Cellular and Molecular Life Sciences (2024) 81:40
https://doi.org/10.1007/s00018-023-05040-y

REVIEW

Secrets and lies of host–microbial interactions: MHC restriction and trans-regulation of T cell trafficking conceal the role of microbial agents on the edge between health and multifactorial/complex diseases

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Received: 27 April 2023 / Revised: 4 October 2023 / Accepted: 6 November 2023
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Abstract

Here we critically discuss data supporting the view that microbial agents (pathogens, pathobionts or commensals alike) play a relevant role in the pathogenesis of multifactorial diseases, but their role is concealed by the rules presiding over T cell antigen recognition and trafficking. These rules make it difficult to associate univocally infectious agents to diseases' pathogenesis using the paradigm developed for canonical infectious diseases. (Cross-)recognition of a variable repertoire of epitopes leads to the possibility that distinct infectious agents can determine the same disease(s). There can be the need for sequential infection/colonization by two or more microorganisms to develop a given disease. Altered spreading of infectious agents can determine an unwanted activation of T cells towards a pro-inflammatory and trafficking phenotype, due to differences in the local microenvironment. Finally, trans-regulation of T cell trafficking allows infectious agents unrelated to the specificity of T cell to modify their homing to target organs, thereby driving flares of disease. The relevant role of microbial agents in largely prevalent diseases provides a conceptual basis for the evaluation of more specific therapeutic approaches, targeted to prevent (vaccine) or cure (antibiotics and/or Biologic Response Modifiers) multifactorial diseases.

Keywords Microbial-Immune balance · Germ-related autoimmune disorders · Micorbial agents in multifactorial disease · Immune cell trafficking · Environment-related balance of health/disease

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Introduction

We recently celebrated the 200th anniversary of Gregory Mendel birth. His work provided the scientific framework to understand a number of diseases that showed a clear pattern of inheritance and were largely independent from "infectious" causes [1]. Earlier, in the eighteenth century Bernardo Ramazzini, considered the father of occupational medicine, had defined several work-related disease-causative agents thus identifying the first disease etiology [2]. Yet, it was in the late nineteenth century that the identification of the biological nature of the causes underlying many (infectious) diseases allowed the greatest progress in our ability to treat and prevent diseases. The recent compact, global, and fast response to the pandemic of COVID-19 has demonstrated the great benefits that identification of biologic etiology of a disease provide to humanity. The large number of microorganisms present in the biologic fluids and in the environment led to the development of criteria, formalized by Koch, to

Published online: 13 January 2024

Table 1 Koch's postulates and selected examples of microorganisms

Koch's postulates	*Escherichia coli*[a] in Diarrhea	*Mycobacterium leprae* in Leprosy	*Treponema pallidum* in Syphilis	*Helicobacter pylori* in Peptic ulcer
The microorganism is trackable in all diseased organisms, but not in healthy organisms	No[b]	Yes	Yes	No[b]
The microorganism must be isolated from a diseased organism and grown in pure culture	Yes	No[c]	No[c]	Yes
The cultured microorganism should cause disease when introduced into a healthy organism	No[d]	Yes	Yes	No[d]
The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent	Yes	Yes	Yes	Yes

[a]We refer to pathogenic *E. coli* as EPEC, ETEC, STEC and similar strains

[b]The microbe can be detected in healthy subjects

[c]The microorganism cannot be cultivated in medium

[d]Only some of the infected subjects will develop disease

establish a causal relationship between a pathogen and a disease [3] (Table 1). These criteria, however, have several limitations due the complexity of pathogen, host and environment relationship; in Table 1 we propose some examples of such exceptions [4–6].

The causes of most diseases cannot be easily reduced to a single factor among the above-mentioned (i.e., infectious or genetic or occupational). Neoplastic [7], cardiovascular [8–10], immune-mediated [11–17] and neurodegenerative diseases [18–20] are therefore defined as multifactorial diseases, as for each of them a complex and not univocally defined combinations of genes, behaviors and "environment" converge, leading to its determination [21–23].

The growing knowledge about the complex host–microbe interactions, the improved diagnostics, the increased opportunity of travels and the globalization revealed the limitations of Koch's postulates. In addition, Koch's criteria should be revised for diseases classified as non-infectious, but with a microbial origin [24–26].

Several microorganisms, including pathogens, pathobionts, symbionts and commensals are able to damage tissue(s) and to trigger different types of immune responses in a balance between elimination and control, in certain cases resulting in the breakdown of tolerance [27–29]. Infection persistence, molecular mimicry, bystander activation, self-antigens release, exceeding antigen presentation and superantigen presentation, each contribute to infection-triggered immune imbalance [30]. Many associations between infections and autoimmune and non-autoimmune disorders have been described [31–35], although a proven evidence is often lacking (Table 2) [27].

Here, we will build on our observations from rheumatoid arthritis (RA) [51, 58, 59, 99–101], Multiple Sclerosis (MS) [102–108] and non-electrocardiographic ST segment Elevation Myocardial Infarction (NSTEMI) [73] to examine the concept of asymptomatic infection(s) in the light of immune impact, and then focus on the role of T cell antigen recognition and trafficking in concealing the responsibility of microbial agents in the etiology and pathogenesis of multifactorial diseases.

Host–microbe interaction and inflammation: a precarious balance between asymptomatic infection and multifactorial diseases

Several lines of evidence point to a prominent role for adaptive and innate immune systems in the pathogenesis of multifactorial diseases where inflammation constitutes the common trait. In these diseases, the overall role of microbial agents has been largely underestimated in the twentieth century, probably because the emergence of overt disease was considered a prerequisite to implicate a microbe, as expected by the "Koch's postulates" [109, 110].

However, thanks to a solid and extensive body of knowledge gathered in the latest decades on the role of microbes in health and disease, we are gaining a new understanding about the impact and consequences of microbial interaction with the host, and primarily with the host immune system. In a seminal paper, Pirofski and Casadevall proposed a compelling model of microbial pathogenesis, or rather host–microbe interaction, where interaction with even the potentially most pathogenic microbe does not necessarily lead to damage and disease [111]. This model highlights the role of asymptomatic infections, defined as a state with microbial replication or persistence in host tissues, with a concomitant host immune response that contains microbial burden, without overt signs or symptoms of disease, resulting in unapparent or subclinical infection [112].

The possibility to shape the host immune responses differs depending upon (symptomatic/asymptomatic) infection lifespan. In chronic-persistent asymptomatic infections (i.e.,

Table 2 Examples of genetic and microbial associations with common autoimmune and non-autoimmune multifactorial diseases

Etiology	Disease	Locus/i associations	References	Most frequently associated microbial agents	References
Autoimmune	Multiple sclerosis (MS)	HLA-DRB1, HLA-DQB1, IL-1, IL-1R, IFN-γ, TNF-α, CTLA-4	[36–39]	*Epstein–Barr virus, M avium subsp. paratuberculosis, C. pneumoniae, M. pneumoniae, C. perfringens type B, H. pylori, Euryarchaeota, Firmicutes, Proteobacteria*	[40–47]
	Rheumatoid arthritis (RA)	HLA-DRB1, CTLA-4, IL2RA, IL2RB, TNF-α, IL4, IL4RA, PTPN22	[48–51]	*P. gingivalis, P. mirabilis, Epstein–Barr virus*, *Mycoplasma*, *Mycobacteriacae*	[52–59]
	Systemic lupus erythematosus (SLE)	HLA, IL2RA, IRF8, IRF5, STAT4, ICAM3, CD11a	[60, 61]	*Epstein–Barr virus*, *parvovirus B19, type 1 human immunodeficiency virus, Cytomegalovirus*	[62–64]
	Type I diabetes (T1D)	IL-10, CTLA-4, IL7R, IL2RA, CD226, PTPN2	[65]	*Coxsackievirus B, Varicella Zoster Virus, Enteroviruses*	[66–68]
Non-autoimmune	Acute myocardial infarction (MI)	NOTCH1, CCL5, CXCR2, CXCL6, IGF1R, GPD1L, OLR1, IL1B, TLR2, HLA-A3	[69–73]	*C. pneumoniae*, *M. pneumoniae*, *Mycobacteriacaee. Parvovirus B19, Cytomegalovirus, Enteroviruses, Lactobacillus, Bacteroides, Streptococcus*, *Aerococcaceae, Ruminococcaceae*	[74–76]
	Alzheimer's Disease (AD)	APO-E, TREM2, ABCA7, DYNC1H1, ITGB1, S100	[77–80]	*Herpes simplex viruses* (various serovars), *H. pylori, P. gingivalis, C. pneumoniae, B. burgdorferi*	[81–86]
	Schizophrenia	GAL3, SHISA9, SETD1A	[87–90]	*T. gondii, Cytomegalovirus, influenza*, slow and latent viruses	[91–94]
	Pan-cancer	Cancer-type specific genes and pan-cancer genes	[95, 96]	*Candida, Mallasezia, Blastomyces, Lactobacillus*	[97, 98]

Acronyms in the table: HLA, Human leukocyte Antigen; IL, Interleukin; IFN, Interferon; TNF, Tumor necrosis Factor; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; PTPN22, Protein Tyrosine Phosphatase Non-Receptor Type 22; IRF, Interferon regulatory factor; STAT4, Signal Transducer And Activator Of Transcription 4; ICAM3, Intracellular Adhesion Molecule 3; CCL, Chemokine (C–C motif) ligand; CXCR, C-X-C chemokine receptor type; CXCL, chemokine (C-X-C motif) ligand; IGF1R, insulin like growth factor 1 receptor; GPD1L, glycerol 3-phosphate dehydrogenase 1-like; OLR1, oxidized low-density lipoprotein receptor 1; TLR, toll like receptor; APO-E, Apolipoprotein E; TREM2, Triggering receptor expressed on myeloid cells 2; ABCA7, ATP Binding Cassette Subfamily A Member 7; DYNC1H1, Dynein Cytoplasmic 1 Heavy Chain 1; ITGB1, Integrin beta-1; GAL3, galectin 3; SHISA9, Shisa Family Member 9; SETD1A, SET Domain Containing 1A, Histone Lysine Methyltransferase

Herpes viruses, *Toxoplasma gondii*, *Trypanosoma brucei*, *Trypanosoma cruzi,* and many other), concomitantly with fully competent immune responses, viable microbial agents in host tissues can impact both innate and adaptive immunity, with either beneficial or unfavorable consequences.

Another good example of the dual effect of long-lasting asymptomatic infection is represented by *Helicobacter pylori (H. pylori)*. On one hand it has been suggested it has beneficial effect to the infected host by protecting against diarrheal infectious diseases, asthma and allergies, inflammatory bowel diseases, and other conditions [113]. On the other hand, in a small percentage of infected subjects, its replication in the gastric mucosa lead to gastritis, peptic ulcer and eventually to gastric adenocarcinoma [114, 115]. In addition, this observation highlighted the interplay between inflammation driven by microbial agents and oncogenesis.

H. pylori represents one of the earliest examples of a microbial agent that did not fully comply with Koch's postulates. Its role suggested earlier by histology, remained undemonstrated for several decades, due to the unexpected culture requirements of the bacterium (microaerophilic conditions or in agar stabs [116]), preventing the fulfillment of Koch's second postulate, which states that a microorganism isolated from a tissue of a diseased organism should be grown in a pure culture (Table 1).

Even when we consider several of the most important human infectious agents, the most-likely outcomes following infections are "asymptomatic". For instance, the deadliest

bacterial agent, *Mycobacterium tuberculosis* (*Mtb*), responsible for 10 million new active tuberculosis (TB) cases and 1.5 million deaths per year, usually infects people without causing overt disease: latent TB accounts for 90–95% of the total *Mtb* infection, (≈ > 2 billion people) [117]. Hepatitis B virus infection usually results in asymptomatic infections with complete viral clearance more likely when infection occurs in adults and "old" children [118]. In endemic areas, exposure to the *Plasmodium* species causing malaria warrants a partial immunity which is maintained through continuous asymptomatic re-infections.

The characterization of the host immune response during latent (asymptomatic) TB infection highlights the dynamic equilibrium between the host and *Mtb*, that can last for the entire life without significantly perturbing the host homeostasis [119]. Yet, during latent TB, *Mtb* replicates in the host tissues secreting highly immunogenic T cell antigens that elicit an immune response that contain *Mtb* replication without causing the damage associated with the clinic disease. Immunization with Bacille Calmette and Guerin (BCG), a live attenuated vaccine administered at birth to protect against TB, activates an innate immune response (trained immunity) that protects children against many other infections [120]. It is reasonable to infer that latent *Mtb* infection [119], which promotes a more robust and long-lasting immune response at local and systemic level than BCG vaccination, may exert an even greater impact that may be beneficial for the human host, thus explaining the competitive selection for *Mtb*-human co-evolution [121].

In general, during and following "transient" infections, where the host–microbe interaction drives microbe removal from host tissues, the impact on the host immune homeostasis may differ between microbes that are eliminated by host tissues within few days, as in most respiratory infections (influenza virus, coronavirus, *Bordetella pertussis*) and microbes that are eliminated following weeks or months as in some gut infections (*Shigella*, *Cryptosporidium*) [122].

Not only microbial viability affects host cellular responses but also the continuous release of microbial antigens and proteinaceous components impacts the immune system. In this context, a seminal paper from Mazmanian showed that a specific product (Polysaccharide A, PSA) from bacteria (*Bacteroides fragilis*) was involved in the modulation of autoimmunity [123]. Indeed, PSA can suppress the production of the pro-inflammatory interleukin-17, and also protect from inflammatory disease inducing secretion of the anti-inflammatory interleukin-10, without the need for the immune cells to cross-recognize non-self-antigens from the bacteria and self-antigens. Indeed, *B. fragilis* establishes a complex and generally beneficial relationship with the host while persisting in the gut as a commensal [124, 125]. This observation led to the development of a new field of research regarding the role of the microbiota as a modulator of the immune system [123, 126] and consequently as a potential regulator of health/disease [127].

Asymptomatic/subclinical gut infections, common in low-resource settings, have been associated with poor child growth, highlighting their impact on gut immune responses and microbiota composition [122]. Similarly, it has been shown that transient viral infections may drive long term consequences on host immune homeostasis with relevant clinical implications [128–131].

Thus, a satisfactory description of host–microbe interaction shall consider the events taking place at cellular and immunological level that occur during asymptomatic infection and analyze their consequences in the short and long terms (Fig. 1).

Trafficking of microbiota-specific antigens from the gut to the thymus induces expansion of specific T cells that once in the periphery may exert their activity, that can either protect against related pathogens or be potentially pathogenic [132]. Starting from the role of microbial agents in enhancing/precipitating immune disorders, we can speculate that an individual susceptibility to microbial colonization, and especially to chronic, persistent, or even unnoticed/asymptomatic infections, may contribute to immune dysregulation contributing to a wide range of diseases.

Microbial colonization starts in prenatal life and leads to early training of the immune system

Two long-held propositions about fetal immune system and microbial agents during pregnancy have recently been disproved. It was in fact held that the fetal environment was a sterile environment (unless some specific infections occurred such as e.g., rubella or syphilis) and that the immune system was largely immature at least until very late in the pregnancy.

Several papers in the last decade ([133–135] and several others] have shown that the fetal immune system appears competent and mature already at the second trimester of pregnancy. On the other hand, it has recently been reported that microbial colonization occurs in several fetal tissues, with a wide range of agents albeit at a low concentration. At the same time, a variable specific T cell repertoire is primed and activated towards a memory phenotype [136]. The effect of such inapparent exposure to microbial agent on the immune system can alter the balance between asymptomatic versus symptomatic infections. Thus, infections with enterotoxigenic *E. coli* will result in asymptomatic infections or diarrhea depending on the presence of an immune system producing high levels of type 2 cytokine before the infection itself [6]. The effect of early exposure to bacterial antigens is not limited to T cells, but extends to and persistently modifies also other components of the immune response including NK cells [137]. Thus, early exposure of

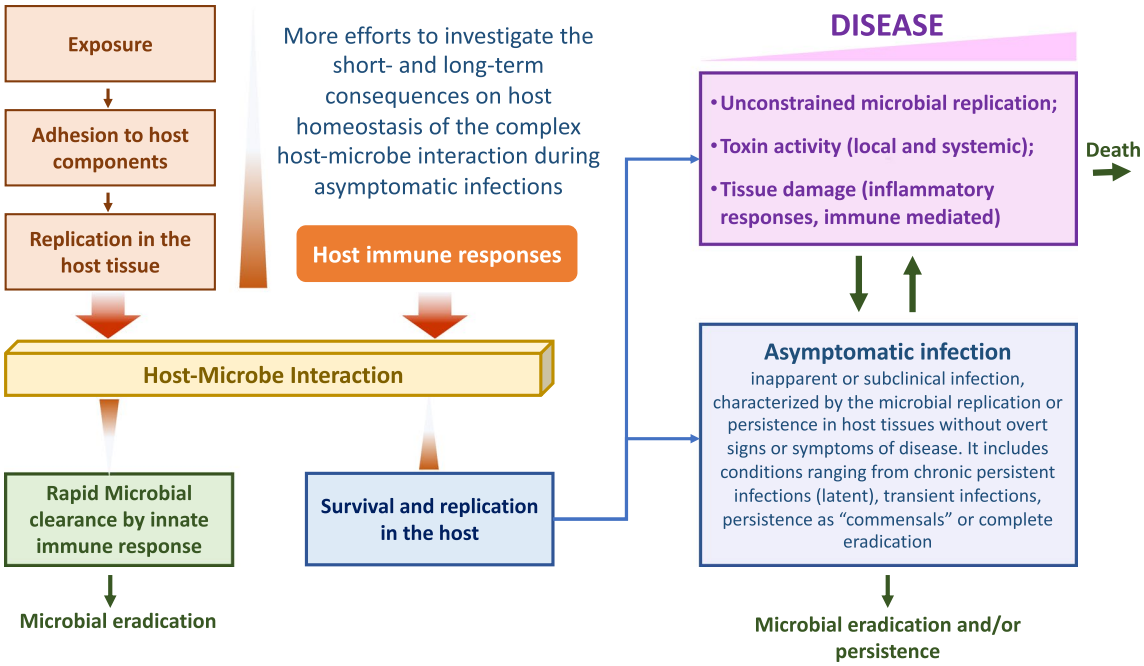

Fig. 1 Key steps in host–microbe interplay. The early events following exposure and adhesion, promote an increase in microbial burden that activates innate and adaptive immune responses. When host immune responses cannot rapidly eradicate microbes, survival in the host occurs in the presence of innate and adaptive immune responses and may lead to rupture of host homeostasis and emergence of overt disease. However, microbes can "transiently" survive and persist in host tissues despite the presence of host immune responses, without causing symptomatic infections and yet contribute to shape cellular and tissue host homeostasis (e.g., respiratory and gut microbiota). Many microbes can persist indefinitely in host tissues (commensals or latent infection) without perturbing host homeostasis at an extent that results in symptoms: the continuous interplay between host and microbes during these asymptomatic lifelong infections can have an impact on human health (e.g., EBV infection)

the immune system to microbial antigens may have permanent effects that influence response to vaccines, or development of inflammatory diseases later in life [138].

Cross-mimicry and the complexity of T cell antigen recognition: distinct infectious agents can lead to the same autoimmune diseases

T cells recognize the antigens as a complex of foreign peptides (epitopes) assembled with one's own HLA-encoded molecules. In each individual, 10–15 HLA-encoded molecules are present, each selecting a repertoire of 8–15mer peptides limited by the requirement of some residues at two to three so-called anchor positions. HLA genes are highly polymorphic, therefore the HLA haplotype (i.e., the repertoire of HLA encoded molecules of each individual) is highly variable among individuals within a non-inbred population [139–141].

In practical terms, it means that each repertoire of HLA-encoded molecules of a given individual binds only a distinct repertoire of foreign epitopes and, according to such antigen recognition model, individual immune response will focus on a set of epitopes per each antigen that is at the same time limited (restricted) at the individual level because of one's own (HLA) haplotype, but is highly variable at the population level because of the HLA extensive polymorphism.

The very same situation occurs when the antigen is not a foreign molecule but is a self-molecule. The restriction mechanism applies both for the development of tolerance (each individual is tolerant to a "limited" set of self-epitopes, specific and distinct from any other individual) and to the development of self-reactive immunity in the case of autoimmune diseases (each patient will respond to a private set of self-epitopes, despite all suffering the same clinical manifestations) [142–144].

A noteworthy characteristic of autoimmune diseases is that patients affected by a given disease share at least one HLA allele, with a wide range between 40 (such HLA DRB1*15 in Multiple Sclerosis and HLA-DR4 in rheumatoid arthritis) and 90% (such as HLA-B27 in Ankylosing Spondylitis or HLA-DR3/DR4 haplotype in type 1 diabetes with early onset). This implies that the self- or allo-reactive T cell responses of a subgroup of autoimmune patients are skewed by a limited repertoire of restricting elements. As shown in Fig. 2, a common microbial agent may express one or more epitopes potentially cross-reactive with human ones, in the contest of an HLA allele. If the response to a cross-reactive protein is able to drive a disease, the large presence

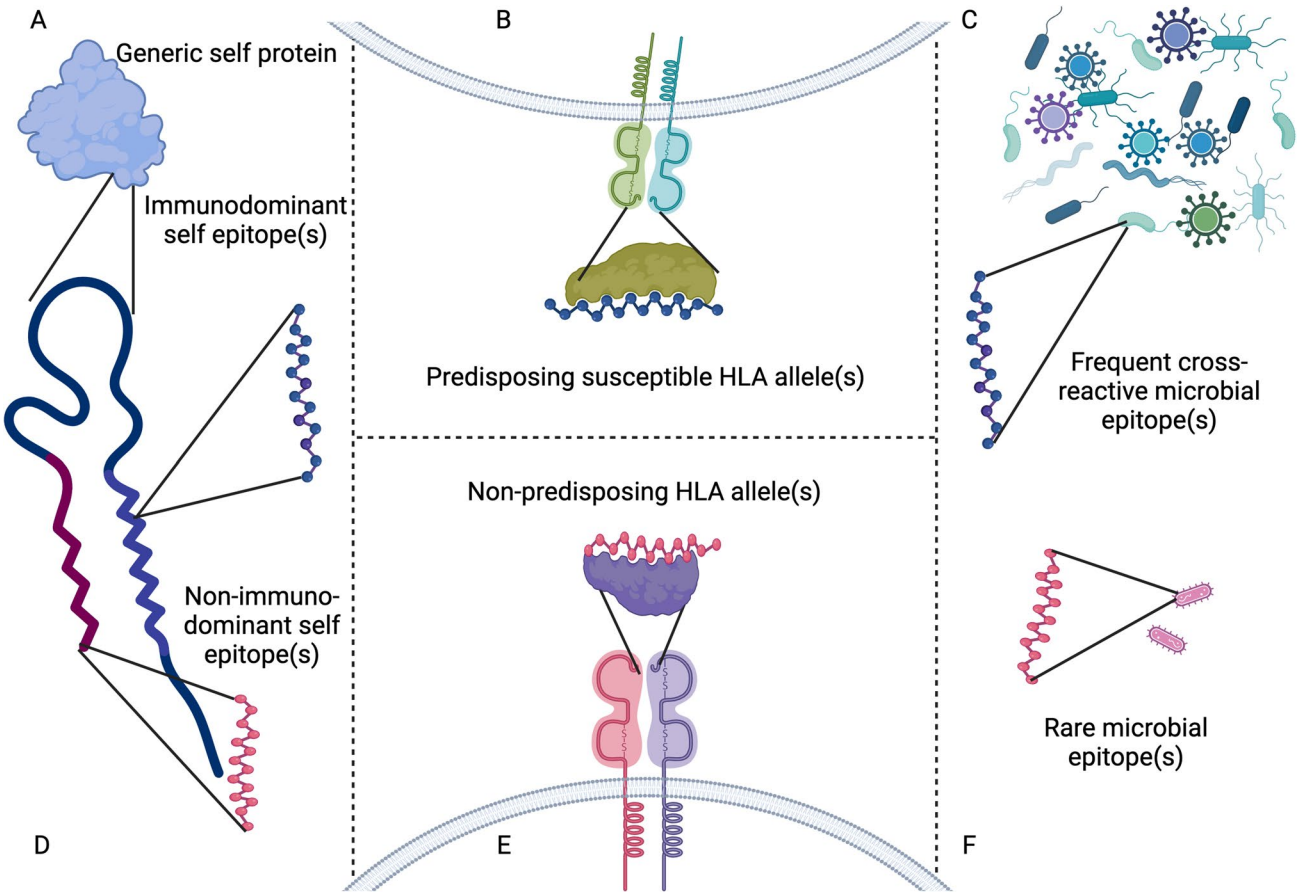

Fig. 2 HLA alleles behave as predisposing or not-predisposing depending on the frequency of cross-reactive microbial agents. Immunodominant self-antigen(s) derived from a generic self-protein (**A**) and presented antigen(s) from common microbial agents (**C**) can cross react only in presence of a predisposing/susceptible HLA allele (**B**). On the other hand, other epitope(s) from the same generic self-protein (**D**) may be cross-reactive with an antigen from a rare microbial agent (**F**) and can eventually lead to the development of the same disease in presence of a non-predisposing HLA allele (**E**)

of the microbial agent in the environment will result in a frequent association of the disease to that HLA allele. Conversely, patients affected by the same autoimmune disease but not sharing that very HLA allele will be characterized by distinct T cell responses. If the microbial agents carrying a potentially cross-reactive epitope in the contest of another HLA allele is rare in the environment, there will be no epidemiologic association between this latter HLA allele and the disease.

Thus, when studying "multifactorial diseases" and the role that the T cell responses may potentially play in such context, the HLA haplotype of each patient should be assessed and if the frequency of a given allele is overrepresented in a subpopulation of patients then patients should be examined separately, according to their positivity or negativity for such allele in order to define microbial agents potentially involved in the determination of the disease, to predict disease course and to target the best treatment approaches (Fig. 2) [99, 101].

Two bacteria for one disease: the example of rheumatoid arthritis

RA is an autoimmune disease leading to a wide range of organ-specific and systemic damages. Type II collagen, highly represented in the synovial membranes, is likely one of the main targets, not the sole, of CD4 + T cells that drive a cell-mediated response during RA contributing to the clinical outcome of the disease. At the same time, anti-cyclic citrullinated peptide (ACPA) and Rheumatoid Factor (RF) antibodies (IgMs specific for the constant region of IgGs) are consistently present, mediating systemic inflammation and providing reliable biomarkers of disease [145]. An infectious pathogenesis for RA had been suggested many years ago, based on the observation that it is possible to induce an adjuvant dependent arthritis in the mouse, due to *Mtb*-derived adjuvant components [146].

Two alleles (HLA-DR4 and DR1) are present in 40% to 50% of RA patients, sharing a similar binding pocket and

presenting the same or a similar repertoire of epitopes. In line with the above proposed reasoning, we examined the collagen-reactive T cell repertoire composition in RA, identifying shared TCRs among patients that were enrolled, genotyped and selected based on their HLA-DR4 [99, 100, 147]. Moreover, we found that this TCR repertoire was detectable in a cluster of RA patients in a moderate/severe disease state, with a low response to first line drugs, usually conventional disease-modifying antirheumatic drugs, (DMARDs) and who most needed to rapidly switch to second line therapy, generally with the addition or a combination with a biotechnological DMARDs [51]. In a second set of studies, we reported that a pathogenic protein of *Glæsserella parasuis* (*G. parasuis*) is recognized by the very same T cells that recognize human collagen II within HLA-DR4 and DR1 [59]. *G. parasuis* is the bacterium responsible for Glæsser disease in swine, a disease characterized by a combination of meningoencephalitis, polyserositis and polyarthritis. Surprisingly, we found that the contact between *G. parasuis* and humans was not a rare event and was not limited to patients suffering of immune-mediated arthritis. The DNA of *G. parasuis* was detectable also in healthy subjects, and among them in young adults more frequently than older individuals. From these data it can be reasonably suggested that the contact with *G. parasuis*, although traceable in a large healthy population, acts as a trigger for RA only in the subgroup of individuals sharing the high-risk HLA alleles. In other words, this is a striking example of the very tight link between environment and genetics in the regulation of immune responses. Since *G. parasuis* cannot be found in all DR4/1$^+$ RA patients during overt disease and it likely acts early in life and in an HLA-restricted manner, it would be very difficult to reproduce RA in laboratory animal models by infection [148]. Thus, this microorganism contradicts almost all of Koch's postulates. Nature however provided a model in swine (that shares the same collagen II epitope cross-reactive with *G. parasuis* with humans).

It is likely that other (possibly, less common) microbial agents play the same role in RA patients with a different HLA haplotype [149–155]. The presence of *Haemophilus spp*. (most-likely *H. parainfluenzae*) in oral cavity acts as immunomodulatory commensal bacteria, negatively associating with the levels of serum C-reactive protein (CRP) and the serum titers of ACPA and RF in RA [156, 157]. As recently demonstrated, environmental pathogens might act as triggers for autoimmunity and it could possible to determine recognized epitope(s) and the microbial agent(s) involved in distinct autoimmune and non-autoimmune diseases, starting from TCRs/HLA and immune response [158]. The oral microbiome exerts bystander effects in the immunomodulation downregulating CD86 expression in human submandibular gland cell line cells by *Rothia mucilaginosa*, while IFN-γ-induced expressions of class II HLA, CD80, and CD86 appear to be modulated by pretreatment with *Streptococcus salivarius*, *R. mucilaginosa*, *Fusobacterium nucleatum*, *Prevotella melaninogenica*, and *Prevotella histicola* [159].

Other bacteria are detectable in RA patients at a very high frequency (approximately, 90%), and much higher amount than in healthy individuals, namely *Porphyromonas gingivalis* (*P. gingivalis*) and *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) [58, 160–162]. In the context of periodontitis, they are both able to promote the citrullination of peptides, considered one of the main mechanisms underlying the B cell autoimmune response, thereby producing new epitopes for self-antibody recognition. However, T cell cross reactivity with collagen cannot be found neither for *P. gingivalis* nor for *A. actinomycetemcomitans*. It can be proposed that full-blown RA depends on a first early contact/infection with a bacterium able to drive a collagen-reactive T cell response, followed by a second microbial agent promoting citrulline-specific B cell-mediated responses. Intriguingly, the actual incidence of RA and HLA-DR4/1 in the general population (that is 0.01) is very close to the value resulting from the multiplication of (frequency of HLA-DR4$^+$/DR1$^+$: 0.08) × (frequency of *G. parasuis* infection at early age: 0.5) × (frequency of *P. gingivalis* infection: 0.2) in the general population.

In addition, or alternatively, it can also be suggested that *P. gingivalis* or *A. actinomycetemcomitans* may drive pathogenetic mechanisms in RA other than via antigenic recognition. The growing body of literature about this topic corroborates the idea that RA could be enhanced or even directly induced by asymptomatic trafficking of oral/gut microorganisms to joints, or indirectly through the mouth-to-gut transmission permeabilizing the intestinal barrier. These mechanisms could cause a breakdown of tolerance to self-antigens, especially in the cases of microorganisms, such as *P. gingivalis*, able to resist to innate immunity [163]. Similarly to what happens in Multiple Sclerosis (MS) with Epstein–Barr Virus (EBV) infection [42, 164–166], preceding the onset of the disease [167] infectious agents can modify antigen processing in infected B cells [164] or in macrophages (Fig. 3).

Several distinct "ectopic" microbial agents may activate a converging T cell repertoire, leading to the same disease: the example of N-STEMI

Acute coronary syndrome (ACS) is the prototypic multifactorial disease of the western world. Based on clinical and ECG presentation, it is clinically divided in unstable angina, non-ST segment Elevation Myocardial Infarction (N-STEMI) and ST segment Elevation Myocardial Infarction (STEMI) this latter showing a high severity of the ACS outcome. In all types of ACS, inflammation plays a

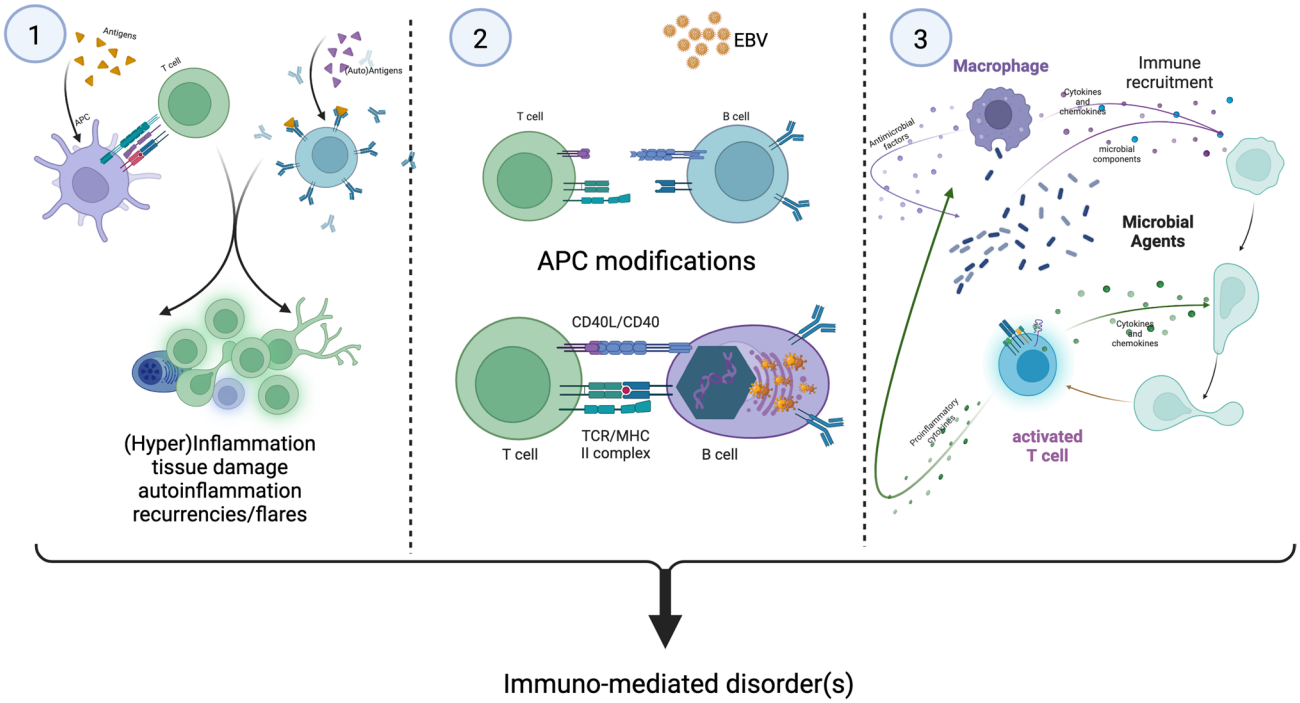

Fig. 3 Two microbial agents for one disease. Panels 1 and 2 show how two microbes may lead to a single autoimmune disease, one activating the T cell response and the other inducing the B cell response (1) or modifying the antigen processing or presentation by B cells (2). Panel 3 illustrates the possibility that microbial agents modify the activation, processing and presenting ability and secretory behavior of macrophages rather than B cells

prominent role [168, 169]. When we examined the repertoire of T cells in the epicardial adipose tissue (EAT) we found that a large fraction (approximately, 50%) of samples from N-STEMI patients at their first episode shared the presence of a public TCR [73]. Distinct individuals use the same receptor to specifically recognize a given antigen/epitope. Arguing that the finding of this shared clonotypic receptor could imply a common MHC, we found that HLA-A0301 allele was enriched in N-STEMI patients and poorly represented in other subgroups with other cardiac diseases, and that most of patients sharing the common public TCR also shared the HLA-A0301 allele. To the best of our knowledge, the association between ACS and HLA alleles had not been previously reported.

To examine the interaction between the public TCR and HLA-A0301, we performed in silico analyses that allowed us to deduce a hypothetical optimal sequence for the epitope driving the T cell response [73]. In a previous work, some bacteria belonging to the gut microbiota could be found in EAT during N-STEMI and it has been demonstrated that the non-inflamed EAT obtained from patients suffering from valvular pathology contained a very limited, if any, DNA from bacteria, in contrast with EAT from Acute Coronary Syndrome patients and from Stable Angina patients [169]. When we searched the genome of these bacteria, for sequences able to generate peptides homologous to the one we had described in silico as optimal candidate for the formation of "shared TCR/peptide/HLA A03 complexes", we found that sequences from three bacteria (*Ruminococcus*, *Rickettsiales* and *Cyanobacteria*) were all good candidates [73]. Thus, sources of candidate epitopes, HLA restricting element and TCR could all be found in the appropriate anatomic district of N-STEMI patients at disease.

Therefore, we suggest that T cell recognition restricted to small peptides irrespective of the source of the peptide itself, opens the way to the possibility that more than one microbial agent leads to activation of a converging TCR repertoire and to disease, confounding the picture about the role of microbial agents in the determination/triggering of the disease (Fig. 4).

The pathogenic effect of this allo-specific response is probably linked to the "ectopic", non-"physiologic" distribution of one or more microbial agents, as the emigration of gut microbiota from the gut, an immunomodulatory anti-inflammatory district, or in general from the periphery to the cardiac endothelium or the Epicardial Adipose Tissue, considered the "lymph node of the heart", a site devoid of anti-inflammatory properties. This hypothesis was suggested also for Multiple Sclerosis (MS), showing immuno-histology evidence of anti-EBV CD8-mediated response within the brain of MS patients [42]. The fact that a massive EBV reactivation occurs in MS patients following a bone-marrow

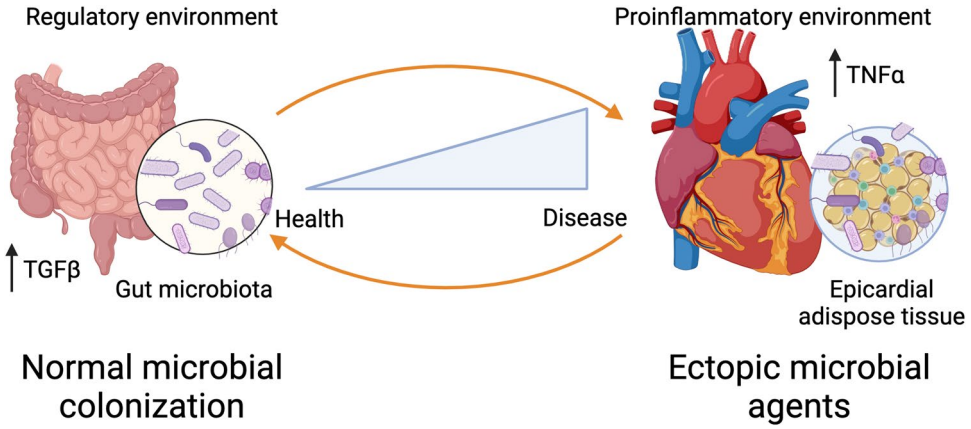

Fig. 4 Tissue specific microenvironment modulates the pro- and anti-inflammatory attitude of T cells (when in Rome do like Romans do). Microbial agents participate to immune system modulation in the immuno-regulatory environment of the gut, for example amplifying the production of TGFβ [211]. Yet, the same or similar species of microbial agents ectopically located act as detrimental and negative stimulator of immune system when spread to "non-modulatory" tissues (such as the hearth in the figure), breaking immune tolerance and generating a pro-inflammatory environment and inducing pro-inflammatory cytokines such as TNFα [169, 212, 213]

transplantation without recurrence of disease [170] points to the relevance of the need for microbial agents and T cells to traffic to an appropriate site in order to drive a complex disease, as it will be discussed below.

Microbial agents-dependent inflammatory diseases development: two models of regulation of T cells trafficking and homing to target organs

Modulation of trafficking properties of pathogenic T cells can explain the clinical course of many multifactorial diseases that alternate periods of flare and quiescence. It has been reported that infections often precede such flares [9, 171–178]. The pathogenesis of flares of diseases in fact may rely on the migration of previously activated T cells to the sites where they can exert a pro-inflammatory role leading to the clinical symptoms. To summarize, T cells need to be activated/reactivated, egress from the lymph nodes, cross the endothelia and finally home to the target site. A large array of ordinated cell–cell and cell-soluble molecules interactions are needed for each of these processes to occur. On the T cell side, the main molecules involved are integrins (LFA-1, mainly), selectins, chemokine receptors and CD44. All these molecules, together with the other involved in these processes, have been widely studied, not only to understand mechanisms underlying immune/dis-immune disorders, but also to find potential new targets of therapy for different diseases.

As we describe below, microbial agents can regulate the expression of these molecules, both in *cis*-with respect to antigen recognition, by cognate-dependent mechanisms, i.e., depending on the recognition of the microbial agent by the TCR and on activation of dendritic cells, DC, and in *trans*, i.e., by cognate-independent mechanisms, with microbial derived motives interacting directly with T cells.

The cognate recognition of a peptide/MHC complex on the surface of a DC leads to numerous effects in the T cells that regulate directly or indirectly their trafficking (*cis*-regulation). The first molecule regulated by the cognate interaction is LFA-1, normally expressed in a low-binding affinity conformation. Upon TCR interaction with the peptide/MHC complex, its conformation is modified into a high-binding affinity form, leading to a stabilization of the immune synapsis, further promoting T cell activation. At the same time, LFA-1 is relevant for the firm adhesion of T cells to endothelia during the extravasation process; T cell activation regulates various ligands of the selectins, responsible of the rolling—extravasation phases—with the same mechanisms involved in the diapedesis of all leukocytes.

Another example of *cis*-regulation of T cell trafficking by microbes is operated by CD103 (α7β4 integrin) on $CD8^+$ T cells. This molecule is required for the crossing of endothelia by (T) cells. Suarez-Ramirez and co-workers [179] have observed that the expression of CD103 is regulated by TGF-β secretion, by the APC, that is in turn dependent on TLR4 [180].

Furthermore, chemokine receptors (CR) on T cells are also finely regulated by TCR. A paramount model for the role of CR in the organ-specific T cell trafficking is the involvement of CXCR3 in the T cells homing to the Central Nervous System (CNS). Indeed, the expression of CXCR3 accompanies the infiltration of CNS by T cells in a large variety of disease of infectious origin [181–184], as well as in multifactorial diseases such as Alzheimer's Disease (AD) [185] and MS [186]. The pattern of CR expressed by T cells depends on their naïve/experienced status, and on

the secretory and effector phenotypes [107], that in turn are in part dictated by the activation of DC by infectious agents, via Pathogens' Associated Motif Pattern Receptors [106]. It is however interesting to note that CNS infiltration is not absolutely dependent on CXCR3 expression [184], and therefore other molecules can bypass the role of CXCR3 in T cell homing to the CNS.

The *cis*-regulation of trafficking via modulation of the repertoire of CR appears to be deterministically dependent on the infectious agent that had originally led to DC activation and T cell priming. It predicts that re-infections with the same agent will lead to the re-activation of antigen-specific T cells that will maintain the same trafficking properties. On the other hand, infection by other unrelated agents will not interfere with this loop, unless cross-mimicry exists between the initial and the subsequent infectious agents (Fig. 5).

Since the first reports of the presence of several TLRs on human [187] and mouse [188] T cells, the possibility was raised that microbial agents act directly on T cell. The first lines of evidence showed a role for TLRs in the co-stimulation of naïve T cells and on promotion of pro-inflammatory cytokines secretion. In 2013, however, we first demonstrated that TLR2 expressed on T cells modifies their trafficking out of lymph nodes, following activation in vivo [104], and that it also regulates the distribution of CNS infiltrates [106] (*trans*-regulation of T cell trafficking). We later showed that all TLRs expressed by T cells were able to modulate levels and alternative splicing of the mRNA specific for CD44 variants in mouse and human T cells, possibly via the β-catenin pathway [107]. The repertoire of CD44 variants elicited and the need for concurring TCR engagement depended on the TLR engaged. The type of CD44 variant in turn dictated the trafficking properties of activated T cells within the CNS. The same role for CD44 variants has been shown in regulating the migration of cancer cells [189–194].

Along these results, we suggest that microbial agents can modify the trafficking properties of antigen-experienced T cells also in *trans*-, i.e., in an antigen-independent manner, by acting directly via TLRs expressed by previously activated T cells. In fact, an "unwanted" modification of previously primed T cells trafficking can occur by subsequent encounters with unrelated microbes. Again, more than one

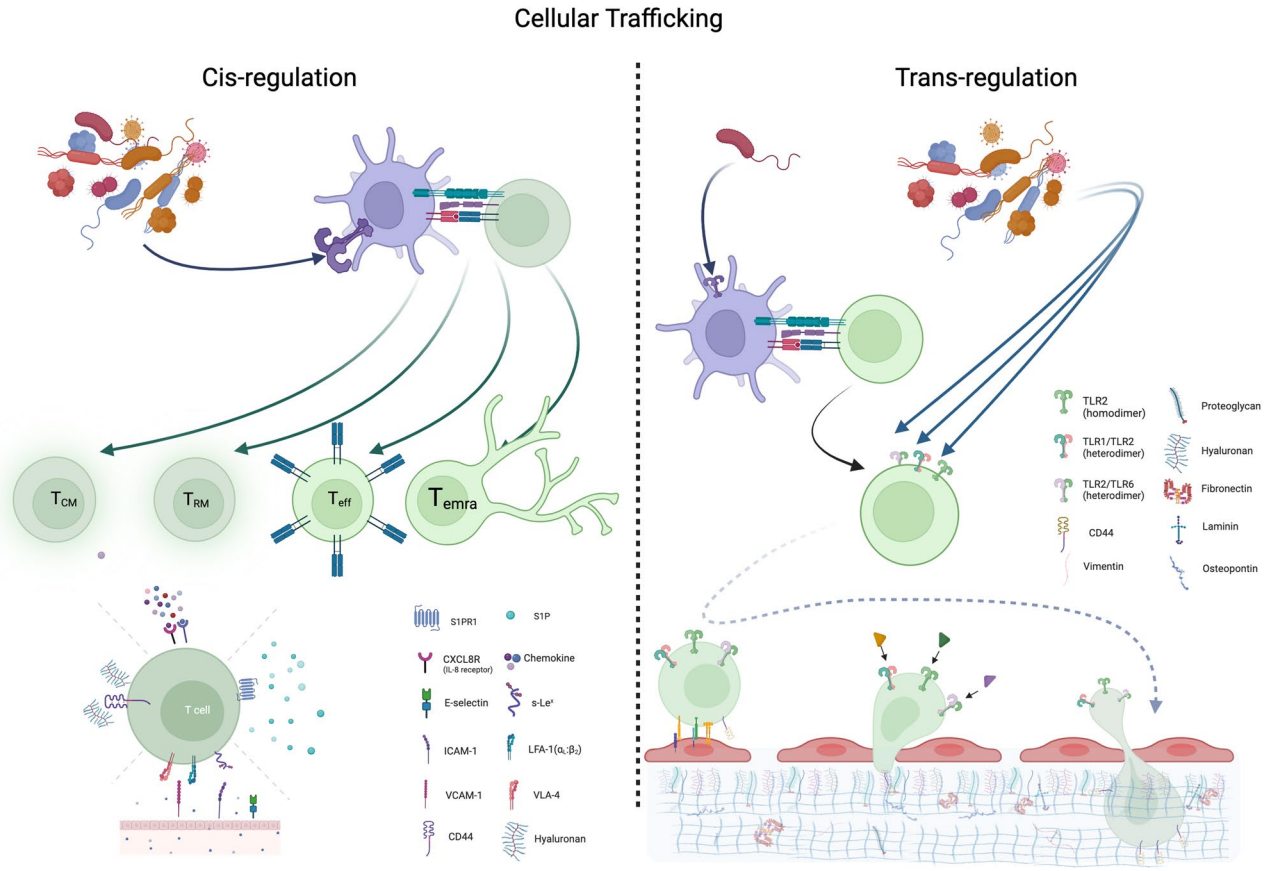

Fig. 5 *Cis*-and *trans*-regulations of T cell trafficking are modulated by microbial agents. In the left panel, microbial agents can modify T cell proliferation and phenotype via APC activation and T-lymphocyte priming (*cis*-regulation of trafficking). *Trans*-regulation on the right panel: different microbial agents can directly modulate the expression of adhesion molecules, such as CD44 variants, and the migration to target tissue(s) (*trans*-regulation of trafficking)

microbial agent concurs in the determination of a multifactorial disease, one by priming pro-inflammatory T cells, others leading to clinical flares through the modulation of trafficking. As said above, such a sequential role for multiple and, in this case, even variable microbial agents result in confounding the role of infection/colonization in the etiology of multifactorial/complex diseases (Fig. 5).

Opportunities and challenges

The role that microbial agents play in the determination and recurrences of multifactorial common diseases opens the way to new therapeutic approaches, but also poses significant technologic and scientific challenges [195].

Traditionally, host-microbial interaction studies classically focus on the definition of the cellular and molecular mechanisms of pathogenesis, the identification of microbial virulence factors and host responses accountable for the emergence of the signs and symptoms of disease. The impact of microbial agents and of silent infections should be evaluated in the context of the complex interplay between microbes and their hosts, with a proper assessment, in the short and long terms, of the immunological consequences on host homeostasis. Modulation of innate and adaptive immune responses by asymptomatic infections may in fact have beneficial consequences on the human host having broad immunological and biological implications on development of effective and lasting immune responses. As said above, early life exposure, to microorganisms is able to prime the immune system, generating different consequences in the further individual host–pathogen interactions and impacting on memory and cell polarization [136–138] (Fig. 6).

Differentiation of specific T cells populations is affected by microbial-fermented products as is the case of butyrate, produced by groups of gut bacteria as *Clostridia*, that induces regulation of Treg cells [196], thus contributing to establish immunological homeostasis in the gut. Interestingly, microbiota-derived butyrate was shown to curb autoimmune responses in a model of RA by inducing follicular regulatory T cells (TFR) [197] and supplementation of short-chain fatty acids (SCFAs) ameliorated microbiota-driven allergic lung inflammation by inhibiting T cell and DC-dependent processes [198].

Similarly, vaccines and vaccination strategies may influence the host-microbial interaction and its consequences. For instance, immunity elicited by vaccines can be effective in preventing infection, or rather may only prevent disease and these differences can impact on the ability of a given vaccine to reduce the corresponding microbial circulation in the community. In this regard, it has been observed that there is a higher burden of *Bordetella pertussis* (*Bp*) infection in vaccinated subjects than previously anticipated [199], with asymptomatic or pauci-symptomatic infections more frequent among those immunized with the acellular pertussis (aP) vaccine compared to those immunized with the inactivated whole cell pertussis (wP) vaccine or those previously infected with *Bp* [200, 201]. Interestingly, in Japan, where vaccination with the aP vaccine is completed with four doses within 24 months of age, adolescents show antibody titers higher than elementary school children [202], supporting the hypothesis that *Bp* asymptomatic infections at school age are responsible for the observed boosting effect. Immunity elicited by these asymptomatic infections among vaccinated subjects seems to protect against subsequent *Bp* infections, similarly to what observed following natural infection or vaccination with wP [199].

These observations highlight the many consequences that vaccines may have in the dynamic host–microbe interactions at cellular and tissue level, with a yet unexplored impact on the innate and adaptive immune responses (immunophenotypes, T cell trafficking, etc.) and shall be properly considered if we aim to design immunological therapeutic interventions to prevent or treat multifactorial diseases.

A first opportunity is of course to prevent the occurrence of "infection-induced" complex diseases, by means of vaccination against the drivers. Such a possibility poses several challenges to immunologists and public health researchers as well.

First, how to identify the driving microbial agents. We suggest that in some cases the scientific community can proceed to a sort of "reverse immunology" approach, studying the TCR distribution first, by single-cell sequencing the target organs or the draining lymphoid tissues. If some TCR sequences appear to be shared by a fraction of patients, the next step would be to determine if a common HLA allele or alleles with a similar binding groove is/are also shared by the cohort. Then, by means of one of the methods recently proposed [20, 73, 99, 100, 203, 204], it will be possible to determine the epitope recognized and from that the microbial agents involved.

A second challenge would be how to vaccinate without posing the risk of accelerating the development of the disease itself rather than preventing it. Thus, a careful definition of a molecular target must be performed, avoiding the induction of an immune response towards the very molecule that is the target of the pathogenic immune response.

Finally, it must be understood that this approach will be limited in its success to the cohort of subjects that share the same HLA predisposing alleles and a wide fraction of cases will not be prevented anyway. Thus, a careful consideration of costs and benefits by public health researchers must be assessed.

Treatment by antimicrobial therapy would of course be a second opportunity. Several observational papers have examined the effect of antibiotic treatments on the

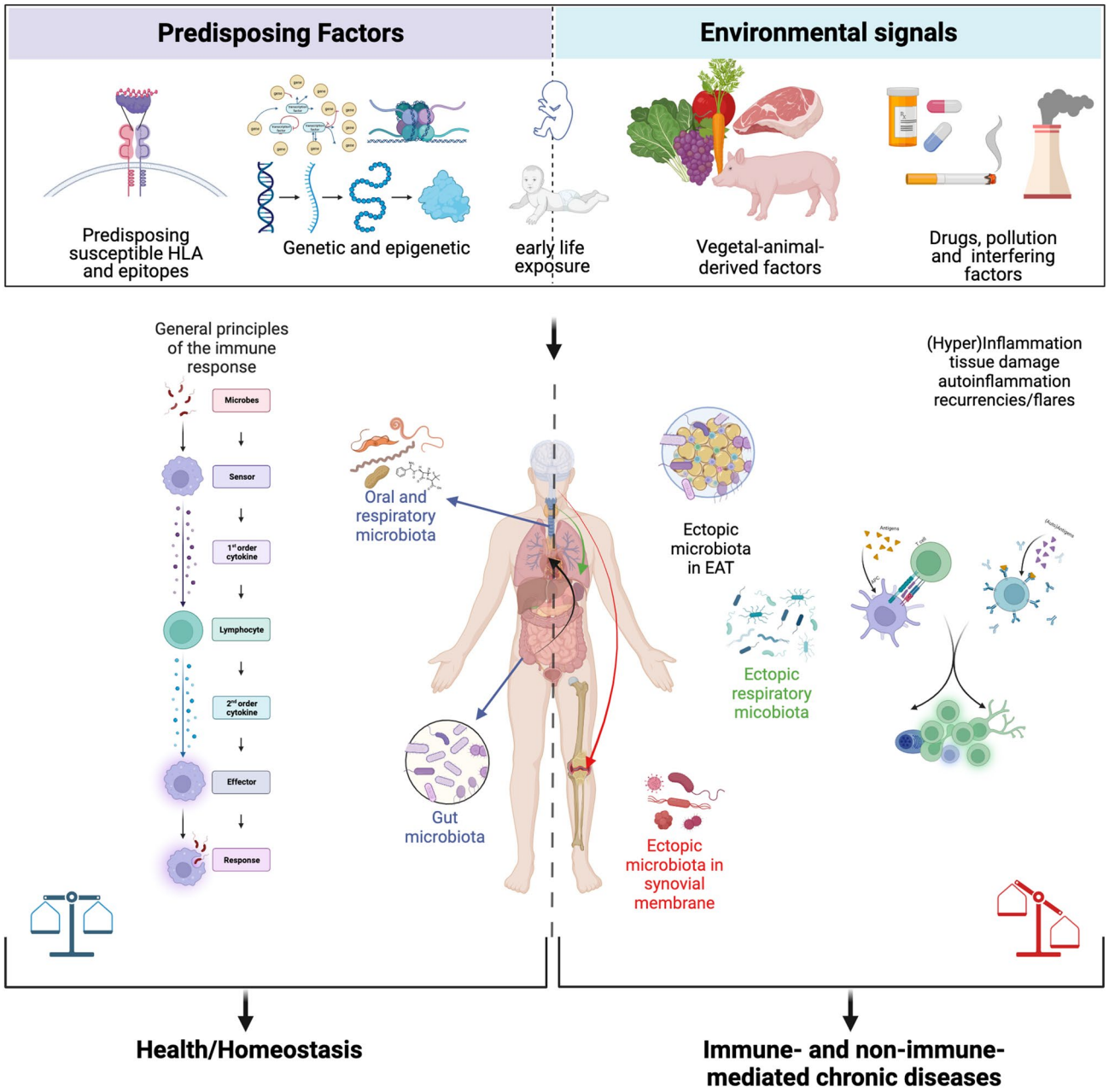

Fig. 6 Every cloud has a silver lining. Examples of main potential pathogenetic effects of microbe-immune interactions. The upper boxes show some of the possible predisposing and environment derived factors contributing both to homeostasis and immune dysregulation. Left side of the figure displays that the combination of these factors can guarantee the health/homeostasis with a "normal" distribution of microbiota(s) and balanced immune responses. On the other hand, as shown in the right side of the figure, these factors can determine different impacts on microbial-immune responses and consequently have the potential to cause/enhance/exacerbate chronic disease. EAT: Epicardial Adipose Tissue. ACS: Acute Coronary Syndrome

diseases we are focusing on in this work, mostly showing a favorable effect on the diseases progress. Prolonged (> 14 days) treatment with antibiotics of various classes associated with a lower incidence of MS in the following 3 years [205]. In the same disease, the tetracycline Minocycline is in a phase 3 trial, and halved progression of Clinically Isolated Syndrome to MS for at least 6 months [206]. Treatment with tetracyclines was also able to reduce the risk of myocardial infarction [207], although in that publication no further distinction between STEMI and N-STEMI was examined. According to the evidence about the role of periodontopathic bacteria, several antibiotics have been reported to be useful in the treatment of RA, as reviewed in [208].

The use of antibiotic has however to be taken with caution, especially in a preventive setting. In fact, the epidemiological danger of antibiotic resistance will be one of the most important health emergencies of the very near future. The damage generated by any adverse effects of prolonged/preventive antibacterial therapies could also outweigh its benefits, possibly overcoming the risk of developing a complex disease. Preventive antibiotic therapy may also perturb the microbiota, leading to a more pro-inflammatory status and thereby accelerating inflammatory diseases. An intriguing observation was that subjects that had been treated with antibiotics were at higher risk to develop RA, although with the caveat that this observation may rather reflect a higher incidence of infections leading to the development of RA, rather than a direct effect of the antibiotic itself [209].

Interfering with specific mechanisms involved in T cell trafficking can provide another opportunity in the treatment of complex diseases. One main advantage of this approach is that it does not need to identify the specific microbial agent driving the disease. It however requires that therapeutic agents (be them antibodies or small molecules) must be precisely tailored on their targets to avoid side effects that can be dramatic. As an example, antibody against the binding site of CD44, shared by all CD44 variants, has been shown to be an excellent tool to prevent experimental MS, but cannot be used in humans due to life-threatening side effects [210]. However, we have shown that v8- and v7-CD44 isoforms are selectively enriched in cells from the CNS fluid, and only the v7-variant is associated with active inflammatory flares. Thus, it is likely that a therapy tailored on CD44v7 may actually be more effective and less dangerous than a total blockade of CD44 [107].

Conclusion

We show here how that the role of infectious agents lies on a blurred edge between asymptomatic infections and triggering of complex diseases, and that the assessment of their role in the development of multifactorial disease is concealed by the complexity of T cell recognition and trafficking regulation (Fig. 6). It is becoming clear that the etiology of infectious diseases cannot be simply "reduced" to the role of a microbe, but it is rather the results of a complex interaction between the microbe and the host, with the disease being usually the least likely outcome. Yet, the host–microbe interaction taking place during symptomatic or asymptomatic infection, with the possibility to shape immunophenotype and cell trafficking, can have a relevant and even dominant role in the determination and clinical course of several common "multifactorial" diseases. The technological advances of the latest 10 years have provided tools powerful enough to study this complex network. At present, given the ever-increasing evidence in this field briefly summarized here, the biomedical community is possibly required to be open to a cultural framework shift, in which microbial agents re-gain the central stage in many and largely prevalent human diseases. Resources and expertise should consequently be oriented toward the molecular identification of biologic agents and the fine characterization of mechanisms of pathogenesis, to pave the way for new therapy targets and tools.

Author contributions Conceptualization, FR, GD, LI, MS and GDS; data curation, FR, GD, and GDS; writing—original draft preparation, FR, GD, and GDS; writing—review and editing, FR, GD, LI, MS and GDS; supervision, FR and GDS; All authors have read and agreed to the final version of the manuscript.

Funding This work received the support of "Fondazione Cassa di Risparmio di Perugia", Project 2021.0347 (GDS).

Availability of data and materials Not applicable.

Declarations

Conflict of interest The authors declare no conflict of interest.

Consent for publication All the authors revised and approved the final version of this manuscript, giving their consent for publication.

Ethics approval and consent to participate Not applicable.

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