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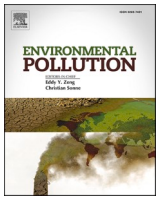

Review

Dysregulation along the gut microbiota-immune system axis after oral exposure to titanium dioxide nanoparticles: A possible environmental factor promoting obesity-related metabolic disorders☆

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ABSTRACT

Food additives are one major hallmark of ultra-processed food in the Western-diet, a food habit often associated with metabolic disorders. Among these additives, the whitener and opacifying agent titanium dioxide (TiO_2) raises public health issues due to the ability of TiO_2 nanoparticles (NPs) to cross biological barriers and accumulate in different systemic organs like spleen, liver and pancreas. However before their systemic passage, the biocidal properties of TiO_2 NPs may alter the composition and activity of the gut microbiota, which play a crucial role for the development and maintenance of immune functions. Once absorbed, TiO_2 NPs may further interact with immune intestinal cells involved in gut microbiota regulation. Since obesity-related metabolic diseases such as diabetes are associated with alterations in the microbiota-immune system axis, this raises questions about the possible involvement of long-term exposure to food-grade TiO_2 in the development or worsening of these diseases. The current purpose is to review the dysregulations along the gut microbiota-immune system axis after oral TiO_2 exposure compared to those reported in obese or diabetic patients, and to highlight potential mechanisms by which foodborne TiO_2 NPs may increase the susceptibility to develop obesity-related metabolic disorders.

1. Introduction

The wide use of engineered nanomaterials in various industrial sectors is due to the innovative properties of constitutive nanoparticles (NPs) linked to their size range (1–100 nm). Such small dimensions give them a high surface-to-volume ratio that allows them to acquire unique physicochemical properties (i.e., optical, mechanical or photocatalysis) compared to their bulk forms (Nel et al., 2006; Weir et al., 2012; Xia et al., 2009). However, these advantages have led in turn to an increasing use in daily consumer products (e.g., drugs, food, clothing, cosmetics), raising concerns about the possible risks for human health after chronic exposure through different routes including inhalation and transdermal and oral exposure. The concerns are related to the strong ability of NPs to cross biological barriers such as lungs, intestine, blood-brain barrier and placenta, and their accumulation in systemic organs. Some NPs are also known as adjuvant to immune responses, as genotoxic substances and cancer-risk factors, or as possible environmental factors favouring the development of food allergies (Bettini et al., 2017; Guillard et al., 2020; Heringa et al., 2018; Issa et al., 2022; Javurek et al., 2017; Pele et al., 2015). In addition, several studies indicate that NPs could also act as endocrine disruptors chemicals (EDCs), possibly promoting the development of thyroid, reproductive and metabolic disorders in humans, but their mode of action remains unknown (Priyam et al., 2018). However, the metabolic-related hazards after chronic oral exposure to inorganic NPs are poorly documented compared to other routes of exposure, while NPs are added in the human diet due to their common use as processing aids and additives during food manufacturing, as well as in food packaging and storage (Chaudhry et al., 2008; Hwang et al., 2012; Srinivas et al., 2010). Several *in vivo* and *in vitro* studies highlighted various effects of foodborne (metals and metals oxide) NPs on the immune system (proinflammatory or immunosuppressor) and intestinal microbiota (biocidal) (Barreau et al., 2021; Bettini et al., 2017; Lamas et al., 2020), two body's compartments where chronic dysregulation in their intricate dialogue is viewed as promoting

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metabolic disorders such as obesity (Scheithauer et al., 2020; Sommer and Bäckhed, 2013). In this context, whether daily exposure to food-borne NPs may participate to the global spread of obesity worldwide is currently under investigation.

Among these NPs, titanium dioxide (TiO_2) is widely used worldwide as food additive for its colouring/opacifying and brightening properties (e.g., candy, pastries, ice cream, ready-made dishes, etc.) (Peters et al., 2014; Weir et al., 2012; Yang et al., 2014). Food-grade TiO_2 is also used as an antimicrobial agent in food contact materials (Yu et al., 2011) or as a coating agent upon pharmaceutical tablets and oral capsules (Palugan et al., 2022). The food additive TiO_2 (referred to as E171 in Europe) is manufactured as a powder containing 17–55% of NPs (number-based) depending on commercial sources, exposing the consumers orally to a significant amount of non soluble TiO_2 NPs (Bettini et al., 2017; Weir et al., 2012; Yang et al., 2014). In 2021, the European Food Safety Authority (EFSA) estimated that exposure rates to food-grade TiO_2 ranged from 0.9 to 31.3 mg/kg body weight (bw)/day (d) in children and from 0.3 to 15.9 mg/kg bw/d in adults, depending on the consumption *scenario* (EFSA Panel on Food Additives and Flavourings, 2021). As a result of daily oral intake, NPs pass the epithelial barrier from the small to the large intestine (Coméra et al., 2020) where they are potentially managed by the intestinal immune cells (i.e., macrophages and dendritic cells), but can also directly reach the systemic circulation *via* passive passage and accumulate in various organs (e.g., liver, spleen, placenta) up to a materno-foetal transfer in humans (Guillard et al., 2020; Heringa et al., 2018). Noticeably, the non-absorbed fraction of TiO_2 NPs stagnates in the lumen of the gastrointestinal (GI) tract where NPs can directly interact with the gut microbiota in addition to epithelial cells lining the gut lumen. The potential hazards due to oral exposure to TiO_2 leads to numerous debates in the scientific community and, in the face of uncertainties, has led the public policies to advocate the precautionary principle and to suspend the use of this food additive, starting in France in 2020, followed by a ban at European level in 2022. The ban of food-grade TiO_2 was based on its capacity to induce oxidative stress (Dorier et al., 2017) and genotoxicity (Charles et al., 2018), as well as to its ability to alter intestinal and systemic immune response and promote precancerous colorectal lesions in rodents (Bettini et al., 2017; Bischoff et al., 2022; Nogueira et al., 2012). These effects observed in rodents were suggested to occur in Humans (Bischoff et al., 2020). Due to its biocidal properties, TiO_2 can also induce gut microbiota alterations, also called dysbiosis (Cao et al., 2020; Li et al., 2018). As intestinal inflammation and dysbiosis are important players in the development of chronic diseases such as inflammatory bowel disease, obesity and diabetes (Scheithauer et al., 2020; Sommer and Bäckhed, 2013), an alteration of the microbiota-immune system axis induced by chronic ingestion of TiO_2 may contribute to susceptibility to these diseases. In particular, food additives are considered one of the etiological factors contributing to the adverse health effects of the Western diet (Srour and Touvier, 2021). In addition, the presence of TiO_2 particles in the pancreas of people with type 2 diabetes (Heller et al., 2018) and also in post-mortem liver biopsies (Heringa et al., 2018) suggests a possible correlation between TiO_2 consumption and the development of metabolic disorders in humans.

In this review, we summarize studies showing the impacts of oral exposure to TiO_2 on the microbiota-immune system axis and we compare the effects of these inorganic NPs to dysbiosis and intestinal inflammation found in obese patients. This comparison will evaluate and provide critical input into the mechanisms by which exposure to a common food additive (TiO_2) composed of NPs may contribute to the development of metabolic disorders as environmental obesogens.

2. The microbiota-immune system axis: a major player in digestive physiology

2.1. Intestinal microbiota

Human gut microbiota is a complex ecosystem composed mainly of bacteria, but it also includes archaea, viruses, fungi and protozoa. With colonization of the GI tract beginning at birth, the adult human intestine (mainly the colon) contains 100 trillion bacteria, composed of several hundred species and at least 7000 different strains. The Firmicutes and Bacteroidetes phyla represent about 90% of the bacterial population, while other species are Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria (Huttenhower et al., 2012; Qin et al., 2010). The whole genome of the gut microbiome is approximately 150 times larger than that of humans and endows these microorganisms with a wide variety of metabolic capabilities with key roles in host physiological functions (Qin et al., 2010). Indeed, the gut microbiota is a barrier against invasion of intestinal pathogens and contributes throughout life to maintain intestinal homeostasis (Kamada et al., 2013; Lamas et al., 2018a; Moens and Veldhoen, 2012; Smith et al., 2007). It is also involved in the degradation of non-digestible carbohydrates and proteins to form vitamins, short chain fatty acids (SCFAs), or aryl hydrocarbon receptor (AhR) ligands which are essential for the development and differentiation of the intestinal epithelium and immune system (Comalada et al., 2006; Orchel et al., 2005; Stockinger et al., 2014; Wong et al., 2006). The AhR receptor is a transcription factor expressed by many cell types. In addition to its role in the metabolism of xenobiotics, AhR plays an important role in various physiological functions such as immune and metabolic functions (Kamada et al., 2013; Lamas et al., 2018a; Moens and Veldhoen, 2012; Larigot et al., 2018; Smith et al., 2007). In these settings, AhR can be activated by a wide variety of exogenous (e.g., 2,3,7,8-tetrachlorodibenzo-p--dioxin (TCDD) and benzo [α]pyrene (BP)) or endogenous (e.g., indole and indole-3-acetic acid) ligands (Lamas et al., 2018b; Rothhammer and Quintana, 2019). It is important to note that the effects of AhR activation are ligand-, cell-, and context-specific (Guyot et al., 2013; Lamas et al., 2018b; Rothhammer and Quintana, 2019). Thus, opposite effects in the same cell or organ may be observed depending on the ligand nature. Chronic exposure to certain exogenous AhR ligands, such as TCDD or BP, may have deleterious effects (Ojo and Tischkau, 2021; Pelclová et al., 2006) while different studies show that endogenous AhR ligands produced by the microbiota have protective effects in the gut (Agus et al., 2018; Lamas et al., 2020, 2018b; 2016; Rothhammer and Quintana, 2019). In addition, depending on the inflammatory status of the animals, similar AhR ligands may promote the differentiation of pro-inflammatory Th17 cells or anti-inflammatory Treg cells (Julliard et al., 2014; Zhou, 2016).

Beyond the intestine, it is now well established that the gut microbiota is able to modulate the function and/or development of systemic organs, such as the brain and liver. The ongoing dialogue between systemic organs and microbiota is made possible by the bacterial production of SCFAs, AhR ligands, polyamines or retinoic acid able to affect distant organs directly through the bloodstream or indirectly *via* nerve signalling or modulation of intestinal hormone secretion (Dinan and Cryan, 2017; Foster et al., 2016; Llorente and Schnabl, 2015; Mazagova et al., 2015). In addition to regulate the growth, fate and effector functions of B and T cells through epigenetic and metabolic controls (Hesterberg et al., 2018), polyamines can also modulate lipid and glucose metabolism in adipose tissue and liver (Ramos-Molina et al., 2019). On the other hand, retinoic acid modulates the differentiation of regulatory T cells (Benson et al., 2007; Mucida et al., 2007), as well as neuronal functionality (Jacobs et al., 2006; Maden, 2007) and, in the mouse model of non-alcoholic fatty liver disease, reduces lipid accumulation and steatosis in the liver (Kim et al., 2014; Tsuchiya et al., 2012; Yang et al., 2018). The composition and activity of the microbiota play an important role in gut-liver and gut-brain axes, and dietary

modifications can have a significant impact on these interactions. The liver and gut microbiota have equal metabolic capabilities and because of its beneficial effects on human health, the intestinal flora should be considered as a true vital organ whose activities are to be considered in host physiology and disease development (Gill et al., 2006).

2.2. Interactions between microbiota and the intestinal immune system

The intestinal barrier function is an important and dynamic interface consisting of the intestinal epithelium, the gut-associated lymphoid tissue (GALT) and the intestinal microbiota. The gut barrier function allows absorption of nutrients while acting as a physical and immunological defence preventing massive entry of dietary antigens and pathogens, including environmental toxins (Cassard et al., 2017; Delgado-Rizo et al., 2017; de Kivit et al., 2014; Macpherson and Uhr, 2004). Ongoing dialogue between these compartments is required to achieve intestinal homeostasis, which involves collaboration between immune cells (macrophages, dendritic cells (DC), T and B cells), epithelial cells producing antimicrobial peptides and enzymes such as lysozymes produced by Paneth cells. In addition, the GALT is also composed of isolated or aggregated lymphoid follicles that form Peyer's patches (PPs) in the small intestine. By the microfold (M) cells at their apical pole, PPs are involved in the transport through the intestinal epithelium of luminal antigens or bacteria in order to present them to the underlying immune system. Within the *lamina propria*, DC can also capture antigens from the gut lumen *via* the extension of their dendrites through the epithelium. These cells then migrate into the mesenteric lymph nodes (MLNs) and present antigens to T cells. Furthermore, antigen uptake by cells of innate immunity (DC and macrophages) at PPs or *lamina propria* induces either a tolerogenic response to harmless antigens from food or microbiota (Coombes et al., 2007; de Kivit et al., 2014; LeBien and Tedder, 2008), or the activation of an immune response to pathogens (de Kivit et al., 2014; Ohno, 2016) (Fig. 1). In homeostasis, DC promote induction of the tolerogenic response by activating regulatory T cells (Tregs) capable of producing interleukin-10 (IL-10) with immunosuppressive properties that inhibit the secretions of other lymphocytes (T helper, Th) responsive for inflammatory responses (Coombes et al., 2007; de Kivit et al., 2014; LeBien and Tedder, 2008). Conversely, in the presence of a pathogen, cells of innate immunity produce pro-inflammatory cytokines such as tumour necrosis factors-α (TNF-α) and IL-1β that initiate the adaptive immune response by recruiting Th lymphocytes capable of producing notably interferon-γ (IFN-γ) and IL-17 (de Kivit et al., 2014; Ohno, 2016) (Fig. 1).

The gut microbiota is essential for the maturation and development of the GALT, as demonstrated by the presence of an immature immune system in mice lacking a microbiota in their intestine (germ-free mice). These animals have a decrease in MLNs and PPs size as well as the number of immune cells, including $CD4^+$ T cells within the *lamina propria* and αβ $CD8^+$ intraepithelial T cells, inducing a reduction in the ability to fight pathogens (Smith et al., 2007; Sommer and Bäckhed, 2013). All these alterations in the immune system return to normal after colonization of the digestive tract by the intestinal flora (Chung et al.,

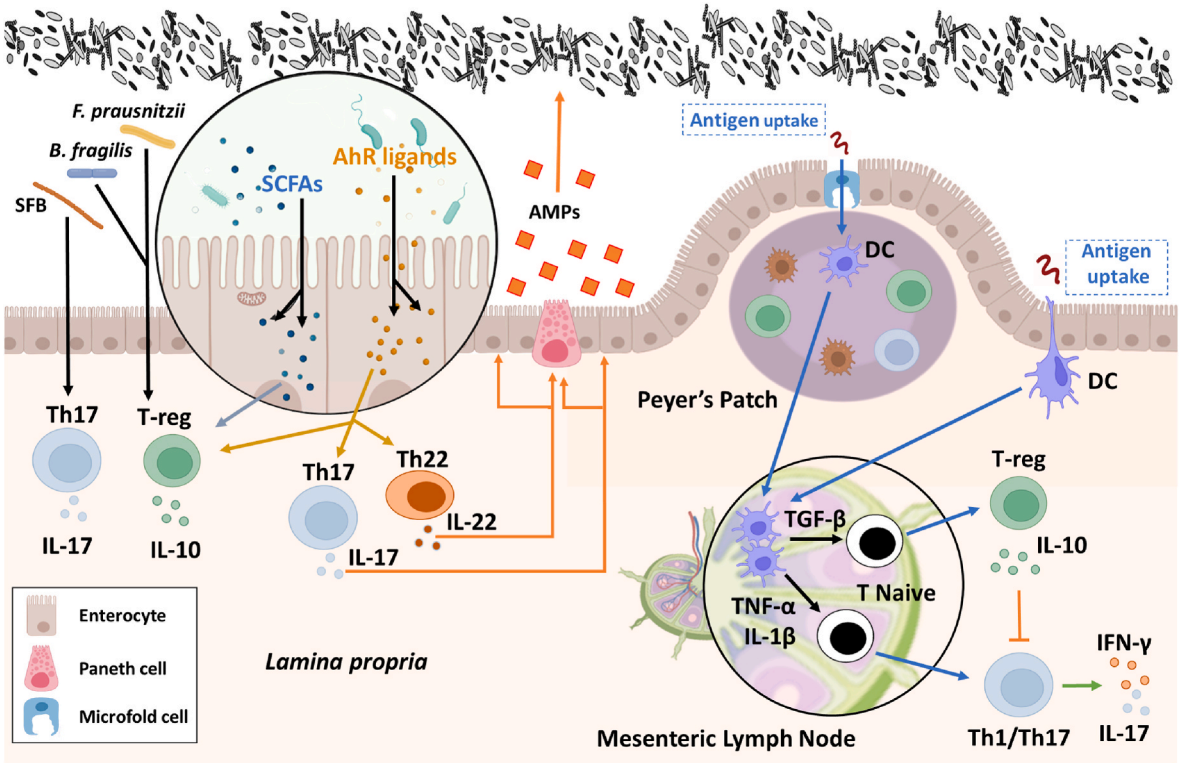


Fig. 1. Schematic representation of the interrelationship between the gut microbiota and the intestinal immune system
Dendritic cells (DCs) sample antigens that pass through the epithelial barrier *via* microfold cells or capture them from the gut lumen directly by extending dendrites through the epithelium. Some of these DCs migrate to the mesenteric lymph node and promote the tolerogenic response by the production of transforming growth factor β (TGF-β) that led to naïve T cells differentiation into regulatory T cells (Treg) capable of producing interleukin-10 (IL-10) with anti-inflammatory properties. In the presence of a pathogen, DCs and other cells of innate immunity produce tumour necrosis factor-α (TNF-α) and IL-1β that promote the differentiation of T helper (Th) 1 and 17 cells producing pro-inflammatory cytokines such as interferon-γ (IFN-γ) and IL-17. Metabolites produced by the gut microbiota, such as short-chain fatty acids (SCFAs) and aryl hydrocarbon receptor (AhR) ligands are essential for the development and differentiation of the intestinal epithelium and immune system. Through activation of AhR expressed by Th17, Th22 and Treg cells, AhR ligands modulate the production of IL-17, IL-22 and IL-10 respectively. On the other hand, both IL-17 and IL-22 cytokines induce the production by Paneth cells and intestinal epithelial cells of antimicrobial peptides (AMPs) that in turn shape the microbiota composition, and are involved in colonization resistance against pathogens. In addition, *Bacteroides fragilis* and *Faecalibacterium prausnitzii* exhibit anti-inflammatory effects *via* recruitment of Treg, while segmented filamentous bacteria (SFB) promote pro-inflammatory effects by inducing IL-17 production.

2012). Recent studies have shown that some microorganisms in the gut exhibit anti- or pro-inflammatory properties. In mice, segmented filamentous bacteria induce the development of pro-inflammatory Th17 cells in the *lamina propria* of the small intestine (Gaboriau-Routhiau et al., 2009; Ivanov et al., 2009). In contrast, other bacteria such as *Bacteroidetes fragilis* (Round and Mazmanian, 2010; Telesford et al., 2015) and *Faecalibacterium prausnitzii* (Breyner et al., 2017; Quévrain et al., 2016; Sokol et al., 2008) cause an anti-inflammatory response *via* the production of metabolites and/or recruitment of Tregs. Indeed, many metabolites produced by commensal bacteria, such as SCFAs and AhR ligands, can regulate immune cell functions (Lamas et al., 2016; Levy et al., 2016; Rooks and Garrett, 2016) (Fig. 1). In the gut, SCFAs interact notably with epithelial cells, DC and T cells, modulating the production of enzymes and transcription factors but also different aspects of cell development, survival and function (Corrêa-Oliveira et al., 2016; Donohoe et al., 2011). An *in vitro* study demonstrated that SCFAs modulate T-cell activation and response towards a tolerogenic profile (Gurav et al., 2015). In addition, AhR ligands produced by the gut microbiota modulate the differentiation of monocytes, Tregs, and Th17 cells as well as the production of cytokines through AhR activation (Agus et al., 2018; Goudot et al., 2017; Lamas et al., 2018b; Lee et al., 2017; Quintana et al., 2008). Intestinal epithelial cells (IEC) may modulate the effects of AhR ligands on GALT cells (including macrophages, DC, innate lymphoid cells (ILC), Th17/Th22 cells, and intraepithelial lymphocytes) by regulating the intestinal availability of these ligands. Both GALT immune cells and IEC express AhR, and activation of this receptor by microbial ligands is crucial for the regulation of the immune response in the gut (Lamas et al., 2018b).

Reciprocally, the GALT also modulates the microbiota, leading to intestinal homeostasis *via* the establishment of a balance between the different players in the GI tract. Indeed, the production of IL-22 and IL-17 b y Th17/Th22 cells and ILC following AhR activation, induces secretion by Paneth cells and epithelial cells of antimicrobial peptides such as β-defensin 2 and Regenerating islet-derived 3γ (Reg3γ) and Reg3β, which are capable of regulating the microbiota composition and limiting pathogen colonization (Agus et al., 2018; Lamas et al., 2018b) (Fig. 1). In addition, studies in mice showed that a deficiency of the immune response can induce intestinal dysbiosis that may contribute to the development of chronic diseases. For example, mice invalidated for the *Card9* (caspase recruitment domain 9; *Card9*$^{-/-}$) gene encoding a key protein for the innate immune response, have increased sensitivity to colitis that is dependent on the gut microbiota (Lamas et al., 2016). Indeed, the transfer of *Card9*$^{-/-}$ mouse microbiota to wild-type mice is sufficient to transmit susceptibility to colitis; conversely, the inoculation of *Lactobacillus* strains producing AhR ligands in these animals decreases the severity of intestinal inflammation (Lamas et al., 2016). Similarly, dysbiosis is observed in mice invalidated for the *Tlr5* (Toll-like receptor 5; *Tlr5*$^{-/-}$) gene encoding a receptor capable of detecting bacterial flagellin (Vijay-Kumar et al., 2010). *Tlr5*$^{-/-}$ mice exhibit a dysbiosis associated with metabolic disorders characterized by insulin resistance, hyperlipidaemia and increased fat mass, and all of these effects are recapitulated in wild-type mice colonized with the microbiota from *Tlr5*$^{-/-}$ mice (Vijay-Kumar et al., 2010).

Altogether these data demonstrate the importance of the microbiota-immune system axis in intestinal homeostasis and assume that ingestion of NPs exhibiting biocidal and/or immunotoxic properties may alter intestinal balance and promote the development of chronic diseases.

3. Impacts of TiO_2 on the gut microbiota-immune system axis

Oral bioavailability studies in rodents and humans showed very limited systemic absorption of TiO_2 (from 0.1 to 0.6% of the initial dose) (Jones et al., 2015; Kreyling et al., 2017). These data indicated that 99% of the ingested TiO_2 remains in the gut lumen where these biocidal particles can interact with commensal bacteria and induce alterations in their composition and metabolic activity before passing the epithelial barrier and interacting directly with the immune cells for its absorbed fraction.

3.1. TiO_2 and gut microbiota

Few studies have investigated the impact of TiO_2 on gut microbiota even though it is widely used for its bactericidal properties in agricultural chemicals (Rodríguez-González et al., 2019), "clean" materials (cement, self-cleaning glass, flooring) (Padmanabhan and John, 2020) and packaging (Zhang and Rhim, 2022). *In vitro* studies showed that dietary TiO_2 (E171) and TiO_2 NP models (i.e., 100% nanometric particles) could alter the growth of commensal bacteria including *Lactobacillus* (Baranowska-Wójcik et al., 2021; Radziwill-Bienkowska et al., 2018). Using artificial digestors, another study determined the impact of TiO_2 NPs and different batches of E171 on a human bacterial community, *in vitro*, consisting of 33 bacterial strains isolated from faeces of a healthy volunteer (Dudefoi et al., 2017). After 48 h of treatment, the authors observed minor effects on bacterial ecology, restricted to a decrease in *Bacteroides ovatus* and an increase in *Clostridium cocleatum* (Dudefoi et al., 2017). However, after a longer exposure to TiO_2 NPs (5 days), another *in vitro* study showed further changes in the phenotypic characteristics of the human microbiota, with no change in SCFA production (Taylor et al., 2015). Various *in vivo* studies have also been conducted in rodents, using different routes of administration (gastric feeding, addition to drinking water or food) and exposure times. In mice exposed to TiO_2 NPs for one week, no alteration in the composition of the faecal microbiota was observed (Chen et al., 2017). In contrast, longer exposure to TiO_2 NPs for 28 days in mice induced alterations in faecal microbiota composition with increased abundance of Actinobacteria but also Proteobacteria, which have potentially deleterious effects (Li et al., 2018). In the same study, the authors also observed a decrease in the proportion of Bacteroidetes and Firmicutes, including *Lactobacillus* known to have beneficial effects for the host (Li et al., 2018). In addition, a recent study in mice fed for 8 weeks with a low- or high-fat diet supplemented with E171 or TiO_2 NP models (200 mg/kg bw/d) reported a dysbiosis regardless of the TiO_2 formulation, i.e., food-grade or not (Cao et al., 2020). These effects on the gut microbiota are greater in mice exposed to TiO_2 NPs and fed a high-fat diet, including increased Firmicute abundance and decreased Bacteroidetes and *Lactobacillus*, accompanied by decreased production of SCFAs (notably the butyrate) by the gut flora (Cao et al., 2020). This latter study suggested that physiological alterations induced by an unbalanced diet may be aggravated by chronic exposure to TiO_2 and highlighted a potential link between exposure to this common food additive and susceptibility to develop metabolic disorders. Meanwhile, due to the absence of standardized tests for assessing NP-related effects on the gut microbiota *in vivo*, deciphering the potential for TiO_2 impacts on human health remains challenging and requires long periods of exposure at appropriate doses mimicking human daily levels through diet.

3.2. TiO_2 and GALT functions

Despite numerous *in vitro* studies showing the immunotoxic effects of TiO_2 NPs on bone marrow-derived cells or pulmonary and systemic immune cells (Alsaleh and Brown, 2018; De Matteis, 2017), their impact on GALT functions and host health consequences are still poorly explored. However, a direct interaction between intestinal immune cells and inorganic particles *in vivo* is suggested by different studies in rodents showing an accumulation of titanium in PPs and the mucosa of the ileum and colon after ingestion of E171 or TiO_2 NP models (Bettini et al., 2017; Brun et al., 2014; Chen et al., 2017; Janer et al., 2014). In humans, TiO_2 particles have also been observed in PPs and colon biopsies from patients with chronic inflammatory bowel disease (Gatti, 2004; Hummel et al., 2014; Powell et al., 1996). In addition, a modulation of immune cell populations within PPs was shown in rats exposed to the human relevant dose of 10 mg/kg bw/d of E171 or TiO_2 NPs (Bettini et al.,

2017). The proportion of DC ($CD103^+$, $MHCII^+$) is thus increased after 7 days of exposure regardless of the origin of the TiO_2; a transient effect, however, because not found after 100 days (Bettini et al., 2017). In contrast, a 100-day exposure to E171 induced a decrease in the frequency of T cells ($CD4^+$, $CD25^+$) and Tregs ($CD4^+$, $CD25^+$, $Foxp3^+$), suggesting immunosuppressive properties of the food additive within PPs following chronic exposure (Bettini et al., 2017). In this study, a micro-inflammation was observed in the colonic mucosa while after *in vitro* re-stimulation, the systemic immune cells isolated from the spleen of these animals exhibited a marked pro-inflammatory profile (Bettini et al., 2017), showing distinct immunomodulatory effects of the E171 additive depending on the local or systemic immune cell location. Induction of micro-inflammation in the colonic mucosa was confirmed in other *in vivo* studies in rodents exposed for shorter durations (7 and 56 days) to TiO_2 NPs and/or E171 *via* drinking water or gavage (Cao et al., 2020; Chen et al., 2017; Pinget et al., 2019). In addition, the effects of TiO_2 NPs on the immune response of the colon are accentuated on a high-fat diet and appear to be partly mediated by the gut microbiota (Cao et al., 2020). The involvement of the microbiota in the pro-inflammatory effects of TiO_2 NPs was assessed through a transfer of flora by gavage once weekly for 8 consecutive weeks with a faecal suspension from the faeces of mice exposed to TiO_2 NPs (Cao et al., 2020). However, as the faeces of exposed animals contain between 5.37 and 14.37 μg titanium/mg faeces (Cao et al., 2020), it cannot be ruled out that intestinal inflammation in colonized animals was also the result of a direct effect of unabsorbed TiO_2 NPs transferred with the stool. In the small bowel mucosa, a study in mice exposed by gavage to TiO_2 NPs (100 mg/kg bw/d) found increased T cell count and Th2 (IL-4)-type cytokine production, as well as Th1 pro-inflammatory cytokine secretion (TNF-α and IFN-γ) after 10 days of exposure (Nogueira et al., 2012). In contrast to previous findings, no intestinal inflammation or changes in immune populations (DC, Th and Tregs) within PPs were observed in rats exposed for 7 and 100 days to E171 incorporated into the pellets at different doses (4, 400 and 5000 ppm) (Blevins et al., 2019). Apart from this last report, all of these studies show that ingestion of TiO_2 is accompanied by a change in the intestinal immune balance that can alter the microbiota-immune system axis and contribute to the development of chronic diseases.

4. Can alterations in the microbiota-immune system axis induced by TiO_2 promote the development of metabolic disorders?

4.1. Microbiota-immune system axis alterations in metabolic disorders

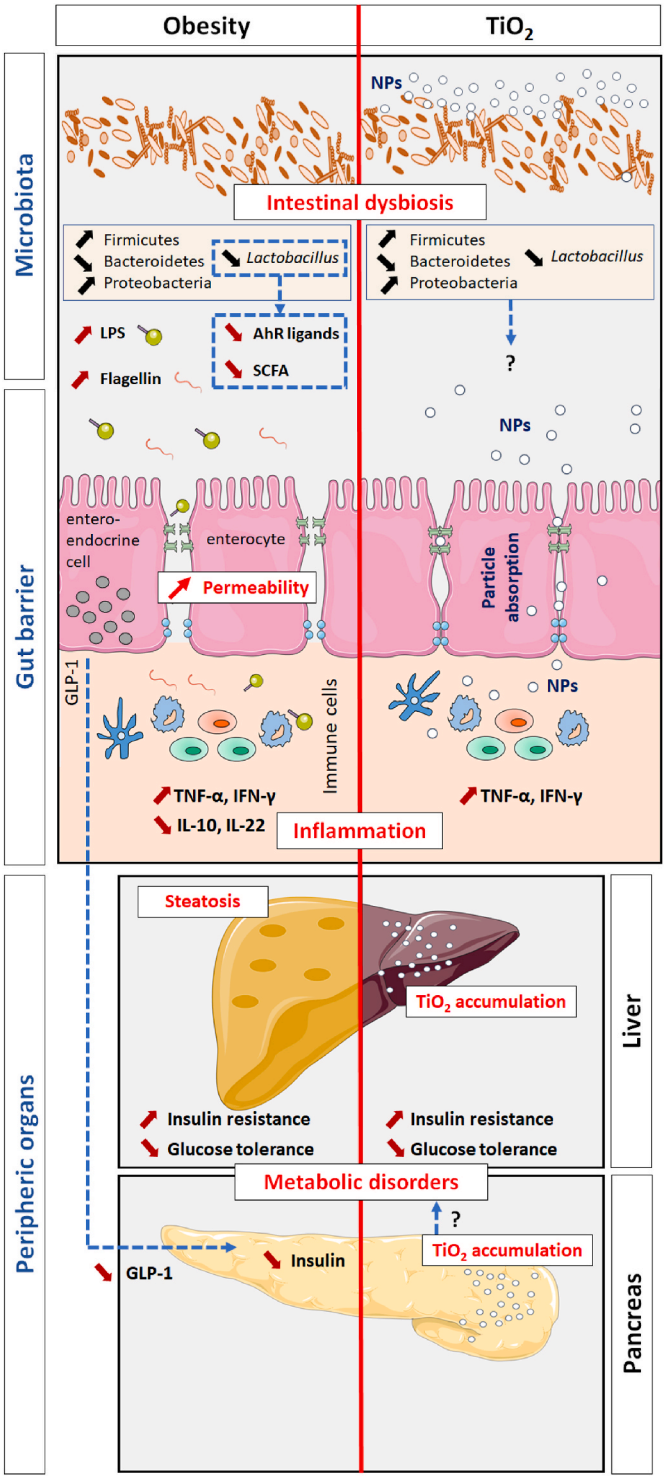
Although their aetiology is multifactorial, it is recognized that altered intestinal homeostasis plays a key role in the development of metabolic diseases such as obesity or type 2 diabetes (T2D), especially through dysbiosis, low-grade intestinal inflammation and increased intestinal barrier permeability (Gurung et al., 2020; König et al., 2016; Riedel et al., 2021) (Fig. 2). Different studies show that dysbiosis due to consumption of a high-fat diet leads to an increase in the intestinal lumen of microbial product levels such as lipopolysaccharides (LPS) and flagellin, inducing a pro-inflammatory response and an increase of the gut permeability following activation of Toll-like receptors (TLR). An increased permeation of the gut facilitates the passage into the bloodstream of these bacterial components (LPS and flagellin) and the promotion of systemic inflammation and metabolic disorders (Araújo et al., 2017; Chassaing et al., 2014; Sanz and Moya-Pérez, 2014).

A decreased abundance of *Lactobacillus* has also been reported in obese patients as well as a defect in AhR ligand production by the microbiota (Natividad et al., 2018). Various bacteria, including *Lactobacillus*, are able to metabolize the essential amino acid tryptophan to AhR ligands such as indole, indole-3-acetic acid, tryptamine and indole-3-aldehyde (Lamas et al., 2018b, 2016; et al., 2018; Zelante et al., 2013). Recent studies have shown that a decreased ability of the microbiota to produce AhR ligands plays a role in the pathogenicity of obesity through a mechanism involving reduced production of GLP-1 (glucagon-like peptide 1) and IL-22, which contributes to an increase of gut permeability and translocation of LPS (i.e., endotoxemia) inducing inflammation, insulin resistance and hepatic steatosis (Natividad et al., 2018; Taleb, 2019). IL-22 produced by gut immune cells participates in the process of mucosal healing (Pickert et al., 2009) and the production of antimicrobial peptides by the gut epithelial cells, such as Reg3γ and Reg3β (Sonnenberg et al., 2011; Stelter et al., 2011), which can modulate the composition of the microbiota. Intestinal IL-22 production defect has been observed in mice fed high-fat diet and administration of IL-22 corrected many metabolic disorders, including hyperglycaemia and insulin resistance (Wang et al., 2014). Indeed, IL-22 is able to induce beneficial effects on metabolism by improving insulin sensitivity, preserving the intestinal barrier and its endocrine functions by decreasing endotoxemia and chronic inflammation, and by regulating lipid metabolism in the liver and adipose tissue (Wang et al., 2014). Similarly, treatment with AhR agonists and the administration of *Lactobacillus* capable of producing AhR ligands, help to reduce the onset of metabolic disorders *via* an improvement of the intestinal barrier functions and GLP-1 intestinal hormone production (Natividad et al., 2018). In addition, indole, which is an AhR ligand, prevents LPS-induced alterations in cholesterol metabolism and decreases liver inflammation in mice (Beaumont et al., 2018). Other AhR ligands reduce intestinal permeability and inflammation in an *in vitro* model of intestinal cells (Caco-2/TC7 cells) (Postal et al., 2020). In addition, a correlation between a high inflammatory score and low AhR expression was observed in the jejunum of patients with severe obesity (Postal et al., 2020). Collectively, these data show that the AhR/IL-22 signalling pathway is a key regulator of intestinal and metabolic homeostasis.

Different studies showed also a decrease in the proportion of bacteria that produce SCFAs, including *Lactobacillus*, within the *gut* microbiota of patients suffering from obesity (Le Chatelier et al., 2013; You et al., 2022). SCFAs, mainly acetate, propionate and butyrate, are absorbed from the intestine. Butyrate is used as an energy source by colonocytes and for epithelial regeneration (Hartstra et al., 2015; Lin et al., 2012; Shoaie et al., 2013). After reaching the bloodstream, propionate is used in hepatic gluconeogenesis, whereas acetate serves as a substrate for cholesterol synthesis (Harris et al., 2012; Lin et al., 2012; Shoaie et al., 2013). As previously discussed, SCFAs have anti-inflammatory effects but are also involved in various physiological processes. Acetate participates in *de novo* lipid synthesis in colonic epithelial cells (Zambell et al., 2003) and, butyrate as well as propionate reduce food intake by stimulating leptin production, an anorexigenic hormone (Harris et al., 2012; Lin et al., 2012; Xiong et al., 2004). Butyrate is also able to improve intestinal barrier function and regulates apoptosis, cell proliferation and differentiation (Brahe et al., 2013). In addition, treatment of mice with butyrate reduce obesity through increased energy expenditure and improved insulin sensitivity (Vrieze et al., 2012).

It is also interesting to note that the inflammatory response induced by the decrease in SCFA production by the microbiota resulted in increased expression of the gene encoding nitric oxide synthase, *Nos2*, as well as the production of nitrate by the host, a substrate favouring the growth of Enterobacteriaceae belonging to the Proteobacteria phylum (Byndloss et al., 2017). The proportion of Proteobacteria is increased in the gut microbiota of patients with chronic diseases such as obesity and colorectal cancer (Verdam et al., 2013; Wang et al., 2012), and some authors suggest to use the abundance of Proteobacteria as a biomarker for the progression of these diseases (Shin et al., 2015). Proteobacteria have been shown to have pro-inflammatory potency in different mouse models of obesity and colitis-associated colorectal cancer (Arthur et al., 2014, 2012; Carvalho et al., 2012; Fei and Zhao, 2013; Garrett et al., 2010, 2007). The pro-inflammatory potential of Proteobacteria is partly due to their ability to produce LPS, which also contributes to the development of metabolic disorders. Regarding the obese potential of Proteobacteria, for example, it was shown in germ-free mice that

resistance to developing an obese phenotype under a high-fat diet is overcome by inoculating these animals with an *Enterobacter* population (belonging to the phylum Proteobacteria) isolated from faeces of obese individuals (Fei and Zhao, 2013). All of these data demonstrate that some Proteobacteria are capable of inducing intestinal and systemic inflammation that contributes to the development of obesity.



(caption on next column)

Fig. 2. Schematic representation of the physiological alterations of the microbiota-gut barrier axis driven metabolic dysfunction in obese patients compared to those associated to food-grade TiO2 exposure
Obesity is characterized by dysbiotic gut microbiota with an increase of the Firmicutes/Bacteroides ratio and Proteobacteria proportion, as well as lower abundance of SCFA- and AhR ligands-producing bacteria while lipopolysaccharides (LPS) and flagellin levels are increased in the intestinal lumen. The bacterial metabolite imbalance contributes to a decreased production of glucagon-like peptide 1 (GLP-1) and IL-22 resulting in gut barrier disruption. These effects allow the leakage of LPS (metabolic endotoxaemia) and flagellin, both participate to mucosal low grade inflammation and metabolic disorders (insulin resistance, glucose intolerance, and hepatic steatosis). Interestingly, some alterations in the gut microbiota from obese people and intestinal inflammation, insulin resistance and glucose intolerance were also reported in rodents exposed to TiO_2. In addition, TiO_2 particles accumulates in human liver and in the pancreas of patients with type 2 diabetes suggesting that a chronic exposure to food-borne TiO_2 could be involved in the development of metabolic disorders in humans.

4.2. *The effects of TiO_2 on systemic organs and metabolic disorders*

In the context of risk assessment, determining whether chronic exposure to foodborne TiO_2 particles can promote or induce the onset of chronic diseases remains a challenge. Human studies have shown the presence of nano- and micro-metric particles of TiO_2 in the liver or spleen (Heringa et al., 2018). Different studies in rodents showed an increase of spleen weight associated with altered immune response after oral exposure to TiO_2 NPs (Sang et al., 2014, 2012; Tassinari et al., 2014). Interestingly, splenomegaly was reported in association with obesity and the metabolic syndrome (Chow et al., 2016; Tsushima and Endo, 2000). In the liver, TiO_2 NPs induced detrimental effects through induction of oxidative stress, cellular apoptosis but also by disrupting hepatic metabolism (Chen et al., 2019; Cui et al., 2010). Moreover, oral exposure for 90 day to high dose of TiO_2 NPs (50 mg/kg bw/d) in rats led to lipid metabolism disorders and resulted in hepatotoxicity through the gut-liver axis (Chen et al., 2022). Another study showed that liver injuries were aggravated in rats exposed to TiO_2 NPs combined with glucose (1.8 g/kg) compared to TiO_2 NPs alone (Chen et al., 2015). Given the central role of the liver in glucose metabolism in humans (Adeva-Andany et al., 2016), it is possible that these hepatotoxic effects induced by TiO_2 exposure may contribute to the onset of metabolic disorders. Thus, it has been shown that an exposure of mice for 14 or 18 weeks to a dose of TiO_2 NPs above the human exposure levels (64 mg/kg bw/d) led to the onset of glucose intolerance associated with increased blood glucose due to insulin resistance (Hu et al., 2016, 2015). Glucose intolerance appeared earlier in mice exposed to TiO_2 NPs (50 mg/kg bw/d) from 3-weeks old compared to mice exposed at adult age (10-weeks old) (Hu et al., 2020). As glucose intolerance is an important risk factor for the development of diabetes (Unwin et al., 2002), these data suggest that exposure to TiO_2 NPs from childhood could favour the development of metabolic disorders in adulthood (Fig. 2). An exposure to TiO_2 NPs also aggravated metabolic disorders induced in adulthood by a diet. Indeed, in a fructose-induced metabolic syndrome mouse model, hepatic inflammation, fibrosis and apoptosis as well as oxidative stress and intestinal permeability and inflammation were worsened after oral exposure to TiO_2 NPs (20 mg/kg bw/d) for 8 weeks (Zhao et al., 2021). In addition, the presence of TiO_2 particles was found in the pancreas of patients with type 2 diabetes while they were absent in healthy volunteers, suggesting a correlation between TiO_2 consumption and the onset of diabetes (Heller et al., 2018) (Fig. 2). While these different studies show that dietary exposure to TiO_2 particles may contribute to the development of metabolic disorders *via* direct effects on systemic organs, the consequences of daily oral intake on the microbiota-immune system axis are still poorly explored, although it is known to play a key role in susceptibility to metabolic diseases.

4.3. Potential role of TiO_2 in alterations of microbiota-immune system axis inducing metabolic disorders

The majority of the results described above show that exposure to TiO_2 particles induces changes in the composition of the gut microbiota characterized by an increase in Firmicutes/Bacteroidetes (F/B) ratio associated with a decrease in *Lactobacillus* in favour of Proteobacteria (Cao et al., 2020; Chen et al., 2017, 2019). Such an imbalance in the bacterial community promotes the growth of Proteobacteria with pro-inflammatory potential (Rizzatti et al., 2017; Shin et al., 2015) at the expense of beneficial bacterial strains such as *Lactobacillus* (Lamas et al., 2020, 2018b; 2016; LeBlanc et al., 2017; Natividad et al., 2018; Zelante et al., 2013) (Fig. 2). In addition to its use to assess the capacity of the microbiota to produce SCFAs(Mariat et al., 2009; Voreades et al., 2014), the F/B ratio is often considered an informative parameter for the general state of the microbiota, and is increased in obesity-related pathologies (Ley et al., 2006; Turnbaugh et al., 2006). Interestingly, a decrease of *Lactobacillus* was observed in obese patients (Natividad et al., 2018). As mentioned previously, a defect in the production of AhR ligands by *Lactobacillus* participates in the development of metabolic disorders by reducing activation of the AhR/IL-22 signalling pathway (Natividad et al., 2018). A lower abundance of *Lactobacillus* caused a drop in the production of SCFAs which play a key role in metabolic homeostasis (Harris et al., 2012; Lin et al., 2012; Shoaie et al., 2013) and reduced metabolic disorders (Vrieze et al., 2012). A lower bacterial production of SCFAs was notably observed in mice orally given TiO_2 NPs (Cao et al., 2020). Therefore, in response to a depletion in *Lactobacillus*, TiO_2 exposure could dysregulate both SCFAs and AhR/IL-22 signalling pathways along the microbiota-immune system axis hence contributing to the onset of metabolic disorders.

A TiO_2-induced disruption of metabolic homeostasis may also result from the increased proportion of Proteobacteria, partly due to their ability to produce LPS as already stated in this review, and faecal and serum LPS concentrations flared in TiO_2-exposed mice (Chen et al., 2019). Interestingly, high LPS (Guo et al., 2013; Nighot et al., 2017) as well as decreased AhR ligands (Lamas et al., 2018b; Natividad et al., 2018) and of SCFAs (You et al., 2022) are triggers of a loss of gut barrier integrity as commonly found in metabolic diseases. Despite several *in vitro* studies highlighting the deleterious impacts of TiO_2 on the gut barrier (Brun et al., 2014; Faust et al., 2014; Dorier et al., 2015, 2019; Guo et al., 2017), the *in vivo* studies have often reported contradictory results. Some discrepancies could be due to sedimentation of TiO_2 (nano)particles on the intestinal epithelial cells during *in vitro* exposure which could bias the observations. Nevertheless, a disruption of microvilli was observed when Caco-2_{BBe1} cells were exposed to food-grade TiO_2 using an inverted configuration that limits particle sedimentation on top of cell layer (Faust et al., 2014). On the other hand, while some *in vivo* studies concluded on no impact (Bettini et al., 2017; Pinget et al., 2019; Talamini et al., 2019), several others revealed alterations of gut barrier integrity induced by oral TiO_2 (Brun et al., 2014; et al., 2019; Li et al., 2018; Medina-Reyes et al., 2020; Zhang et al., 2021), mainly enhanced intestinal permeability concomitant with downregulated gene expression of tight junction proteins that control intercellular spaces along the epithelium (Brun et al., 2014; Jensen et al., 2019). Such TiO_2-induced permeation of the gut barrier can affect nutrient absorption and metabolism (Gao et al., 2020). Different TiO_2 doses and routes of administration, duration of treatment, tissue sampling sites along the intestine (i.e., ileon or colon) as well as analytical techniques to determine gut barrier defect could contribute to the differences observed between *in vivo* studies. All these data suggest that chronic exposure to TiO_2 could disrupt the integrity of the intestinal barrier in a microbiota-dependent and -independent manner, hence promoting the development of metabolic disorders.

Taken together, all data collected in humans and animals showed that TiO_2 effects found along the microbiota-immune system axis, up to the peripheral organs after systemic redistribution of additive particles, contribute to the development or worsening of the metabolic disorders. Nevertheless, a causal link with decreased production of AhR ligands and/or SCFA by the microbiota, as well as increased intestinal permeability, proteobacteria proportion and faecal LPS concentrations remains to be demonstrated (Fig. 2).

5. Conclusion

The significant use of TiO_2 as food additive worldwide has raised concerns due to daily consumer exposure, prompting the European Commission to ban its use in the food chain as early as 2022 in the face of uncertainties about potential health effects, mainly as a genotoxic factor. Nevertheless, dietary TiO_2 remains approved in the EU in the pharmaceutical industry for oral formulations, and outside Europe in food, where its use is exponential, particularly in North America. Studies presented in this review suggest that the antimicrobial and immunotoxic properties of TiO_2 particles may induce functional alterations along the gut microbiota-GALT axis which role is crucial for host's metabolism homeostasis, with effects promoting metabolic disorders in chronically exposed individuals. Authors showed recurrent alterations in the gut microbiota composition in response to TiO_2 exposure, characterized by an increase in F/B ratio and Proteobacteria abundance, associated with a decrease in *Lactobacillus*. Similar changes in microbiota composition were also reported in obese patients, where dysbiosis plays a role in the development of this disease condition, highlighting foodborne TiO_2 NPs as endocrine disruptor-like chemical promoting obesity-related disorders. The mechanisms underlying these health consequences remain to be investigated, from systemic effects on liver functions and pancreas where TiO_2 particulate matter accumulate, but also in the intestine through direct alterations on the microbiota-immune system axis.

These observations on TiO_2 raise the need for additional studies for re-evaluation of NP-containing food additives with antimicrobial properties, particularly given the uncertainties related to long-term consequences on the intricate dialogue between gut microbiota and immune system. In Europe, the new EFSA guidance document on the risk assessment of nanotechnology applied to the food chain raises the need for studies evaluating the impact of nanomaterials on the gut microbiota (EFSA ANS Panel, 2018). The EFSA request is based on the fact that the unabsorbed fraction of inorganic particles is in constant contact with commensal bacteria before being excreted. With the exception of a few studies, the effects of TiO_2 and other foodborne NPs on microbiota metabolic activity remain largely unexplored, whereas this parameter is crucial for assessing biological consequences and potential hazards in humans. In addition, most studies are conducted at high doses with NP models and studies conducted specifically with food additives, such as food-grade TiO_2 powders (E171), are necessary to mimic real conditions of daily human exposure at low doses of mixed micro- and nanoparticles of food-grade TiO_2. Indeed, studies mimicking human exposure to such additives could result in different effects on the microbiota-immune system axis than those observed following exposure to NP models only, i.e., 100% at nanodimension. Furthermore, studies conducted so far are often limited to the direct impact of NP models or food additives on the gut microbiota, overlooking the importance of its ongoing dialogue with the immune system that requires the implementation of integrated approaches to be evaluated, such as flora transfer in germ-free mice. The period of exposure to NPs in life is also rarely considered, whereas perinatal exposure (when the microbiota and immune system begin to interact) is likely to induce greater alterations than those seen with a first exposure in adulthood. Another limitation of the studies described in this review is that microbiota and intestinal immune response alterations were explored after exposure to TiO_2 alone while the GI tract is exposed to a multitude of xenobiotics, including organic EDCs, that may have synergistic or antagonistic effects favouring the onset of metabolic diseases. One of the challenges of the coming years will be to evaluate the cocktail effects of this complex exposome on humans, i.e., organic and inorganic, taking into account exposure to

foodborne particles with different physicochemical characteristics (size, elemental structure, biocidal properties). For a relevant risk assessment, an understanding of the effects of human exposome extended to inorganic (nano)particles will be essential for implementing prevention and remediation strategies, as well as facilitating the design of biocidal-free nanomaterials for safe use along the food chain.

Credit author statement

Lamas, B.: Data curation, Writing- Original draft preparation. Evariste, L.: Data curation, Writing- Original draft preparation. Houdeau, E.: Conceptualization, Supervision, Writing- Reviewing and Editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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