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Invited Review

The link "Cancer and autoimmune diseases" in the light of microbiota: Evidence of a potential culprit

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ABSTRACT

Evidence establishes that chronic inflammation and autoimmunity are associated with cancer development and patients with a primary malignancy may develop autoimmune-like diseases. Despite immune dysregulation is a common feature of both cancer and autoimmune diseases, precise mechanisms underlying this susceptibility are not clarified and different hypotheses have been proposed, starting from genetic and environmental common features, to intrinsic properties of immune system. Moreover, as the development and use of immunomodulatory therapies for cancer and autoimmune diseases are increasing, the elucidation of this relationship must be investigated in order to offer the best and most secure therapeutic options.

The microbiota could represent a potential link between autoimmune diseases and cancer. The immunomodulation role of microbiota is widely recognized and under eubiosis, it orchestrates both the innate and adaptive response of immunity, in order to discriminate and modulate the immune response itself in the most appropriate way. Therefore, a dysbiotic status can alter the immune tonus rendering the host prone to exogenous or endogenous infections, breaking the tolerance against self-components and activating the immune responses in an excessive (*i.e.* chronic inflammation) or deficient way, favoring the onset of neoplastic and autoimmune diseases.

1. Introduction

Cancer and autoimmune diseases (AD) are different pathological conditions in which the immune system seems to play an opposite role: the immune responses are usually suppressed in cancer where the immune system become unable to eliminate tumor cells, while they are altered in AD recognizing self-antigen and developing tissue damages. Despite the many differences and the opposite activation of the inflammatory process as a whole, some interesting similarities exist between cancer and autoimmunity, like the triggering of immune/inflammatory responses that leads to chronic damage, parallel aspects in the microenvironment and evidence of altered microbiota composition [1,2]. In support to this complex relation, numerous evidence suggest that autoimmunity and malignancy are linked in a bidirectional way and clinical features resembling AD are frequently encountered in paraneoplastic syndromes [3]. Consistently, AD are associated to an increased neoplastic risk, mainly regarding hematological malignancies [4,5]. However, it is unclear whether the AD preexist to malignancy ("inflammation-induced cancer") [2] or if immune responses directed against tumor antigens eventually lead to AD ("tumor-induced autoimmunity") [5].

Within this framework, increasing evidence underlies the microbiota and its functions as crucial for the development, growth and effectiveness of the host's immune system.

The human microbiota represent a complex ecosystem, composed of bacteria (mainly) viruses, fungi and protozoans, containing a number of genes (overall the "microbiome") exceeding by more than 100 times our genome, endowing us with functional features that we do not own. Recently it was estimated that a number of bacteria comparable or even higher to that of eukaryotic cells composes the human body [6], with about 30–400 trillion microorganisms living the gastrointestinal tract, especially the large intestine [7,8]. Therefore, the whole organism, in its complexity could be redefined as a network of interactions and associations between different species (both eukaryotes and prokaryotes),

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assuming an ecological connotation [9]. Gut microbiota (GM) exerts fundamental nutritional and metabolic functions (such as carbohydrates fermentation and digestion, metabolism of xenobiotics and vitamin synthesis) [10,11], it contributes to the protection against pathogenic challenges, as well as being fundamental for the development of the gut- associated lymphoid tissue (GALTs) and the maturation of the innate and the adaptive immune system [12]. On the other hand, the immune system itself has developed, in the evolution course, to favor the symbiotic relationship with various microorganisms [13]. The complex of functions orchestrated by microbiota and the immune system, when in equilibrium, allows a more effective response, not only towards pathogens, but also in the recognition of non-dangerous antigens [14]. In eubiosis, the interplay between the immune system and microbiota allows the ideal orchestration of both the innate and adaptive immune response in order to discriminate and modulate the most appropriate response [15]. On the contrary, dysbiosis can alter the immune tonus, rendering the host prone to exogenous or endogenous alterations, breaking the tolerance against self-components and activating the immune responses in an excessive (the so called chronic inflammation) or deficient way. In turn, this might favor the onset of cancer and AD and the human microbiota could represent a non-negligible link between these two conditions. In line with this, several suggestions have been proposed. For example, according to the "hygiene hypothesis", reduced exposure to infections may lead to the increase of allergies and AD, as observed over the last century in developed and developing countries [16,17]. Further, epidemiological studies [18,19] have provided evidence for the formulation of a "cancer hygiene hypothesis" proposing that the rise of incidence some cancers could be explained as the result of an under-exposure to definite microbes, together with a modern lifestyle and the consumption of sterilize and processed food [20]. Otherwise, researchers have suggested that the sex-associated incidence of specific cancers, an aspect that is also a very common feature for AD, could depend on gender-specific differences in the GM composition [21,22]. In the light of these data and models proposed, this review aims at considering the microbiota role in modulating immune responses as a potential mutual culprit for two apparently different conditions such as cancer and autoimmune diseases.

2. Microbiota and immune system

The microbiota role in the development of the immune system is known from the last century, mainly thanks to the studies on germ-free (GF) animals. The comparison with "normal animals" showed functional (such as a reduced gastrointestinal motility and mucus accumulation) [23,24] and morphological [25] gastrointestinal differences, and, notably, a deficient immune system maturation. In detail, the microbiota lack causes defects in primary and secondary lymphoid tissue, such as GALTs [26–28], thymus and spleen [29,30], a lower number of T helper cells and IgA secreting B cells, and smaller Peyer's patches [31]. Hence, it is clear that the bacterial colonization of the gut is crucial for training of the immune system in the tolerance to various microbial antigens, discriminating pathogens and commensals and avoiding the development of allergic and inflammatory diseases [14,29,32]. Moreover, the large intestine microbiota has an impacting role in the maintenance of mucosal and systemic homeostasis [33], and its crosstalk with the local immune cells is essential for the polarization of the specific immune responses, thus exerting immunomodulatory functions [15,34]. Evidence suggests that the way in which the mucosal colonization occurs during infancy may influence the immune system for the rest of life, creating a more or less appropriate immune education and susceptibility to diseases [35]. Moreover, throughout life, microbiota composition of defined niches conveys signals that affect the immune functions, which often result in systemic outcomes, distal to the site of colonization. Although the relationship between microbiota and immune system must be considered bidirectional, given that the immune system shapes the ecology of microorganisms that colonized the human host (choosing the tolerable ones that are beneficial for the human physiology) [36], here we primarily analyze how the microbiota influences multiple aspects of the innate and adaptive arm of the immunity system.

2.1. Microbiota modulation of the innate immune responses

The microbiota effect on innate immune cells has been reported in the development of myeloid cells, innate lymphoid cells and intestinal epithelial cells (IECs) [37,38]. IECs, including enterocytes, globet cells, Paneth cells, although not accounted as innate immune cells, are involved in numerous immune functions [39] and convey many innate immune pattern recognition receptors (PRRs) [40]. Briefly, being localized at the interface between the luminal microbiota and immune system, IECs provide a (physical and biochemical) barrier, secreting mucins and antimicrobial peptides, and interact with APC (antigen-presenting cells), T and B cells, so regulating both the type of immune responses [39]. IECs are able to recognize structurally conserved molecules (derived from bacteria, viruses, and parasites), using receptors of the Toll like receptor (TLR) family and the nucleotide-binding oligomerization domain (Nod)-like receptors. However, IECs are also capable to sense the presence of RNA thanks to the expression of Rig-I (cytosolic helicases retinoic acid-inducible gene-I) and Mda5 (Melanoma Differentiation-Associated protein 5). NOD2, highly expressed by Paneth cells, recognizes microbial peptidoglycan and triggers cellular responses as the cytokines' secretion and the antimicrobial gene expression, thus influencing the GM composition [41,42]. In the GM absence, the production of antimicrobial peptides and inflammatory cytokines by IECs is compromised [43,44]. For example, in GF mice, Paneth cells exhibit decreased expression of the RegIIIγ (Regenerating islet-derived protein III-gamma) a C-type lectin that exerts an antimicrobial activity on Gram-positive microbes [43]. In addition, globet cells show a decreased expression of RELMβ (Resistin like molecule β) [44], a secreted protein able to regulate the macrophagic expression of inflammatory cytokines [45]. Finally, with the lack of microbiota, the IECs show a reduced expression of major histocompatibility complex (MHC) class II molecules, necessary for T cell antigen presentation and activation of adaptive responses, which can be restored by bacterial colonization [46]. Interestingly, microbial products, such as shorty chain fatty acids (SCFAs), can promote the protective functions of IECs and thereby shield the host against infections [47]. Remarkably, the GM impact on IECs is not limited to the regulation of immunological functions, but regards also their hormonal activity, coordinating the circadian clock and controlling the diurnal succession of metabolic activities [48–50].

Concerning the immune cells, the microbiota profoundly influences the maturation and functions of the innate myeloid cells. The myelopoiesis is affected by the GM composition [51] and its metabolites (e.g SCFAs [52]) during and after the hematopoiesis [53–56]. For example, the treatment of pregnant mice with antibiotics, results in offspring with lower myeloid cells [53], while, after hematopoiesis, depletion of microbiota increments the number of pathogenic circulating basophil cells [56] and affects neutrophils ageing [55]. Moreover, the GM presence and SCFAs has a key role in the homeostasis of tissue- resident macrophages (as microglia [57] and dermal [58], alveolar [59,60] and intestinal [61] macrophages), affecting not only their immunological functions but also their interaction with the enteric neurons [62] or their response to tissue injury [63]. Overall, the local and systemic levels of microbial products are essential to drive myeloid cell differentiation and functions, *via* PRRs, influencing the host susceptibility to a plethora of disorders, including autoimmune disease [64,65] and cancer [66,67].

Of note, microbiota influences also the lymphoid compartment of the innate system. Innate lymphoid cells (ILCs) include cytotoxic cells (natural killer, NK) and non-cytotoxic cells (ILC1, ILC2, ILC3) that lack

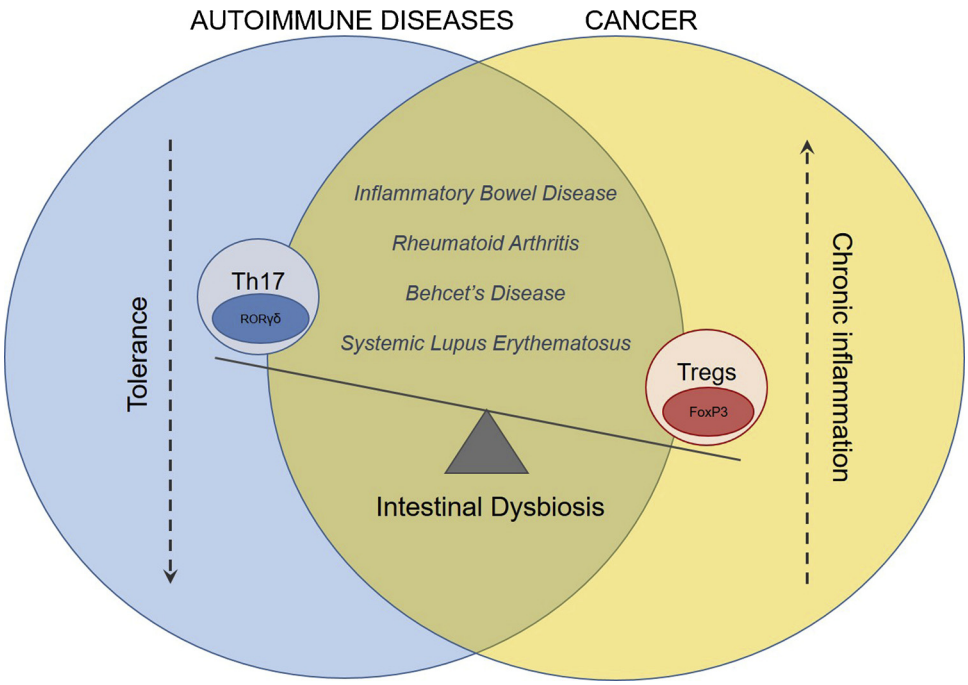

Fig. 1. Gut microbiota and Th17/Tregs' imbalance in autoimmune diseases and cancer.
Intestinal dysbiosis can alter the Th17/Tregs' ratio, favoring the Th17 and depleting the Treg responses. This imbalance can be involved in the etiology of autoimmune diseases (AD) and cancer, and could represent a pathogenic link between both conditions. In detail, Th17 cells are a major player in AD (such as inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus and Behcet's disease) while Tregs conversely inhibit autoimmunity. Then, their reciprocal balance is critical in the tolerance loss. In tumors, both Th17 and Tregs have an ambivalent role, likely depending on the type and stage of cancer. Anyway, especially in the early phases of the carcinogenesis, an imbalance of Th17/Tregs engender a chronic inflammation that can support the cancer establishment.

a B or T cell receptor [68]. They are preferentially localized into barrier tissues and rapidly respond to cytokine milieu, after colonization with microbes [69]. ILC3s, sharing the expression of RORγt (retinoic acid receptor-related orphan receptor γt), are the most studied and heterogeneous subset [70]. CCR6 + ILC3s promote GALTs maturation and IgA production, contribute to the innate host defense to enteric pathogens, and regulate gut homeostasis with commensal microbes by limiting the development of microbiota-specific CD4 + T cell–effector responses in the intestine [71]. Otherwise, T-bet + ILC3s, localized diffusely in the intestinal *lamina propria* expand after microbiota colonization and respond to microbial sensing by mononuclear phagocytes [71,72]. Regarding their development, the role of microbiota is contrasting. Sawa and colleagues have demonstrated that ILC3s usually develop in the absence of microbiota [73,74], while others have showed their impairment, with a reduce expression of IL-22, in GF mice [75,76]. Anyway, it seems clear that the commensal microbiota is crucial, after lymphopoiesis, to ensure the ILC3s' proper functioning [77] and interaction with other players of the immune system like T cells [78–80] myeloid cells [81,82], and IECs [83]. For instance, symbiotic microbes promote a crosstalk between macrophages and ILC3s that is required for the induction of oral tolerance and the intestinal immune homeostasis [81]. Also, the ILC2s' activity, *via* epithelial tuft-cell-derived IL-25 [84], and ILC1s' subset seems to be influenced by microbiota [77,85].

In summary, microbiota shapes both the myeloid and lymphoid arms of the innate immune system and its alterations could contribute to the pathogenesis of complex diseases [86].

2.2. Microbiota and adaptive immune responses

Numerous data support the microbiota role in regulating the adaptive arm of the immune system. In particular, microbes are essential for the establishment of B and T lymphocytes' repertoire and their different functionality.

B lymphocytes, able to produce different isotypes of functionally distinctive immunoglobulins, are essential in the adaptive immune responses. In GF mice, despite their number and maturation looks normal, B cells show a deficit in IgA and IgG1 antibodies production that can be restored after microbiota colonization [87]. Mucosal IgA, secreted crosswise the epithelium, coat and agglutinate their targets to prevent the direct interaction with the host and the improper stimulation of immune system in mucosal tissues [88,89]. IgA play an important role in shaping the GM composition and functionality, controlling their gene expression [90,91]. In the gut, the production of IgA by B cells follows the TGF-β and retinoic acid (RA) by DCs or ILCs [89,92,93]. GM can impact the generation of IgA + B cells *via* TCR and CD40L-dependent interactions, affecting the generation and maturation of GALTs [12,13], or stimulating the DCs of *lamina propria* to express molecules (such as RA, BAFF, APRIL) needed for the development of IgA + B cells through T cell independent mechanisms [94]. Interestingly, GF mice have elevated levels of serum IgE and an exaggerated response to orally induced anaphylaxis that can be reverted with microbiota colonization in early life, affirming the role of gut bacteria diversity for IgE production [95]

GF animals show decreased frequency of T cells' subsets, both T helper (Th), T cytotoxic (Tc) and intraepithelial lymphocytes (IELs) that express the αβ T cell receptor (TCR) [96]. Intraepithelial γδ T cells, even not affected in number [97], show impaired functions in GF mice, documenting a significant GM role on γδ IEL functions [98]. γδ IELs play multiple roles in maintaining mucosal homeostasis following injury [99] and controlling bacterial penetration across injured mucosal surfaces. Their ability to produce numerous chemokines, pro-inflammatory cytokines and the bactericidal lectin RegIIIγ was demonstrated to be microbiota-dependent. In fact, the colonization of GF mice with a specific pathogen-free (SPF) microbiota restored the γδ IELs' ability to promote wound healing [98].

Naïve CD4 + Th cells (key component of the adaptive immune system) under appropriate stimulation differentiate into different subtypes (e.g Th1, Th2, Th17) each identifiable by their expression of transcription factors and cytokines, and regulatory T cell (Tregs). However, this classification does not reflect the capacity of these cells to differentiate one into each other according to the physiologic/pathologic status. For example, in the presence of high amounts of IL-12, a Th17/Th1 profile can be acquired by Th17 cells [100], while IL-1 and IL-6 can stimulate a Treg-Th17 trans-differentiation [101]. The proper regulation and balance of T-cell subtypes is essential in determining one's health status, and ungovernable Th responses can be pathological. Generally, Th1 and Th17 cells are considered effector cells, while Tregs have a regulatory/suppressive role and, traditionally, a persistent Th17-mediated inflammation and a defective activation of Tregs-mediated responses favor autoimmunity [102]. In fact, the fine balance between

Th17 and Tregs has been implicated in several systemic autoimmune disorders, as systemic lupus erythematosus (SLE) [103], rheumatoid arthritis (RA) [104], inflammatory bowel disease (IBD) [105] and Behcet's disease (BD) [106,107] (Fig. 1).

Whether T cells (both Th17 and Tregs) support or not the cancer progression depends on the kind and step of malignancy [108]. Despite a massive inflammatory response by Th1/Th17 cells or a too strong immunosuppression by Tregs, are quite accepted as mechanisms leading to cancer development, other potential mechanisms have been proposed [109,110]. For instance, Th17 cells, by IL-17A, stimulate fibroblasts to upregulate vascular endothelial growth factor (VEGF), resulting in neoplasm neovascularization [111]. Furthermore, Tregs can exert anti-cancer properties, restoring the immunomodulatory equilibrium and engendering the chronic inflammation, as supported by studies correlating the Tregs increase with favorable cancer prognosis, especially in hematological malignancies [112–114]. Hence, the Th17/Tregs' imbalance can be appraise as a shared feature in cancer and AD pathogenesis.

The presence of microbes seems critical for the balancing of systemic Th1/Th2 responses [115], since GF animals are usually Th2–skewed [116], and for the development of specific T effector cells' subset. Hence, the stimulation of TLRs by microbes triggers the transcription of a wide variety of inflammatory mediators [117], such as IL-6 [118], essential to regulate the polarization of Th cells [119]. For example, *Bacteroides fragilis*, that inhabits the lower intestinal tract of about 30–70 % of humans [120], was the first bacterial species identified to be able to correct the Th1 and Th2 cell imbalances observed in non-gut lymphoid tissues of GF mice [120]. In contrast, segmented filamentous bacteria (SFB) were found to be potent inducers of Th17 cells in the intestinal *lamina propria* [121], while colonization with Staphylococcus epidermidis, a commensal skin bacterium, is able to induce Th17 cells in specific pathogen free (SPF) mice [122]. The RORγt + Th17 (typically producing IL-17A, IL-17 F and IL-22) [123,124] important to defend the host from extracellular bacteria and fungi, to generate antigen-specific IgA responses [125] and to recruit granulocytes into the infected sites and modulate their functions [126], are absent in the small intestine and in the skin of GF mice [127,128]. Interestingly, cutaneous Th17 are affected by skin microbiota but not by GM, suggesting that tissue commensal microbes locally regulate mucosal Th17 [122]. Remarkably, *Bacteroides fragilis* can suppress Th17 responses by promoting Tregs through TLR2 signal [129]. Tregs (mainly producing the anti-inflammatory cytokine IL-10) are capable of recognizing commensal derived antigens [130], maintaining the tolerance to intestinal microbes [131] and are essential for suppress the aberrant activation of myeloid cells, γδ T cells and Th17 cells [132–134]. GF mouse colon contains decreased Tregs, which can be restored through colonization with a variety of intestinal microbes, in particular *Clostridium* species [135,136]. The mechanisms by which Clostridia promotes Tregs' differentation is not clear, but it could be through the action of SCFAs, obtained by dietary fiber fermentation [137–139]. For example, butyrate, enhancing histone H3 acetylation in the promoter and conserved non-coding sequence regions of the Foxp3 locus, drive the differentiation of naïve CD4 + T cells into Tregs [138] Anyway, also *Lactobacillus reuteri*, *Lactobacillus murinus*, *Helicobacter hepaticus* and *Bacteroides fragilis*, increase the proportion of IL-10 producing Tregs in mice [140–144].

Finally, in GF mice, $CD8^+$ T IELs are impaired in number and cytotoxic activity [145–147], thus conditioning also the modulation of other immune cells, such as marginal zone B cells, plasmacytoid DCs and invariant natural killer T cells (iNKT) that show impairments in GF animals [148–151].

The iNKT cells, also known as type I or classical NKT cells, are a distinct population of T cells that express an invariant αβ T TCR and a number of cell surface molecules in common with NK cells. iNKT cells recognize glycolipid antigens presented by CD1d (the non-polymorphic MHC class I-like molecule) and have been implicated in different immune-related diseases. Their multi-functional responses enhance microbial and tumour immunity as well as suppressing autoimmune disease and promoting tolerance. In GF animals, the iNKT are decreased and hyporesponsive to antigen stimulation in the peripheral tissues, the spleen and the liver [151], while are increased and hyperesponsive in the lung and colon mucosal tissues [152,153]. The hyporesponsiveness can be normalized through colonization with bacteria expressing iNKT antigens in adult mice [151] while the amplified iNKT response in mucosal tissue seems to be reverted by GM colonization during the early life but not thereafter [152,153].

3. Cancer immunosurveillance and microbiota

Growing evidence confirms that microbes directly influence the carcinogenesis process [154–156] (e.g causing DNA damages [154], or indirectly [157–159], interacting with the immune system. For example, the *Fusobacterium nucleatum* promotes colorectal cancer (CRC) acting in both ways: i) inducing epithelial cell proliferation [156] and so generating a proinflammatory microenvironment that is favorable to cancer progression [157] or ii) producing proteins able to block the cytotoxic anti-tumoral activity of T and NK cells [160,161]. In addition, *Helicobacter pylori* (Hp) is the strongest recognized risk factor for the gastric adenocarcinoma and Malt-lymphoma [162]. *Hp* causes a chronic gastritis that may last decades, starting a multistep precancerous process for the most frequent histologic type of gastric adenocarcinoma: the intestinal type [162,163]. Anyway, in a more complex vision, both pathogen and commensal microbes can influence the cancer development having impact on different "hallmarks of cancer", including the modulation of anticancer immunity [164,165].

As previously described, the microbiota is essential to modulate immune responses, preserving the tissue homeostasis and so the health status. Perturbation of the microbiota composition can disrupt this balanced ecosystem, determining a chronic/abnormal activation of the immune system that can support the tumor growth. Different data sustain the importance of microbes' presence to avoid tumor formation, especially for their role in promoting cancer immunosurveillance. First, the correlations between the number of childhood infections [18] or the socioeconomic status [19] and the cancer incidence have provided the basis for the "cancer hygiene hypothesis" that is under- exposure to microbes (typical of the modern Westernized lifestyle), could increase the incidence of some cancers [19]. Interestingly, this theory resemble the one proposed for the development of immunologic disorders such as AD [17]. Second, numerous studies have documented that the antibiotic treatments are associated with an increased frequency of various tumors, such as gastric, colon, lung, breast and prostate cancer [166,167]. Even if some antibiotics may have a direct carcinogenic effect [168], it is more plausible that the tumor development is due to the following dysbiotic state that, in turn, affects the anti-cancer immunity [169,170]. There are also more direct proofs in favor of the role of commensal microbes in promoting immunosurveillance [171, 172,173]. For example, Sivan et al. have demonstrated the ability of the commensal *Bifidobacterium* to enhance the antitumor immunity [173].

Antitumor immune responses are considered a beneficial form of autoimmunity that can be deeply modulated by microbiota [15]. According to the immunosurveillance theory, cancer cells are recognized as "not self" and eliminated by the immune system. This happens unless they manage to escape immune recognition, because of the pressure imposed by the immune system itself (immunoediting), and generating an immunosuppressive environment [174–177]. Consequently, the immunosurveillance is possible thanks to the immunogenicity of cancer cells that, in turn, depend on the expression of antigens (such as tumor associated antigens, TAAs) and of adjuvant molecules. In this scenario, the microbiota play a role both in ensuring the health status of the immune system and affecting cancer cell antigenicity and adjuvanticity [15]. Regarding the first aspect, it is conceivable that GM might arouse an antitumor response *via* antigen mimicry or cross-reactivity, not only

at the intestinal level but also in distance sites. Interestingly, the cross-reactivity between microbial and self-antigens have been widely documented also for AD [178,179], which in turn are characterized by changing in microbiota composition [180]. It is plausible that the *lamina propria* T cells, once primed by local microbial antigens, could move to extra-intestinal sites towards cancer cells, following chemokine gradients generated by the growing tumor mass [172,181,182]. Alternatively, purely microbial antigens could invade the mucosal barrier and translocate from the intestine to the mesenteric lymph nodes and other sites. Finally, microbial proteins instead of translocate beyond the mucosal barrier could be captured by local DCs that migrate to the draining lymph nodes and prime T cells. In all cases, it will be possible to explain the long-range effects of the microbiota on immunosurveillance [183,184]. A strong evidence of cross-reactivity between tumor and microbial antigens that elicit immunosurveillance comes from the observation that adoptive transfer of *B. fragilis*-specific T cells, but not TRL2/TRL4 agonists, can reduce the growth of fibrosarcomas in mice [185]. Moreover, a recent study by Balachandran's group supports this view, showing that TAAs associated with the long-term prognosis of pancreatic cancer patients are comparable with infectious pathogen-encoded peptides rather than antigens relative to AD or allergic disorders [186].

The adjuvanticity, namely the presence of one or more non-antigenic co-stimulus, determines whether the antigen triggers an immune response and the nature of the latter, driving the acquisition of a specific T cell phenotype (e.g Th1, Th2, Th17, or Tregs). During co-evolution with the host, microbiota-derived PAMPs (pathogen-associated molecular patterns), antigens and metabolites imprint the effector and suppressive arms of the immune system and affect the cancer immunosurveillance. Recent data suggests a regulation of the immune tonus mediated by the recognition of microbial structures through PRRs [187,188]. For example, the TRL4 has been involved in microbial regulation of anti-tumor immune responses. In particular, the authors observed that total body irradiation enhances the efficacy of adoptively transferred tumor-reactive T cells in $Rag2^{-/-}\gamma c^{-/-}$ mice thanks to the translocation of microbial LPS that enhanced DCs and self/tumor-specific Tc lymphocytes activation, leading to greater tumor regression, *via* TRL4 signaling [188]. Moreover, frequent genetic polymorphisms in PRRs [189] may influence tumor progression through a "disturbed" detection of microbiota [190]. In addition, microbiota can elicit the secretion of cytokines (and other immune mediators), influencing the immunostimulatory or immunosuppressive reactions, such as the tendency to mount Th1/Tc1 (characterized by IFN-γ production), Th2/Tc2 (with production of IL-4 and IL-13) or Th17/Tc17 (dominated by the production of IL-17) responses [165,191], that play different roles towards cancer [192,193]. For example, the commensal bacteria can stimulate the *lamina propria* DCs to secrete IL-6, TGF-β and IL-23 needed to elicit the Th17 development [128], which have pro- or anti-tumorigenic properties depending on cancer type [194,195]. In other words, microbiota-imprinted immune cells migration and bacteria translocation can affect immunosurveillance either by priming of microbial antigen-specific tumor antigen-cross reactive T cells (antigenicity) or by the modulation of immune tonus (adjuvanticity) [15]. Finally, thanks to the paracrine/endocrine effects of cytokines and the DCs' ability to reach draining lymph nodes and spreading into the body, the microbiota can influence the immune "destiny" of tumors (control or escape) also at distance. In addition, microbial metabolites that are commonly present in human plasma [196] may cause long-range alterations; triggering various metabolite-specific receptors expressed by immune cells. For instance, as demonstrated in animal model of obesity-associated hepatocellular carcinoma, deoxycholic acid (DCA), a secondary bile acid (produced by *Clostridium* genus), can sustain tumor growth promoting inflammation [154]. Moreover, SCFAs (in particular acetate, propionate and butyrate) and other metabolites, by favoring the expression of Foxp3 gene [138], and boosting Tregs functions, may have an impact on carcinogenesis [197,199] and immune tolerance [200]. In addition proofs exist for a role of nicotinic acid, homoserine lactone, N-acetylmuramic acid and N-acetylglucosamine that are known to be immunosuppressive [198,201]. Finally, the microbiota importance in cancer immunosurveillance has become evident by the data, which suggest its role in influencing the effectiveness of anticancer treatments [202,203]. Studies in mice and human has highlighted the GM role in mediating tumor responses to chemotherapeutic agents [66,160,204–207], allogeneic hematopoietic stem cell transplantation [208], and immunotherapies, including those targeting PD-1/PD-L1 axis [173] or cytotoxic T lymphocyte–associated protein 4 (CTLA-4) [185,209–211]. In detail, some groups have observed that a great level of microbiota diversity and the presence of some "health-associated bacteria", like *Akkermansia muciniphila, Faecalibacterium prausnitzii, Bifidobacterium* spp and *Bacteroides fragilis*, are correlated with immunotherapies responsiveness. Moreover, *Enterococcus hirae* can alter the immune tonus, polarizing the T cell response towards a Th1 profile (anti-cancer) and increasing the intratumoral Tc:Tregs cell ratio in the context of cyclophosphamide treatment [204,205]. Then, even if the precise mechanism by which the microbiota mediates its beneficial effects must be determined, it is conceivable that some commensal microbes are responsible for the regulation of the immune tonus that dictates the ability of the immune system to engage in clinically significant anticancer responses [212,213]. In conclusion, the association between microbiota and cancer immunosurveillance seems not questionable, and even if the linkage mechanisms are not fully elucidated, it is reasonable to consider the microbiota manipulation/editing as a potential intervention for cancer prevention and for the efficacy increase of anticancer treatments.

4. Microbiome and autoimmunity

GF animals' models and clinical observations suggest an association between dysbiosis and AD pointing to the pathogenic role of microbiota in the autoimmunity development [214]. Interestingly, many AD have a female sex bias, and animal studies have shed some light into commensal microbes' effects on hormonal status and gender bias in autoimmunity [215,216]. Moreover, alterations of microbiota composition and function, associated with loss of gut barrier integrity and inflammation, have been observed in various AD [217,218], such as Type 1 Diabetes [219,220], Multiple Sclerosis [221], SLE [222,223] and RA [224,225]. In addition to predisposing genetic factors, environment and diet can contribute to the AD pathogenesis [226,227], and dietary changes, antibiotic use, or excessive hygiene can lead to dysbiotic states that, in turn, drive chronic inflammation, a best AD hallmark such as the inflammatory bowel disease (IBD) [228]. Different hypotheses have been suggested to explain the pathogenic role of microbiota in autoimmunity: i) the molecular mimicry [229,230]; ii) the bystander T cell activation [231]; iii) the epitope spreading [232]; finally iiii) the post-translational modifications of luminal proteins by microbial enzymes which in turn, induce the generation of immunogenic epitope triggering the autoimmunity [233].

The molecular mimicry theory is based on the similarity between microbial epitopes and self-epitopes [234], and, as previously discussed, is exploitable in anti-cancer immunity. This mechanism has been sustained by experiment data [235] and it is conceivable that chronic AD are sustained by cross-reactivity with colonizing commensals [236,237]. For example, our group documented the molecular mimicry between Hp antigens and H+, K+ –adenosine triphosphatase in human gastric autoimmunity. In detail, we have demonstrated that Hp-infected patients with gastric autoimmunity harbor *in vivo*-activated gastric CD4 + T cells that recognized both H+, K+-adenosine triphosphatase and Hp antigens. We characterized the submolecular specificity of such gastric T cells, identifying the cross-reactive epitopes from nine Hp proteins. Finally, we documented that the cross-reactive Hp peptides induced T cell proliferation and expression of Th1 functions [178].

Table 1
Summary of evidence regarding the association between the discussed autoimmune disease and cancer and gut microbiota alterations. GM = gut microbiota; RA = rheumatoid arthritis; BD = behcet's disease; SLE = systemic lupus erythematosus; IBD = inflammatory bowel disease; CRC = colorectal cancer; CIA = collagen-induced arthritis.

Auto-immune disease	Reports on cancer association			Studies on GM dysbiosis		
	Observations	Kind of study	Ref	Observations	Patients	Ref
RA	↑ risk of NHL ↓risk of gastric cancer	Retrospective Korean study	[297]	↑ *Lactobacillus*, ↑*Bacteroidaceae* ↑*Lachnospiraceae*, ↑S24-7	Arthritic mice (CIA)	[306]
	↑ risk of lymphoma	Retrospective Japanese study	[298]	↑*Prevotella copri*, ↓*Bacteroides*	USA patients	[310]
	↑risk of lymphoma, lung cancer	Meta-analysis	[300]	↑*Prevotella copri*	Japan patients	[224]
	↑ breast and prostate cancer mortality	Texas population-based study	[301]	↑*Lactobacillus* spp.	China patients	[311]
	↑ breast and lung cancer mortality	South Korea retrospective cohort-study	[302]	↑*Collinsella*, ↑*Eggerthella*, ↑*Actinomyces*, ↑*Turicibacter* ↑*Streptococcus*,↓*Faecalibacterium*	USA patients	[225]
SLE	↑ risk of lung, bladder, and liver cancer	Meta-analysis	[329]	↑*Proteobacteria*, ↓*Odoribacter* ↑*Blautia*, ↓unnamed genus (*Rikenellaceae*)	Virginia patients	[337]
	↑ risk of thyroid cancer	Korea population-based study	[330]	↑*Clostridiaceae*, ↑*Lachnospiraceae*	Lupus-prone mice	[338]
	↑ risk of malignancy	Taiwan Pediatric population-based study	[331]	↓*Firmicutes/Bacteroidetes*	Asturias patients	[222]
				↑*Rhodococcus*, ↑*Eggerthella*, ↑*Klebsiella*, ↑*Prevotella*, ↑*Eubacterium*, ↑*Flavonifractor* ↑*Incertae sedis*, ↓*Dialister*, ↓ *Pseudobutyrivibrio*	China patients	[345]
BD	↑ risk breast cancer, hematological malignancies, NHL	Taiwan population-based study	[352]	↓ *Roseburia*, ↓ *Subdoligranulum*,	Italy patients	[357]
	↑risk leukemia, lymphoma, oropharyngeal, thyroid and prostate cancer	Korea population-based cohort study	[353]	↓*Clostridium* spp., ↓*Methanoculleus* spp., ↓ *Methanomethylophilus* spp., ↑*Bilophila* spp., ↑ *Parabacteroides* spp., ↑*Paraprevotella* spp	China patients	[358]
IBD	↑CRC	Meta-analysis	[258]	↓*Firmicutes*, ↓ Clostridia cluster IV ↓*Faecalibacterium prauznitsii*,↑*Escherichia coli*	UK patients	[272]
	↑ CRC and small bowel cancer	Meta-analysis	[259]	↓*Roseburia*, ↓*Faecalibacterium*, ↑*Ruminococcus gnavus*	USA patients	[273]
	↑ primary intestinal lymphoproliferative disorders	French prospective observational cohort-study	[260]	↓*Faecalibacterium prausnitzii*, ↓Clostridium leptum group ↑*Proteobacteria*, ↑*Actinobacteria*	France patients	[274]
	↑ anal squamous cell carcinomas	Systematic review	[261]	↑*Ruminococcus gnavus*, ↓*Faecalibacterium prausnitzii*, ↓*Bifidobacterium adolescentis*, ↓ *Dialister invisus*, ↓unknown of Clostridium cluster XIVa	Belgium patients	[276]
	↑ CRC and cholangiocarcinoma	Finland population cohort-study	[262]	↑ *Enterobacteria*	France patients	[275]

In a different study, we have also demonstrated that the HP-NAP (*Helicobacter pylori* neutrophil-activating protein) is a TLR2 agonist able to induce the expression of IL-12 and IL-23 by neutrophils and monocytes. Addition in culture of HP-NAP,induced the shifting of the cytokine profile of antigen-activated human T cells from Th2 to a Th1 cytotoxic phenotype, operating as an immune modulator. Finally, we found that *in vivo* HP-NAP elicited an antigen-specific Th1-polarized T cell response in the gastric mucosa of *Hp*-infected patients [238]. In addition, Su and colleagues has observed that healthy subjects hold memory T cells specific to viruses (to which they have never been exposed), that cross-react with commensal antigens, testifying that microbiota can induce cross-reactive lymphocytes [239]. Finally, in the gut, up to 25 % of antibodies are polyreactive to commensal and self-antigens [240]. Increased B cell polyreactivity is due to impaired tolerance pathways that are well determined in patients with RA, T1D, and MS [241–243] Bystander activation concerns the concomitant presentation of a self- and a microbial antigen to antigen-specific T cells during tissue damage, with the triggering of PRRs, that delete tolerogenic signals [231]. In detail, the microbiota, during the violation of mucosal barriers or under homeostatic conditions (in genetically predisposed individuals), may trigger a break in tolerance that revokes tolerogenic signals of auto-antigen specific B and T cells. For instance, in GF [244] or antibiotic treated [245] mice has been shown a reduced induction of experimental autoimmune encephalomyelitis, restored by recolonization with SFB (Segmented filamentous bacteria) that induces intestinal Th17 cells [244]. In addition, bystander effects initiate and exacerbate Th17-mediated inflammation in RA mouse models [246,247]. Interestingly, Campisi et al. have demonstrated that *C. rodentium* infection causes self-antigen release from apoptotic host cells, which, in turn, are presented, together with bacterial peptides, to APCs that empower autoreactive Th17 cells [248]. These data strengthen the idea that gut inflammation, arising from infection can initiate the course of local and systemic autoimmunity.

Further, during an immune response to microbial antigens, due to the tissue damage and cell apoptosis, an epitope spreading (the concomitant release and presentation of microbial and self-antigens) can trigger the break of self-tolerance [232]. In dysbiotic conditions, the disruptions of the mucosal barriers and the commensal-specific immune recognition can switch from tolerogenic to effector responses, thus driving the tissue destruction and possibly epitope spreading [249].

Finally, it is appointing the “amplification of autoimmunity” by pro-inflammatory cytokines, produced by innate and adaptive immune cells, in the presence of some commensal microorganisms. Some examples are the Hp, previously reported [238] and the SFB that, favoring the Th1 and Th17 cell responses [121,250], can contribute to autoimmunity [246].

The mechanisms explaining the role of microbiota in AD must be yet fully elucidated, but even if our understanding of microbiota–immune system interactions comes principally from studying GM, commensal microorganisms can have an impact not only in other autoimmune “barrier disease” but also systemically [233,251]. Indeed, an impairment of the gut barrier can result in bacterial translocation, which then stimulates immune reactions in distant organs. Otherwise, dysbiosis could be responsible for the setting of the immune tonus toward Th17 polarized responses and Tregs’ pauperization [223], that is closely involved in autoimmunity [246,252], besides having a potential pathogenic role in cancer [110,253] (Fig. 1). Studies showing a role of mucosa-associated microbiota in systemic autoimmunity are increasing. For instance, elevated intestinal colonization of the commensal *Akkermansia muciniphila* and an increased frequency of IgA-coated fecal bacteria were significantly associated with the expression of HLA–B27 and arthritis development in rat [254]. An enrichment in adherent-invasive *E. coli* has also been found in people with IBD–associated spondyloarthritis, and this observation correlates with systemic Th17 cell activation and anti-*Escherichia coli* seroreactivity [255]. Finally, GM can remotely regulate systemic autoimmunity by driving the induction and exodus of gut T follicular helper cells [247].

5. Influence of microbiota in “cancer associated” autoimmune diseases

To date, a bidirectional association between cancer and AD is marked [3], even if the common underlying pathophysiological mechanisms remain unclear. Surely, both conditions are linked by the impairment of the immune responses and by a perturbed composition and function of microbiota that, in turn, interacts at multiple levels with the immune system. Here we focus on some representative AD that show a branded association with cancer, for which a potential pathogenic role of microbiota can be speculate (Table 1).

5.1. Inflammatory bowel disease

IBD is an inflammatory disorder where both autoimmune and immune-mediated phenomena are involved [256]. It is widely accepted that IBD is highly associated with colorectal cancer [257]. In detail, the two subtypes, ulcerative colitis (UC) and Crohn’s disease (CD), increase the CRC risk by up to 20 % and 8% after 30 years of disease occurrence, respectively [258]. Other cancers that usually arise after a chronic intestinal inflammation include small bowel adenocarcinoma [259], intestinal lymphoma [260], anal cancer [261], and cholangiocarcinoma [262,263]. IBD likely involves an aberrant immune response against environmental agents [264,265] or commensal microorganisms [266,267]. Indeed, several studies support the idea that specific microbes or GM dysbiosis can drive IBD in genetically susceptible individuals [266]. In addition, besides specific genetic mutations and other environmental triggers, chronic inflammation and GM are considered as etiological CRC factors. The most direct evidence that specific microbes cause intestinal inflammation comes from studies in animal models of IBD [268–270]. In addition, various clinical observations have documented a perturbation of microbial composition in IBD patients that usually record a decreased microbial diversity, and changes in *Firmicutes*’ classes [271,272]. In detail, a decrement of *Clostridia* and other butyrate-producing bacteria, as *Faecalibacterium prausnitzii* and *Roseburia* spp. [273], and an increase of *Enterobacteriaceae* are frequently reported [274,275]. In CD, Joossens et al. have identified a dysbiosis signature characterized by five bacterial species: *Ruminococcus gnavus*, *Faecalibacterium prausnitzii*, *Bifidobacterium adolescentis*, *Dialister invisus*, and an unknown of *Clostridium* cluster XIVa [276].

Aligned, a growing body of evidence associates a dysbiotic microbiota with CRC [277–279]. Notably, patients with CRC and IBD share similar microbiota’s alterations, like an augment of *Proteobacteria* and decreased *Firmicutes* [280], suggesting a microbial linkage between the two conditions. Common factors contribute to dysbiosis in IBD and CRC patients, including inflammation, diet, drugs, and host genetic alterations that can influence (quantitatively and qualitatively) the intestinal microbiota [281]. For example, single nucleotide polymorphisms and mutations of some genes, associated with inflammatory response or immune regulation are highly connected to dysbiosis [282,283], probably following the dysregulation of immune system [284,285]. In addition, diet heavily affects the microbiota composition and the quality of the microbial fermentation products, such as SCFAs [286,287]. Butyrate, one of the main end-products of anaerobic bacterial fermentation of dietary fiber, has important homeostatic functions in human colon, enhancing epithelial barrier integrity, inhibiting inflammation, and preventing carcinogenesis [288]. In addition, butyrate is able to induce Tregs’ differentiation *via* several mechanisms [289] and to exert anti-cancer effects by stimulating CD8 + T cells [290]. Thus, a butyrate insufficiency, caused also by low levels of butyrate-producing bacteria has been implicated in IBD pathogenesis and in cancer development [273,289,291].

Of note, even if considered an anti-neoplastic agent, butyrate can

stimulates proliferation of colon epithelial cells, and depending on its concentration, it can lead to cancer development, suggesting a double-edged role ("butyrate paradox") [292,293].

In conclusion, it is noteworthy that inflammatory processes can perturb the microbiota and elicit tumor development but, similarly, dysbiosis and cancer establishment can induce inflammation. Then, the relationship between microbiota, inflammation and cancer remain confusing and it is unclear whether dysbiosis in IBD and cancer is cause or consequence. However, it remains an interesting common feature on which further investigations are definitely recommended.

5.2. Rheumatoid arthritis

The RA pathogenesis is characterized by dysregulation of multiple aspect of the innate responses that are also implicated in carcinogenesis [294] and over time RA has been associated with an increased cancer risk, mainly hematological (like non-Hodgkin lymphoma, NHL) and solid malignancies (e.g gastric cancer) [295–297]. However, there is also studies not confirming this association [298] and the discrepancy obtained may belong to numerous factors, such as environmental and country variances, genetic risk factors, patient compliance, and co-morbidities [299]. Anyway, a recent meta-analysis have confirmed the increased risk of lymphomas and lung cancer, but not other tumors, in RA patients [300]. Interestingly, RA have an impact also on cancer survival, as mortality is significantly increased in RA patients that develop breast, prostate [301] or lung cancer [302].

RA is a systemic AD characterized by chronic inflammation at joint levels and is three times more common in women. As for other AD, the RA triggering implies a genetic predisposition and environmental factors, among which, to date, a dysbiotic microbiota appears to have a hight impact [303,304]. Animal models show an altered GM composition associated with arthritis (characterized by prevalence of *Desulfovibrio*, *Prevotella*, *Parabacteroides*, *Odoribacter*, *Acetatifactor*, *Blautia*, *Coprococcus* and *Ruminococcus* genera) that is also associated with a Th17 polarized immune tonus, which is interestingly mitigate in GF or antibiotic treated mice [246,305–308]. As previously discussed, mice models also suggest that GM alteration at mucosal sites can alter both the local and systemic immune responses eliciting joint inflammation [303,309]. Recent data have further documented a dysbiosis in RA patients, with the enrichment of *Prevotella copri* (also associated with colitis susceptibility) [224,310], *Lactobacillus* spp [311], *Eggerthella*, *Actinomyces*, *Turibacter*, *Streptococcus* and *Collinsela* reads, that show positive correlations with the pro-inflammatory cytokine IL-17 [225]. Moreover, a decreased species richness and diversity was positively correlated with disease progression and inflammatory parameters, suggesting a GM role in the RA pathogenesis [225].

Interestingly, neutrophils are largely involved in the AD pathogenesis, including RA, and cancer [1]. Together with Th17 lymphocytes, they are the major producers of IL-17 and a systematic review by Punt et al. suggests the tumorigenic role of IL-17-producing neutrophils instead of Th17 [312]. In fact, in different malignancies (ovarian, endometrial, prostate, breast, colon, and lung) neutrophils are the main IL-17 source and the most abundant tumor-infiltrating immune subset that, in turn, recruit immunosuppressed cytotoxic T cells and promote angiogenesis and metastasis [313–315]. At the same time, neutrophils are the major component of the immune infiltrates in RA [316] and, as source of IL-17, a relevant arthritis mediator [317]. Moreover, neutrophils contribute to the RA pathogenesis and other AD (in particular Systemic Lupus Erythematosus, SLE) casting neutrophil extracellular traps (NETs) that lead to the generation of autoantibodies [318,319]. In cancer, the role of NETs is controversial but it is plausible that they could be tumorigenic, promoting migration and immune escape of cancer cells or generating a physical barrier between cancer and immune-competent cells [320]. In this framework, the interaction between neutrophils and dysbiosis is of particular interest and Vong's group has observed a different ability of intestinal microorganisms to elicit NETs [65,321,322]. Interestingly, the probiotic *Lactobacillus rhamnosus*, whose administration has been proven to attenuate various types of experimental arthritis, including collagen-induced arthritis (CIA) and to inhibit arthritogenic autoantibodies [323], dampen the neutrophils' ability to form NETs [322]. Furthermore, NETs, which correlate with saliva microbial diversity in patients with chronic obstructive pulmonary disease [324], have been associated with the pathogenesis of RA-related autoimmunity in the lungs [325].

In summary, even if there are still no direct proofs linking microbiota to RA and cancer, increasing evidence shows the presence of an intestinal dysbiosis in RA patients that, in turn, can drive inflammation and promote carcinogenesis.

5.3. Systemic lupus erythematosus

SLE is characterized by the presence of aberrant autoantibodies to nuclear and cytoplasmic antigens that compromise numerous tissues, such as skin, kidneys, lungs, joints, brain and heart [326,327]. SLE is distributed worldwide and occurs in both genders although higher rates are observed in adults, in women and in non-Caucasians [328]. It has been associated with various cancer types (solid and hematological) [294]. A meta-analysis have shown an increased cancer risk in SLE, especially for lung, bladder and liver [329] and recently, a systematic review by Mao et al., has confirmed an increased risk of different malignancies (NHL, vagina/vulva, kidney, leukemia, esophagus, pancreas, lung, head/neck, thyroid, liver) particularly among females and Asians patients with SLE [330]. Moreover, a study from pediatric Taiwan's registry has shown that children with SLE were more susceptible to cancer compared to non-SLE children [331]. The SLE etiology is unclear, and its pathogenesis may involve genetic, epigenetic, hormonal, and environmental factors [326]. The latter seem closely involved in SLE etiology, as supported by the observation that the incidence of SLE is higher in African Americans than West Africans, although these two populations are genetically comparable [332]. Since oral antibiotics are known to trigger lupus flares [333–335], and considering that diet, drugs, and environmental microbes can influence the composition of the microbiota, the role of commensal bacteria in SLE has been recently proposed [336,337]. Mouse models have documented amplified bacterial diversity and altered GM, like increased levels of *Lachnospiraceae* and low levels of *Lactobacillus* spp. [338,339] in lupus-prone mice *versus* controls. As previously mentioned, some *Lactobacillus* strains have been demonstrated to inhibit the formation of NETs [322] that are involved in the SLE pathogenesis [340]. Interestingly, in this animal model, interventions aimed to change the GM composition, like diet or probiotics' administration, were able to ameliorate symptoms and avoid disease progression [338,341]. Similarly to other AD [342,343], a cross-sectional study by Hevia et al. have shown in SLE patients a decreased *Firmicutes/Bacteroidetes* ratio [222], which is also considered an important marker for intestinal dysbiosis of colorectal precancerous lesions [344]. Even if another study did not confirm the *Firmicutes/Bacteriodetes* ratio variation in SLE patients [337], the existence of a typical GM profile in SLE has been documented, and seems to be characterized for the abundance of *Rhodococcus*, *Eggerthella*, *Klebsiella*, *Prevotella*, *Flavonifractor*, *Incertae sedis* and *Eubacterium* genera [345]. Finally, Lopez and colleagues have investigated the *in vitro* properties of fecal microbiota of SLE patients demonstrating its ability to induce a strong Th17 polarization and, more interestingly, a possible Treg-Th17 trans-differentiation [223]. This, not only supports the role of microbiota in SLE pathogenesis [346–348], but also confirms the ability of microbiota to set the immune tonus in a propitious way favoring the development of other diseases (*e.g.* cancer).

5.4. Behcet's disease

BD is a rare vasculitis recently classified at the crossroad between autoimmune and autoinflammatory disorders [349] that may increase

cancer risk. It is characterized by variable clinical manifestations, including oral and genital aphthae, cutaneous lesions, ocular, gastrointestinal, neurologic involvement, and arthritis [350]. Its prevalence in the Mediterranean, Central Asia, and in the Far East is significantly higher than in Europe and the United States [351]. A Nationwide population-based study in Taiwan has documented a higher risk of NHL, hematological malignancy and breast cancer in female patients with BD [352]. In addition, BD patients in the Republic of Korea showed a higher risk for leukemia, lymphoma, oropharyngeal cancer, thyroid cancer, and prostate cancer compared with controls [353]. The BD etiology remains unknown but both genetic and environmental factors clearly contribute to the disease development [354,355]. Remarkably, the involvement of oral microbiota has also been considered in the BD pathogenesis given the high frequency of oral ulcers [356]. Our group has recently provided evidence for a peculiar GM dysbiosis in BD patients, with reduced biodiversity, and a decrease in SCFAs' production [357]. In detail, a significant depletion of well-known butyrate producers, *Roseburia* and *Subdoligranulum*, and a corresponding decrease of butyrate production in BD patients has been documented. Furthermore, Ye et al. have confirmed a lower level of butyrate-producing bacteria *Clostridium* spp. and methanogens (*Methanoculleus* spp. *Methanomethylophilus* spp.) in fecal samples from active BD patients, also enriched in *Bilophila* spp., a sulfate-reducing bacteria and several opportunistic pathogens (*e.g.*, *Parabacteroides* spp. and *Paraprevotella* spp.) [358]. As previously discussed, the butyrate impairment could favor a reduced Tregs mediated control, promoting powerful immuno-pathological T cell responses [359], which may be involved in BD pathogenesis but also in cancer establishment [110].

6. Conclusions

As recently reported, especially in the more developed countries, the condition of well-being, to which we rightfully recognize the contribution to life extension and to the improvement of its general conditions, has also brought even less welcome gifts. A sedentary lifestyle, high fat/high-calories and/or poorly balanced diets, abuse of drugs (especially antibiotics), urban environments, all have affected the delicate, constitutive crosstalk between microbiota and host immune system. Accordingly, the effectiveness and the plasticity of this complex system has been reduced, along with its functions. Thus, in those developed societies, whereas the relationship between microbiota and the host has been more hit and challenge, a remarkable increase of inflammatory, autoimmune diseases and cancer has unfortunately been observed [20]. Despite all the differences (that might be surely significant), nevertheless both cancer and AD are characterized by a situation of "ecological complexity" that involves a crucial common player, i.e. the immune system, which differently displays and interacts with other causal actors such as microbiota. Both supported by its influence on the immunomodulation and by its ecological dimension, the microbiota role on the host's functions could constitute a promising field of research in order to shed a light on these pathological situations, also by offering a different and more complete perspective on the etiology and the development of specific diseases. However, the road is still long and not free from adversities. At present, the mechanisms underlying these complex interactions are not yet fully understood and we must moderate the enthusiasm with patience and critical attitude [360]. This is also because the level of complexity (which involves multiple layers, from the biochemical one, to the genetic one, up to the epigenetic one and beyond) is such that it would require a critical and rigorous approach. Anyway, these difficulties should not discourage the future research, as this situation is precisely the task of scientific enterprise.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest

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