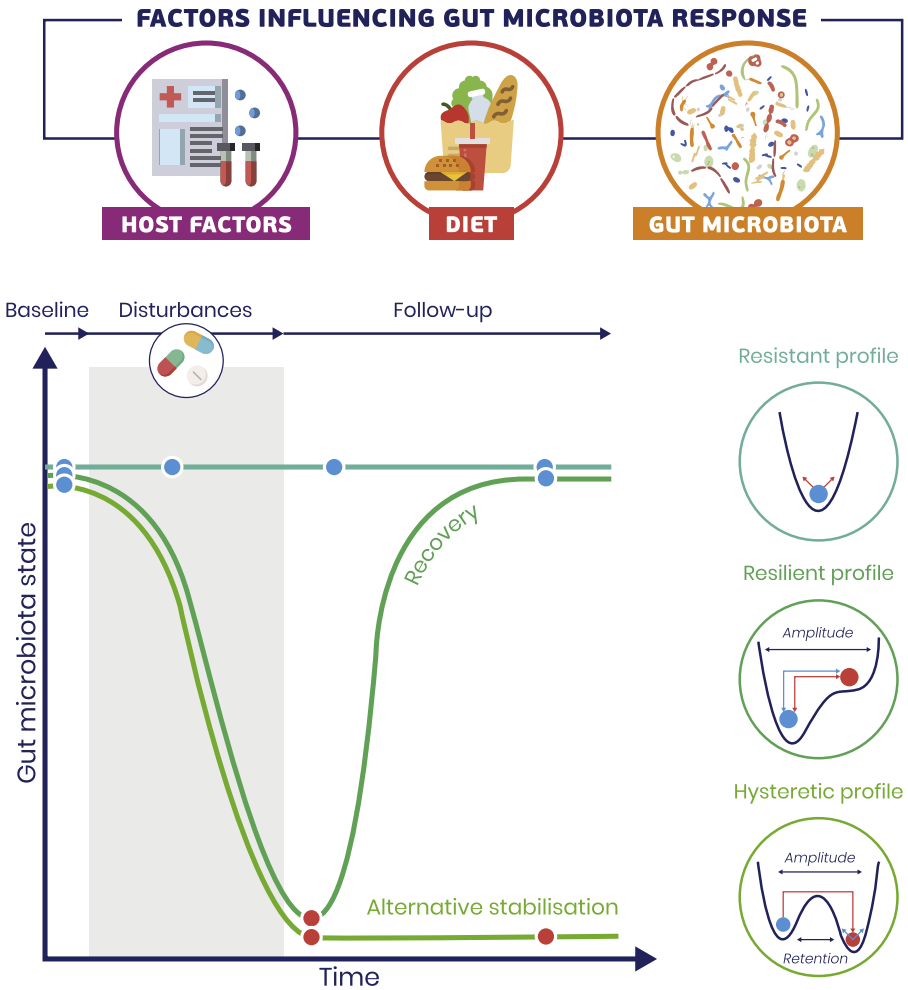

Fig. 3 Gut microbiota response to challenges. After a disturbance, gut microbiota can follow different kinetics, including resistance, resilience and hysteresis. Some factors including diet, host, and gut microbiota features may contribute to the differential responses. Gut microbiota state represented in the y-axis can be estimated by alpha- or beta-diversity for instance, or any markers like a particular taxon or functions. This state can vary over-time (x-axis) from baseline to follow-up measurement after disturbances. Here we show a two-microbiota states model represented by a cyan and a red dot. A resistant profile can be observed when microbiota state remains stable during disturbance with very few changes over -time (i.e., amplitude near zero, state stay as cyan dots over time). Variation (seen as stochastic here) can occur (little red arrows) but are not sufficient to change state as stability potential is high (represented as by a deep well). A resilient profile can be observed when microbiota state changes (amplitude measured higher than zero, from cyan to red dot, red arrow, shallow well) but recovers toat its initial state (cyan dot, cyan arrow). A hysteretic profile can be observed when microbiota state changes (amplitude measured higher than zero, from cyan to red dot, red arrow) and did not recover after disturbance during follow-up (retention measured higher than zero), and reaches an alternative state (red dot with stochastic variation, cyan arrows).

ecosystem (Beisner et al., 2003). A change from a stable state to an alternative stable state can also be explained by a continuous intrinsic modification of the ecosystem (e.g., microbiota diversity loss, pathogen invasion or a specific functional activity) that does not allow it to return to the initial state. In a simple two-species interaction experimental model involving *Bacteroides thetaiotaomicron* and *Klebsiella pneumoniae* strains, Khazaei and colleagues demonstrated that changing oxygen and nutrient led to hysteresis phenomena with multi-stable states. In this case, hysteresis was associated with specific metabolism and gene expression involving sugar transporters such as phosphotransferase systems (Khazaei et al., 2020). Several mechanisms have been hypothesized for a complex community, like species interactions and the presence of keystone species (Shetty et al., 2017; Faust et al., 2015). In summary, the hysteresis potential of an ecosystem, underexplored in human studies, is defined by its initial state, the potential amplitude of resilience, and the existence of tipping points allowing a retention phenomenon despite the end of the disturbance, whether deterministic or stochastic. Since gut microbiome states result from various stochastic and deterministic effects, several types of disturbance, with varying intensity, temporality and targets, could lead to different gut microbiome states, stable or transient.

Human Gut Microbiota Exposure to Acute Disturbances

Human gut microbiota is a dynamic ecosystem exposed on a daily basis to factors such as diet and xenobiotics. We discuss how gut microbiota from healthy subjects respond to short-term acute disturbances with a specific focus on studies that tracked gut microbiota dynamics during and after cessation of the challenge.

Gut Microbiota Response to Antibiotics

Antibiotics have been widely used since the Second World War and the industrial production of penicillin. Antibiotic drugs have been selected and modified to be active against pathogenic bacteria i.e., those causing infections. Strikingly, strict or opportunistic bacterial pathogens are very few when compared to the thousands of harmless bacteria, including those making most of the gut microbiota. Unfortunately, antibiotics are not selective against pathogenic bacteria and their use comes with the price of an impact on the gut bacteria as a whole. The effects of antibiotics on the gut microbiota depends on their pharmacodynamic and pharmacokinetic properties. When taken by the oral route, antibiotics are absorbed in the upper intestine (jejunum) and non-absorbed residues reach the colon where most gut bacteria reside. Hence, the residual concentration of antibiotics will depend on the efficiency of jejunal absorption. When taken parenterally, antibiotics are excreted via the bile and/or the urine. The bile excretion (into the gut) will thereby be connected to the residual antibiotic in the gut. Posology i.e., the quantities of antibiotics administered also matters. For instance, cefotaxime and ceftriaxone are two widely used third-generation cephalosporins that share a very similar spectrum but differ from one another by their bile excretion: 10% of cefotaxime is excreted in the gut compared to 40% of ceftriaxone. Accordingly, one would expect ceftriaxone to have greater impact on the gut than cefotaxime. However, the regimens also differed; cefotaxime is usually given 1 g three times a day while 1 g of ceftriaxone is given once a day, meaning that the intestinal concentrations in patients are probably very close. Indeed, a recent study reported no difference between the two drugs regarding their impact on the intestinal microbiota.

The anti-anaerobic spectrum of antibiotics is a matter of debate (Woerther et al., 2021) since the clinical spectrum of a given antibiotic is based on its activity on bacterial pathogens and its concentration in human tissues when administered at non-toxic dosages. Hence, the clinical spectrum may considerably differ from the impact on the gut microbiota, where very high concentrations of antibiotics can be achieved (Ruppé et al., 2018). An illustrative example is given by ciprofloxacin: it is not considered to be an anti-anaerobic drug from a clinical point of view, but it strongly affects the gut microbiota through significant bile excretion (Dethlefsen and Relman, 2011).

The gut microbiota itself brings even more complexity into the picture. Some intestinal bacteria can destroy beta-lactam residues via the excretion of beta-lactamases. When the microbiota is enriched in beta-lactamase—producing bacteria, it seems to confer overall protection to other intestinal bacteria. The duration of the perturbation caused by antibiotics seems to be variable, depending on the markers used as an endpoint. In 12 volunteers given a 4-day course of meropenem, vancomycin and colistin, the richness and diversity of the gut microbiota were partly restored three months after the exposure (Palleja et al., 2018). Interestingly, Shannon diversity, which has an evenness component, was restored faster than microbial richness, suggesting that some species were lost or severely depleted due to the treatment (Palleja et al., 2018). Modeling of the gut microbiome recovery following exposure to a cocktail of antibiotics led to the identification of a new alternative state, based on richness (Shaw et al., 2019). In 10 volunteers given a 7-day course of ciprofloxacin, vancomycin and metronidazole, recovery was observed after 49 days. Even when exposed to ciprofloxacin alone, the gut microbiota still differs from its baseline composition one month after the end of the exposure (de Gunzburg et al., 2017). The determinants of the duration of recovery remain to be identified.

The best connection between gut microbiota and bacterial infections is probably *Clostridioides difficile* infections (CDI). *C. difficile* germination and growth are inhibited by various intestinal species which transform primary bile acids into secondary bile acids (the latter being responsible for the inhibition effect) (Buffie et al., 2015). Because of the antibiotic intake, bacteria exerting an inhibition against *C. difficile* are eliminated and *C. difficile* spores can then germinate and produce the toxins which cause CDI, provided they possess the toxin genes. The gut microbiota is a major reservoir not only for *C. difficile*, but also for other bacterial pathogens that may be involved in infections (Tamburini et al., 2018). In terms of risk assessment for infections, quantification matters, since

antibiotics can alter the intestinal microbiota by eliminating susceptible bacteria (including those exerting the resistance to colonization) and promoting overgrowth of antibiotic-resistant microorganisms (Donskey et al., 2000; Ruppé et al., 2013).

Besides antibiotics, other drugs such as other antimicrobials (targeting viruses or protozoans) or pH-modifying drugs (such as proton pump inhibitors) can affect gut bacteria (Imhann et al., 2016; Maier et al., 2018; Vich Vila et al., 2020). *Helicobacter pylori* eradication treatment consists most commonly of antibiotics (amoxicillin, clarithromycin, metronidazole, tetracycline) and proton pump inhibitors, sometimes complemented with bismuth (quadruple therapies) (Malfertheiner et al., 2017). Recently, the effect on the gut microbiota of three different *Helicobacter pylori* eradication treatments was compared in a large study enrolling 1620 subjects (Liou et al., 2019). This study showed that the magnitude of gut microbiota alteration and recovery speed depended on the treatment used. A course of triple therapy was associated with recovery within eight weeks, while concomitant therapy and quadruple therapy both induced more durable alterations, up to 1 year (Liou et al., 2019). Other studies also observed variable time of gut microbiota recovery following Hp eradication therapy (Gotoda et al., 2018; Hojo et al., 2018; Yanagi et al., 2017). Altogether, these studies highlight that the gut microbiota response to antibiotics and potentially other drugs is variable between subjects and treatments.

Gut Microbiota Response to Travel

Traveling abroad has been hypothesized to affect the composition of the gut microbiota in that it exposes the subject to potential stressors such as diet change, food and water contaminated by fecal material, and occasional drugs such as those used for malarial prophylaxis. Nonetheless, a first study on the gut microbiota's long-term stability did not report any remarkable effect of traveling among the five subjects who were followed (Rajilić-Stojanović et al., 2013). Using 16S rRNA profiling, Ruggles et al. analyzed the gut microbiota of five adults and two children living in an urban environment and visiting a rainforest village for 16 days. They did not observe any significant change in the microbiota of the adults. However, the microbiota of the two children tended to drift toward the villagers' microbiota (Ruggles et al., 2018). Regarding the acquisition of multidrug-resistant bacteria during travel (and especially multidrug-resistant Enterobacterales, MRE), this hypothesis has been tested by various cohorts, including travelers from industrialized countries to other destinations such as tropical regions. As antibiotic resistance has become globalized and especially hits low- and middle-income countries, several studies reported a high rate of MRE acquisition in the gut of travelers (Mulvey et al., 2016; Ruppé et al., 2015). Fortunately, the median of intestinal carriage of MRE after return was short (<1 month). Nonetheless, travelers appeared to be long-term carriers, some of them still carrying the travel acquired MRE one year after return. A subsequent study observed that the gut microbiota of long-term carriers differed from that of fast-clearers (Leo et al., 2019). As for the microbiota's global composition, only minor changes (an increase of Proteobacteria) in the microbiota composition were observed after traveling to a tropical region (Leo et al., 2019). The same study observed that travelers with gut microbiota enriched in *Prevotella copri* were more prone to diarrhea than others. The microbiota of travelers who acquired an MRE was not different from that of travelers who did not, a finding which was recently confirmed in a cohort of 40 Swiss traveling to India (Pires et al., 2019). Using qPCR, another study involving 122 Dutch travelers showed a high rate of acquisition of antibiotic resistance genes (ARG) during their journey, especially those encoding extended-spectrum beta-lactamases and plasmid-mediated quinolone resistance (Von Wintersdorff et al., 2014). A similar ARG enrichment pattern (especially ARG encoding resistance to sulfonamides and trimethoprim) was observed using shotgun metagenomics in 35 Swedish students returning from the Indian subcontinent or Africa (Bengtsson-Palme et al., 2015).

While these studies focused on travel as a source of infection, other studies focused on diet contribution. In one study of the gut microbiota from Chinese subjects who experienced a 6-month trip from Beijing to Trinidad and Tobago, a shift in gut microbiota was observed, using global gut microbiota structure by beta-diversity, with higher similarity toward that of local subjects followed by recovery to pre-travel composition, one month after return. The shift was thought to be in response to adherence to the local diet, with a higher intake of fish and seafood, dairy products and refined grains (Liu et al., 2019). Vangay et al. showed that a more extreme challenge, i.e., immigration from Thailand to US, induced a shift in gut microbiota within nine months of US residence, in parallel to increase of weight and change of diet (increase in protein content and reduced diet diversity). The major changes consisted of increasing the ratio *Bacteroides*/*Prevotella* (Vangay et al., 2018). Globally, the effect of travel on gut microbiota is multifactorial in response to a new environment with changed microbes and diet.

Gut Microbiota Response to Dietary Changes

Diet, and more specifically the diversity of fruits and vegetables, is one of the factors most associated with variation of the microbiota in cross-sectional studies (Falony et al., 2016; Manor et al., 2020, Mcdonald et al., 2018), the healthy food diversity index being positively correlated with microbiota alpha-diversity (Claesson et al., 2012). Various studies have investigated gut microbiota's response to diet (for reviews, see (Leeming et al., 2019; Leshem et al., 2020; Sonnenburg and Bäckhed, 2016). Most of the studies that monitored the longitudinal response of gut microbiota during a dietary intervention, either through an overall diet shift or consumption of a single nutrient, revealed a variable magnitude of response among individuals, followed by a rapid return (within days) to baseline. Notably and counter-intuitively, a monotonous diet was not associated with higher gut microbiota stability over a short period compared to a variable diet (Johnson et al., 2019; Gurry et al., 2018). The hallmark study of David et al. tracked the dynamics of the gut microbiota of subjects that followed a 5-day diet enriched solely by either an animal or a plant-based product (David et al., 2014b). Fiber content reached 25.6 g per 1000 kcal on the plant-based diet while it fell

to nearly zero on an animal-based diet. Shannon's diversity did not significantly change in any of the diets. In contrast, distance to baseline (assessed by Jensen–Shannon distance) increased rapidly but transiently only for subjects adopting the animal-based diet. This change occurred by one day after the start of the diet and was transient as beta-diversity did not differ from baseline within two days following cessation of the diet. Transient changes in the relative abundance of specific taxa were also observed in subjects who consumed a diet enriched with a single dietary compound (Martínez et al., 2013; Hiel et al., 2019). For example, a 2-week intake of 9 g/day of inulin resulted in a transient shift of gut microbiota, assessed by sparse PLS-DA, and increased *Bifidobacterium*. The initial state was restored three weeks following cessation of the inulin enriched diet (Hiel et al., 2019).

Interestingly, a recent study enrolled 80 participants with two different dietary challenges of 2 weeks each (fructooligosaccharides and polydextrose), followed by a 4-week follow-up. Both diets induced global gut microbiota changes, assessed by alpha- and beta-diversity, which were maintained in the follow-up period, as well as subject-specific changes (Creswell et al., 2020). However, most of the studies so far have been limited to the study of gut microbiota independent of clinical data. In a recent study, subjects were exposed to a 12-month controlled diet, either a low-carbohydrate or a low-fat diet, for weight loss (Fragiadakis et al., 2020). A transient alteration of gut microbiota was observed, assessed by a change in Bray-Curtis dissimilarity, despite continuously controlled diet, and weight loss, showing that resilience of gut microbiota was independent of clinical evolution. In another study, gut microbiota changes following a 14-day diet reduced in carbohydrates, were found to be larger within the first 7 days following the start of the diet than after 7 days (Mardinoglu et al., 2018). This illustrates the microbiota's capacity to rapidly respond to a drastic dietary change, so as to stabilize even during the maintenance of the diet. These studies highlight that host factors may exert a homeostatic force on gut microbiota.

Gut Microbiota Response to Exogenous Strains

While the challenges mentioned above are expected to alter gut microbiota, the ingestion of exogenous bacterial strains introduced through diet or for a medical purpose (live biotherapeutics) constitute a relatively modest challenge for gut microbiota. Shown by multiple studies, reviewed by Derrien and van Hylckama Vlieg (2015); Kristensen et al. (2016), the resulting resistance or permissivity to the newly ingested strains is relevant to uncover ecological factors that are associated with the plasticity of gut microbiota. While it is common to refer to "colonization resistance" to invading pathogens (Buffie and Pamer, 2013), the term has been little used in the context of probiotics. Most probiotic strains transiently integrate the endogenous microbiota in humans (Alvarez et al., 2020; Mcnulty et al., 2011; Zmora et al., 2018), perceived as evidence for the resilience of gut microbiota, although at a much lower magnitude than other challenges mentioned above. Occasionally some strains persist longer, from weeks to months, in some subjects. For example, the persistence of the strain *B. longum* AH1206 in gut microbiota from healthy subjects up to 6 months post-cessation of ingestion was associated with a lower baseline level of resident *B. longum* and of genes involved in carbohydrate utilization (Maldonado-Gómez et al., 2016). Identification of gut microbiota more permissive to exogenous strains has gained interest (Walter et al., 2018). In a study combining animal and human data, the increased persistence of a specific strain from a multistrain fermented milk product, *Lactococcus lactis* CNCM I-1631, depended on the initial configuration in both animals and human. The gut microbiota permissivity to this strain was associated with greater modulation in gut microbiota based on beta-diversity in both animal and human (Zhang et al., 2016). The integration and persistence of an 11-strain mix of lactic acid bacteria and bifidobacteria in human gut microbiota were monitored in various upper and lower intestinal locations coupled with multi-omics and a dense sampling scheme (Zmora et al., 2018). Ingested strains were transiently detected in gut microbiota from healthy subjects, with variability between ingested strains, subject and intestinal locations. In addition, individualized gut mucosal colonization capacity correlated with baseline host transcriptional and microbiome features (Zmora et al., 2018). It seems likely that results from studies based on a mixture of lactic acid bacteria and bifidobacteria will help decipher the ecological principles behind gut microbiota persmissivity and plasticity. This will hopefully translate to intestinal-based next-generation probiotics/live biotherapeutics. Indeed, *Butyricicoccus pullicaecorum* 25–3^{T}, *Oxalobacter formigenes* (Duncan et al., 2002), *Anaerobutyricum soehngenii* (previously *Eubacterium hallii* (Gilijamse et al., 2020)), *Akkermansia muciniphila* (Perraudeau et al., 2020) were also transiently detected in human gut microbiota from healthy subjects following ingestion. Interestingly, strain-level tracking analysis of donor strains introduced by fecal microbiota transplantation (FMT) indicated better integration in type 2 diabetic subjects when closely related strains were present in the recipient's gut (Bouter et al., 2017). Larger and denser longitudinal studies are required to elucidate the ecological factors associated with permissivity or resistance of gut microbiota to exogenous strains, for example the presence of cooperative species (Machado et al., 2021).

Although we have addressed only the fate of ingested strains in a microbial ecosystem not exposed to an additional stressor, gut microbiota might be more permissive to ingested strains and more responsive following a stressor such as antibiotic treatment (Suez et al., 2018).

Gut Microbiota Stability and Resilience Factors

Multiple cross-sectional studies have identified diverse microbial, host and environmental factors that contribute to gut microbiota variation. Emerging longitudinal studies have identified how factors may contribute to variation in response to disturbances. An overview is provided in (Fig. 3).

Gut Microbiota Composition

Alpha-Diversity

With the advent of sequencing-based approaches, many studies have converged toward the association of reduced richness or diversity with a variety of chronic diseases (reviewed in (Durack and Lynch, 2019; Mosca et al., 2016)), leading to acceptance of high alpha-diversity as a surrogate for "good functioning" of gut microbiota. Different studies have shown that gut microbiota richness and diversity is variable between human individuals and between populations. Gut microbiota from non-western populations typically harbors higher alpha-diversity compared to gut microbiota from industrialized populations, suggesting that naïve gut microbiota that preceded industrialization have been altered through cumulated factors, among which diet enriched in fat and sugars and depleted in fibers, increased intake of antibiotics, reduced exposure to microbes (Sonnenburg et al., 2016). From a microbial perspective, alpha-diversity has been associated with enterotypes (Tap et al., 2017; Vieira-Silva et al., 2016), driven by Clostridiales/Ruminococcaceae, *Bacteroides,* or *Prevotella*. The recent integration of absolute bacterial count profiling has led to an additional configuration, *Bacteroides* type 2, which harbors the lowest microbial richness at genus and gene level (Vieira-Silva et al., 2019, 2020). Based on functional analysis, Le Chatelier et al. reported that subjects with high gut microbiota richness were characterized by a higher production capacity for organic acids—including lactate, propionate, and butyrate—combined with a higher hydrogen production potential. Gut microbiota alpha-diversity has been associated with multiple host factors including transit (Roager et al., 2016; Vandeputte et al., 2016), demography, clinical markers related to metabolism and immunity (Manor et al., 2020; Zhernakova et al., 2016; Cotillard et al., 2013, LE Chatelier et al., 2013). The low richness *Bacteroides* 2 enterotype has been associated with systemic inflammation and has a high prevalence in loose stools in humans (Vieira-Silva et al., 2019, 2020).

While higher alpha-diversity has been associated with better resilience in environmental ecosystems (Mccann, 2000), there are currently fewer studies for the human gut microbiota. Elderly subjects with low initial microbiota Shannon diversity had lower temporal stability over a 3-month period (Jeffery et al., 2016). Similarly, in 85 adult subjects, diversity, measured by Shannon Diversity Index, over a 3-month period, was negatively correlated with intra-individual beta-diversity, based on UniFrac distances. *Bacteroidaceae* members were more abundant when gut microbiota was more stable (Flores et al., 2014). Based on metagenomics, the instability (assessed by higher Bray-Curtis dissimilarity) was negatively associated with Shannon index values (Mehta et al., 2018). In a large population-based cohort, *Bacteroides* abundance and baseline species Shannon diversity were positively associated with short-term stability (17 ± 3.3 days), suggesting that gut microbiota with higher alpha-diversity are more stable (Byrd et al., 2020). This converged with findings from a large cohort of 1200 subjects over five years (Frost et al., 2021). Other studies investigated the association between alpha-diversity and stability in the presence of stressors such as diet or FMT. Subjects with higher richness at baseline were less prone to microbiota changes following a 5-day consumption of diet enriched in 40 g of fibers/day (Tap et al., 2015). This was consistent with another study in which subjects with higher baseline Inverse Simpson diversity had a more stable gut microbiota in response to different diets (Salonen et al., 2014). In the context of FMT in type 2 diabetic subjects, gut microbiota from recipient subjects with higher gut microbiota diversity exhibited higher resilience to donor's gut microbiota within the weeks following FMT (Kootte et al., 2017).

Despite small sample size, these studies suggest that, in humans, gut microbiota with higher alpha-diversity is globally more stable and resilient. However, these studies were often limited to a few time points, highlighting the need to perform denser time-series.

The Case of Keystone Species

Keystone species are an example of species, the absence of which would significantly impact the overall ecosystem, despite being of low abundance (Banerjee et al., 2018), given their specific function. In the human gut, dedicated mathematical approaches, based on longitudinal data (Trosvik et al., 2010) or cross-sectional studies (Levy and Borenstein, 2013), have identified *Bacteroides fragilis* and *Bacteroides stercosis* (Fisher and Mehta, 2014), Actinobacteria, and Proteobacteria as candidate keystone species (Trosvik et al., 2010). *Ruminococcus bromii* was previously coined as a keystone species, based on its specialty in the metabolism of recalcitrant polysaccharides, such as resistant starch, which would favor other bacteria's stimulation (Ze et al., 2012, 2013). *A. muciniphila* was proposed as keystone species based on its specific metabolism of mucins, which would support the microbial community in the mucosal environment through the release of mucin sugars (Chia et al., 2018). The removal of candidate keystone species is a direct approach to elucidate their contribution to the global ecosystem. An *in vitro* study examined the effect of removing species on a synthetic community of 14 bacterial strains that represented major species of the human gut microbiota (Gutiérrez and Garrido, 2019). The removal of *Bacteroides dorei* induced the largest shift in gut microbiota composition and metabolites, reflected by a low lactate concentration and higher production of acetate. Overall, these studies suggest that some species' metabolism contributes more than others to the ecosystem functioning and response to disturbances. However, to date, few studies have identified how the absence of specific functional keystone species impacts the response of gut microbiota to disturbances. This area would benefit from the advances in metabolic modeling (Muller et al., 2018) and from the integration of ecological functional units, such as guilds (Wu et al., 2021).

Gut Microbiota Function

Functional redundancy has been a topic of interest as a potential factor of gut microbiota stability and resilience (Moya and Ferrer, 2016). Functional redundancy refers to the fact that different multiple distinct taxa or genomes are able to perform the same focal

biochemical function (Louca et al., 2018). As such, while gut microbiota composition is highly variable between subjects, gut microbiota function is less variable (Huttenhower et al., 2012). Vieira-Silva et al. assessed the functional redundancy through the number of microbial taxa encoding a specific gut metabolic module present in a single sample, in a cohort of 277 samples, and found that functional redundancy was reduced in the low-richness *Bacteroides* enterotype, potentially suggesting a decreased resilience to perturbation (Vieira-Silva et al., 2016). Carbohydrates are abundant in human diets, among which complex polysaccharides, resistant to host digestive enzymes, constitute the major source of nutrients of gut microbes that are equipped with CAZymes, whose number and substrate specificity vary greatly among species (Flint et al., 2012).

Interestingly, functional analysis of species associated with gut microbiota recovery in response to antibiotics, revealed enhanced metabolic potential toward utilization of carbohydrates, both host and dietary derived, including multiple *Bacteroides* (Chng et al., 2020), in line with their greatest variety of glycosyl-hydrolases (Kaoutari et al., 2013). The versatility of the use of dietary and endogenous glycans is considered as a marker of metabolic fitness and has been well studied for *Bacteroides* and *Bifidobacterium* (Singh, 2019). Metabolic cross-feeding between intestinal members was reported to contribute to gut microbiota stability. In an *in vitro* study, communities with low numbers of lactate-utilizing bacteria (metabolized into propionate or butyrate) were less stable and more susceptible to lactate-induced perturbations (Wang et al., 2020). Similarly, enhanced metabolic cooperation between prototrophic and auxotrophic strains relying on B-vitamin allowed the community's stability in the context of dietary deficiencies (Sharma et al., 2019). Overall, the contribution of ecological parameters such as species-species interactions and cross-feeding is understudied and warrants future investigation.

Host and Environmental Factors

Host and environmental factors are associated with gut microbiota variation (**Fig. 1**), yet few studies have examined how different factors impact gut microbiota stability and response to disturbances. Gut microbiota temporal variability was reported to be higher in diseases including metabolic (Frost et al., 2021) and inflammatory bowel diseases (Martinez et al., 2008) compared to healthy controls, especially during disease activity (Lloyd-Price et al., 2019). However, few studies examined how specific clinical markers and environmental factors contribute to gut microbiota stability. In healthy adults, exposure to bowel laxatives and antibiotics were associated with lower gut microbiome stability (Mehta et al., 2018). In a large cohort of over 1000 subjects, the gut microbiota stability, although limited to the study of two time-points five years apart, was associated with sex, high household income, and preserved exocrine pancreatic function (Frost et al., 2021). A recent study evaluated how multiple hosts and diet factors contributed to short-term (17 days) gut microbiota stability. While BMI and circulating triglyceride levels were negatively correlated to stability, some food items, including sweet and raw fruits, were positively correlated (Byrd et al., 2020). The detailed daily tracking of gut microbiota and dietary intake over 17 days, revealed that microbiome stability was positively correlated with diet diversity in the absence of other short-term (17 days) perturbations (Johnson et al., 2019), which also holds for longer-term (5 years) perturbations (Frost et al., 2021).

Other host factors known to interact with microbiota such as IgAs and the mucus layer (**Fig. 2**) have been studied for their role in maintaining bacterial species' stability. For instance, mucin metabolism by primary degraders can serve as a source of nutrients for other bacterial strains, as shown *in vitro* with beneficial microbes such as butyrate producers (Belzer et al., 2017), or pathogens such as *C. difficile* (Engevik et al., 2020). A recent study showed that administration of mucin-derived O-glycans in mice exposed to clindamycin, induced a faster recovery of global gut microbiota structure (assessed by alpha and beta-diversity), with enrichment of *A. muciniphila* and reduction of *C. difficile* (Pruss et al., 2021). This suggests a critical role of mucins and their metabolism by intestinal bacteria in the ecosystem's recovery following a perturbation. The secretion of IgA represents another host-mediated factor that contributes to shaping gut microbiota composition (Kubinak and Round, 2016; Huus et al., 2021). Subjects deficient for serum IgA, characterized by a lower level of fecal secretory IgA and undetectable IgA coating of bacteria, had a trend to lower alpha-diversity but similar gut microbiota stability over a 6–10 month interval compared to healthy subjects (Catanzaro et al., 2019). Last, mechanistic studies based on single species showed that the ability of *B. fragilis* to resist antibiotic treatment relied on the expression of commensal colonization factors within colonic crypts. Thus, the niche within colonic crypts represents a reservoir for bacteria to maintain long-term colonization (Lee et al., 2013) underlining the importance of host factor contributions to gut microbiota stability.

Microbiota-Targeted Approaches to Promote Recovery after an Acute Disturbance

The concomitant emergence of chronic diseases has stimulated interest in the design of strategies targeting the restoration of microbiota-host crosstalk (Vieira et al., 2016; Markey et al., 2020), clinical relevance to promoting gut microbiota recovery following a disturbance. Although CDI is the major clinical indication for which the global restoration of gut microbiota is demonstrated to be beneficial (Baunwall et al., 2020), antibiotic intake has been most studied in relation to gastrointestinal symptoms (Mekonnen et al., 2020, Mcfarland et al., 2016). There is increasing interest in restoring a microbial ecosystem (Gagliardi et al., 2018) and in favoring its recovery following disturbance (Shaw et al., 2019), given that slow recovery can induce higher susceptibility to pathogen colonization (Isaac et al., 2016), and can increase the risk of developing an infection or chronic disease (Sommer et al., 2017).

In this section we review recent approaches (microbial and other) in which gut microbiota recovery was assessed, specifically in the context of antibiotics as this is a topic of high interest, especially if associated with gastrointestinal symptoms.

Microbial-Based Approaches

The clinical association between gut microbiota restoration and clinical benefits in CDI prompted several studies to monitor engraftment of complex microbial ecosystems. The gut microbiota manifests low colonization resistance to the donor's gut microbiota (Fuentes et al., 2014) and durable changes in taxonomy and resistome (Blount et al., 2019; Kwak et al., 2020). As there is increasing interest to shift from undefined microbial ecosystems to defined strain consortia (Vázquez-Castellanos et al., 2019), we address here recent studies in which single or multistrain-based interventions were performed in humans, dependent or not on clinical benefits.

The effect of multi-strain or single strain lactic acid bacteria and bifidobacteria on human gut microbiota recovery following antibiotic treatment has been well studied. However, many studies have relied on low resolution profiling approaches, which did not allow capture of the whole community (reviewed in (McFarland, 2014)). Some studies in adults showed the capacity of some bacterial or fungal strains to modulate the recovery of gut microbiota (Guillemard et al., 2021; Suez et al., 2018; Macpherson et al., 2018; Kabbani et al., 2017). In a high-resolution sampling scheme, Suez et al. showed that ingestion of a mixture of 11 strains (lactic acid bacteria and bifidobacteria, *L. acidophilus*, *L. casei*, *L. casei* sbsp. *paracasei*, *L. plantarum*, *L. rhamnosus*, *B. longum*, *B. bifidum*, *B. breve*, *B. longum* sbsp. *infantis*, *Lactococcus lactis*, and *Streptococcus thermophilus*) by healthy subjects following broad-spectrum antibiotic intake (7-day course of ciprofloxacin and metronidazole) delayed the recovery of both the composition and function of gut microbiota up to several months, based on different intestinal locations (Suez et al., 2018). However, in this study, clinical outcomes related to slower gut microbiota recovery were not assessed. Given the heterogeneity in lactic acid bacteria and bifidobacteria functions and activity, and their interaction with host and gut microbiota (Derrien and van Hylckama Vlieg, 2015), a rational selection of strains is fundamental. Our group specifically selected bacterial strains such as *L. paracasei* CNCM I-3689 and *L. rhamnosus* CNCM I-3690 for their anti-inflammatory and/or anti-pathogenic capacities (Archambaud et al., 2012; Crouzet et al., 2018; Natividad et al., 2018; Martín et al., 2019). *L. paracasei* CNCM I-3689 was shown to reduce the colonization of *Enterococcus faecalis* (VRE) and promoted a faster recovery of some members of the phylum Bacteroidetes and propionate levels in mice exposed to clindamycin (Crouzet et al., 2018). A dairy product containing the strain *L. paracasei* CNCM I-1518 was previously shown to reduce both antibiotic-associated diarrhea (AAD) and *Cd*-associated diarrhea (CDAD) occurrence in hospitalized elderly (Hickson et al., 2007; Dietrich et al., 2014). In a randomized clinical trial, a 7-strain fermented milk product containing yogurt starters and *L. paracasei* CNCM I-1518, *L. paracasei* CNCM I-3689, and *L rhamnosus* CNCM I-3690 was administered to subjects infected with *H pylori* and exposed to eradication treatment (14 days Pantoprazole, clarithromycin, and amoxicillin). A lower intra-subject beta-diversity distance from baseline was observed together with a lower abundance of *Escherichia*, *Shigella* and *Klebsiella* was reported up to one month following cessation of the treatment in subjects who consumed the multistrain product. However, the gut microbiota's alteration was not reflected by gastrointestinal symptoms (Guillemard et al., 2021). In another study, no effect on alpha and beta-diversity compared to the control group was reported after 14-days of ingestion of freeze-dried *L. helveticus R0052* and *L. rhamnosus* R0011 by subjects undergoing amoxicillin-clavulanate treatment, however the supplementation with the probiotic significantly reduced the duration of diarrhea (Macpherson et al., 2018). The ingestion of the yeast *Saccharomyces boulardii* CNCM I-745, used to prevent and treat AAD, was shown to prevent the increase in *Parabacteroides* and decrease of *Ralstonia* in healthy volunteers treated with seven days of amoxicillin-clavulanate in the follow-up (14 days) together with a reduction in AAD scores (Kabbani et al., 2017). Altogether, these studies highlight the heterogeneity among studies of gut microbiota recovery from antibiotics and exogenous strains, and between gut microbiota recovery and clinical outcomes, currently mostly assessed through the study of short-term gastrointestinal symptoms. Immune or other clinical markers might help to better evaluate the association between gut microbiota recovery and host markers.

The extension of the range of organisms with potential health benefits, referred to as next-generation probiotics, or live biotherapeutics, has been an intensive research topic (El Hage et al., 2017; O'toole et al., 2017; Veiga et al., 2020). Animal and *in vitro* models have been used to test the capacity of some strains, rationally selected for a specific function, to modulate the response of gut microbiota following antibiotic administration. In mice bi-colonized by *B. thetaiotaomicron* and *Bifidobacterium adolescentis*, a recovery in diversity (Simpson diversity), concomitant with a higher level of degradation of plant and mucin carbohydrates, was observed compared to mice only fed with *B. thetaiotaomicron*, findings which extended associations found in human (Chng et al., 2020). In the *in vitro* model, Mucosal Simulator of the Human Intestinal Ecosystem (M-SHIME), a 7-member propionogenic bacterial consortium was tested for its capacity to restore gut microbiota following 3-day clindamycin administration (El Hage et al., 2019). The consortium was composed of a lactic acid bacterium, *Lactobacillus plantarum*, and six bacterial strains relying on different propionate production pathways (succinate, acrylate, and propanediol): *Bacteroides thetaiotaomicron*, *Ruminococcus obeum*, *Coprococcus catus*, *Bacteroides vulgatus*, *Akkermansia muciniphila*, and *Veillonella parvula*. The administration of the consortium induced faster restoration of function, reflected by enhanced propionate production and structure of gut microbiota. Recently, the ingestion of a rationally selected consortium (VE303) of eight bacterial strains within *Clostridium* clusters IV, XIVa, and XVII, for their ability to restore colonization resistance to *C. difficile*, was shown to enhance the recovery of some taxa in healthy volunteers exposed to a 5-day treatment of vancomycin (Bobilev et al., 2019). These studies are relevant to guide future selections of bacterial strains targeted for a specific functional capacity (Veiga et al., 2020), especially those promoting faster recovery of the ecosystem.

Dietary Approaches

As diet is a major direct source of nutrients for intestinal bacteria, there is high relevance to study the contribution of diet in shaping microbiota recovery following a challenge. Two hallmark animal studies have examined the effect of diet, and especially fiber intake, on the extent of gut microbiota alteration and recovery following antibiotic intake. In one study, a fiber-deficient diet exacerbated

microbiota alteration and delayed recovery in humanized microbiota associated mice exposed to 5-day ciprofloxacin administration, due to the alteration of the mucus layer that hampered the recovery of mucin users such as *Bacteroides* (Ng et al., 2019). In agreement with that study, the response of the single species *B. thetaiotaomicron* to amoxicillin was shown to depend on nutrients. Mice fed on normal chow (rich in host-indigestible fiber), purified diet (rich in host-digestible carbohydrates), or glucose had variable gut microbiota responses to amoxicillin, highlighting diet as an approach to mitigate the response of gut microbiota to disturbance (Cabral et al., 2019). In addition, the ingestion of single ingredients such as grape pomace and seed polyphenol extracts (Lu et al., 2019), or inulin (Lin et al., 2020), could induce the recovery of gut microbiota in mice exposed to antibiotics, in support of the relevance of diet as an attractive strategy to mitigate the pervasive effect of antibiotics on gut microbiota. A recent clinical study showed that a fiber-free diet reduced the recovery of the gut microbiome on both the composition and metabolite production (Tanes et al., 2021). Future larger clinical studies examining how dietary habits (nutrients, food groups, or overall diet diversity) are associated with gut microbiota response to a challenge will be crucial. Given the high inter-individual co-variation between gut microbiota variability and dietary habits (Johnson et al., 2019), dietary strategies would need to be tailored based on the subject's diet and gut microbiota. Other strategies, non-diet based, have been studied, such as an activated charcoal-based adsorbent (DAV132), which, administered for seven days in healthy subjects concomitantly exposed to 5 days of moxifloxacin induced protection of the gut microbiota gene richness (up to 5 weeks) and of 81% of the species (de Gunzburg et al., 2017). These studies highlight the relevance of protecting gut microbiota from acute stressors with design strategies that rely on diverse modes of action, with either specific or more global impact.

Conclusions

Recent efforts to study microbiota resilience have advanced our understanding of gut microbiota stability and response to challenges. This knowledge may help design novel solutions to prevent critical transitions that durably alter host physiology. Many studies relied on the composition of gut microbiota. However, given high functional redundancy, it will be crucial to decipher the functional response at the genetic, activity, and metabolite levels and determine how they are associated with clinical outcomes. To bridge the gap, detailed longitudinal studies coupled with complementary multiomics based-approaches, and clinical outcomes, will be required. We expect that such studies will improve identification of key species and functions associated with a diverse and resilient. Finally, recent efforts in *in silico* modeling will help predict gut microbiome temporal dynamics in response to disturbances and ultimately improve human health through targeted solutions.

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