



How Far Do Our Opportunities for Intervention Extend?

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Research Article

Volume 11 Issue 2

Received Date: September 11, 2026

Published Date: October 21, 2026

DOI: 10.23880/ooaj-16000316

Abstract

Introduction: Microorganisms are the predominant part of the planet's biological diversity. They have colonized and colonize the human body, transiently and permanently, actively participating in its physiology, metabolism, and immunity.

Objectives: To determine whether cytoskeletal structure, metabolism, humidity, oxygen concentration, temperature, pH, and/or resource availability, individually or in combination, are determinants of the dominant relationships between representatives of the kingdoms and preferences for the corresponding anatomical niches. We need to answer how the qualities of microorganisms change when moving into another niche, whether this leads to local or systemic suppression of the immune system, and whether it affects the composition of the microbiota.

Results: Since the beginning of the 21st century, noncommunicable diseases have predominated over infectious diseases. There are certain obstacles that need to be overcome before the use of members of the 5 kingdoms in the near or distant future in strategies for modifying the microbiota and preventing or treating diseases with conventional medications. In the microbiota, some species have a dominant influence on the immune system independently of others. Mapping the species colonizing ecological niches will allow us to predict possible unintended effects.

Conclusion: Knowledge-based interventions could help us to limit the redirection of T-cell subsets during the transition from acute to chronic infection and limit the occurrence and course of diseases. Nature does not tolerate absolute winners/dominators; therefore, using members of the 5 kingdoms alone or in combination with conventional drugs will have less than a 100% success rate. This limits our ability to always influence the relationships in the holobiont.

Keywords: Holobiont; Pathogens; Microbiota; Probiotics; Prebiotics; Prevention; Interactions

Abbreviations

ACE2: Angiotensin Converting Enzyme 2; ADAM10: A Disintegrin and Metalloproteinase; AhR: Aryl Hydrocarbon Receptor; AIP: Autoinducing Peptide; AMP: Antimicrobial Peptide; AMR: Antimicrobial Resistance; AdV: Adenovirus; CAZymes: Carbohydrate-active Enzymes; CoV: Coronaviruses; CTL(CD8+): Cytotoxic CD8+ T Lymphocytes; DAO: Diaminooxidase; DC: Dendritic Cells; DOL: Division of Labor; DSF: Diffusible Signal Factors; EGF: Epidermal Growth

Factor; EBV: Epstein-Barr Virus; GIT: Gastrointestinal Tract; GLA: Gut-lung Axis; GM: CSF - Granulocyte-Macrophage Colony-Stimulating Factor; GTDB: Genome Taxonomy Database; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HCV: Human Cytomegalovirus; HDAC: Histone Deacetylases; HDV: Hepatitis D Virus; HE: Hemagglutinin Esterase; HFRS: Hemorrhagic Fever with Renal Syndrome; HMO: Human Milk Oligosaccharides; HMPV: Human Metapneumovirus; HNMT: Histamine N-Methyltransferase; HPV: Human Papillomavirus; HRV: Human Rhinovirus; IAV: Influenza A

Virus; Icis: Immune Checkpoint Inhibitors; IFN: Interferon α/β and γ ; IL: Interleukin; iNKT: Invariant Natural Killer T Cells; IPI: Invasive Pneumococcal Infection; IRF1: Interferon Regulatory Factor 1; ISG's: Interferon-stimulated Genes; iTREG: Invariant Regulatory T cells; LAB: Lactic acid bacteria; LEV: Live Enterovirus Vaccine; MAIT: Mucosal-Associated Invariant T Cells; MC: Mast Cells; MCMV: Mouse Cytomegalovirus; MDCK: Madin-Darby Canine Kidney Cells; MERS-CoV: Middle East RESPIRATORY SYNDROME CORONAVIRUS; MHC-I: Major Histocompatibility Complex Class I; MHC-II: Major Histocompatibility Complex Class II; mLN: Mesenteric Lymph Nodes; MPO: Myeloperoxidase; NAAT: Nucleic Acid Amplification Test; NETs: Neutrophil Extracellular Traps; NF- κ B: Nuclear Factor Kappa-Light-Chain-Enhancer Of Activated B Cells; NLRP3: NLR Family Pyrin Domain Containing 3; OUT: Operational taxonomic unit; OS: Overall survival; PCV: Pneumococcal Conjugate Vaccine; PFU: Plaque-Forming Units; PFS: Progression-free Survival; PIV: Parainfluenza virus; PPSV: Pneumococcal Polysaccharide Vaccine; Prp: Cellular Prion Protein; Pspa: Surface Protein Antigen; PRB: Predation-Resistant Bacteria; PRRs: Pathogen Recognition Receptors; QS: Quorum sensing; ROS: Reactive oxygen species; RSV: Respiratory syncytial virus; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; SIDS: Sudden Infant Death Syndrome; Tc: *Tritrichomonas* Casperi; Tmu: *Tritrichomonas* Musculis; TCRs: T-Cell Receptors; TEM: Effector Memory T Cells - CD4+, CD8+ ; TGF- β : Transforming Growth Factor-Beta; TIMP-3: Tissue Inhibitor Of Metalloproteinase-3; TJ: Tight Junctions TNF -Tumor Necrosis Factor; TRAIL: TNF-Related Apoptosis-Inducing Ligand; TREG: Regulatory T Cells, CD4+, FOXP3+ Lymphocytes; TRM: Tissue-Resident Memory T Cells - Subset Of Long-Lived Memory T Cells; WGS: Whole-genome Sequencing.

Introduction

Microorganisms are the predominant part of the biological diversity of the planet. They have colonized and colonize the human body, transiently and permanently, actively participating in its physiology, metabolism, and immunity. In 1969, Robert Whittaker systematized them into 5 kingdoms, including archaea, viruses, bacteria, fungi, and protists. Archaea inhabit the respiratory tract, gastrointestinal tract, urogenital tract, and skin. Habitat, ethnicity, diet, and age determine their diversity. Closely related to bacteria, on the one hand, they support growth, metabolism, and phenotype formation, and on the other hand, the H_2 emitted by the latter is important for their growth. Studies in animal models indicate that archaea can participate in the activation of immune cells, and the methane released by them promotes the production of anti-inflammatory molecules and reduces pro-inflammatory ones.

The viruses associated with us are single-stranded (ss) and double-stranded (ds) DNA and RNA eukaryotic, prokaryotic (bacteriophages), and specific for humans: human endogenous retroviruses HERVs and filoviruses ssRNA non-retroviruses. In eukaryotes, RNA viruses predominate and infect human cells, fungi, and parasites. Among prokaryotic viruses or bacteriophages, dsDNA phages predominate. They infect bacterial cells and archaea, shape the composition of their communities in different niches, and represent about 90% of the intestinal virobiota. HERVs are integrated into the human genome and make up about 8% of it. They are transmitted through vertical transfer. Initially considered to be DNA without biological function due to accumulated "defective" or non-pathogenic mutations, among them there are also segments with biochemical activity, promoter function, and regulatory networks. They have the potential to assemble and trigger an immune response through pathogen recognition receptors (PRRs) or "viral switches". Activation of HERVs alters gene expression and has been linked to both interferon response, brain and placental development, and regulatory proteins in cells of 21 types of tumors. Viral induction of hTERT may cause this. Filoviruses do not integrate into the DNA of the host cell. They cause diseases such as Ebola, hemorrhagic fever, and Borna disease, but carriers of their genetic sequences have evolutionary and adaptive advantages. It is estimated that 50% of the viral composition is unique to each individual, and only a fraction of it is shared between individuals [1-5].

Bacteria are a group of prokaryotic microorganisms. They are "transient" - causing infectious diseases, opportunistic pathogens, and part of the sold probiotics and permanent, mostly non-pathogenic members - colonizers or commensals living in symbiosis with a macroorganism. About 50% of them cannot be cultivated. Permanent members, but in limited populations, they are also causative agents of many diseases, such as *Pneumococcus*, *Staphylococcus aureus*, and others. Permanent members involved in immune regulation are called autobionts, and those causing diseases are called pathobionts. In eubiosis, the host, auto- and pathobionts are in perfect balance. Bacteria are the best-studied immunologically dominant symbionts, but immune reactions cannot be clarified without knowledge of all interkingdom interactions [6-13]. The fungal component has transient and permanent members but is less abundant and diverse. Commensals are in constant relationships with the macroorganism, including opportunistic pathogens. Fungi constantly move along the commensal-pathogen continuum. Together with the other components of the microbiota, they shape the immunity and physiology of the host.

Protists are members of the eukaryotic microbiota. They are predominantly unicellular organisms that share

certain morphological and physiological characteristics with animals or plants, or both. They are thought to have evolved from bacteria and archaea. They exist as spores and cysts in their resting state, and they use photosynthesis, absorption, and engulfment to feed. Bacteria resistant to predation (PRB) by unicellular eukaryotes, packaged in vesicles, gain an evolutionary advantage in nutrient-poor environments, are more infectious than free-living bacteria, and have increased resistance to antibiotics.

Members of the five kingdoms are constantly engaged in dialogues involving physical interactions, quorum sensing, antimicrobial production, immune response modulation, and nutrient exchange [14]. These interactions underlie complex symbiotic, synergistic, competitive, and predatory relationships. The beginning of their clarification was laid by Antonie van Leeuwenhoek, studying the conditions under which bacteria associated with surfaces, in the form of dental plaque, come into contact. They coexist as planktonic forms and organized ecosystems (biofilm). Through glycoconjugated bonds, the former merge and attach to various surfaces, forming an exopolysaccharide matrix. After maturation, cells are released from the biofilm, and are directed to other surfaces [15]. Up to 99% of the bacteria in the human body coexist with representatives of other kingdoms in the form of a biofilm. The oxygen tension gradient determines increased metabolic activity at the surface of the matrix and reduced/quiescence in the deeper layers, and the spatial arrangement of strains is determined by their interactions. The expression of specific genes responsible for the synthesis of biofilm components, bacteriocins, horizontal transfer of plasmids, and stress response is determined by two types of signaling molecules-autoinducers. Their accumulation in the local environment, or quorum sensing (QS), determines the density of bacterial cells. Of these, acyl homoserine lactones (AHL), autoinducer-2, oligopeptides, diffusion signaling factors (DSF), and autoinducing peptides (AIP) are the most recognizable. Their threshold concentration determines the expression of virulence factors, sporulation, and biofilm formation [16-18]. Biofilms provide their members with high resistance to opsonization, phagocytosis, and antibiotics [19].

The term microbiome, introduced in 2001 by Joshua Lederberg, unites the genome of all microorganisms living on and in the human body. Microorganisms colonizing the human body form the human microbiota. The skin and mucous membranes are associated with rich and complex ecosystems composed of bacteria (bacteriota), fungi (mycobiota), viruses (virobiota), archaea, protists, and helminths [20]. The man is host to approximately 100 trillion microbes, most of which reside in the oral cavity and gut. Their interactions and natural selection govern the dynamics of the microbiota, which determines the biology,

ecology, and evolution of the host through its metabolic, protective, and trophic functions. The metabolic function is based on the products of tryptophan (Trp), histidine (His), and phenylalanine (Phe), which regulate homeostasis, the formation of an anaerobic environment, the suppression of pathogen virulence, and the induction of immune tolerance. The protective function is expressed in the production of bacteriocins that inhibit the growth or survival of the pathogen, and the trophic function, through the mobilization of bacteriophages, minimizes the impact of specific strains on commensals. Our microbiota interacts with those of organisms within a given environment. Bacteria that model host physiology are strict anaerobes and are characterized by loss of viability upon transfer. Diversification of most strains is associated with human migration. The phenotype is an expression of the relationship between the host and the microbial genomes associated with it. The concept of the holobiont is based on interspecific symbiosis, formulated by Lynn Margulis in 1991. Initially, it was considered a simple biological unit - a host and a hereditary symbiont.

Now the host and its associated taxonomically diverse microbial communities are considered one. The basis of homeostasis in the holobiont is host-microbe-environment relationships. Ilana Zilber-Rosenberg and Eugene Rosenberg in 2007 introduced the term hologenome, or the sum of the genomes of the host and its associated microbial communities - the collective genome of the holobiont. The human genome contains about 20,000 genes, but our hologenome carries >33 million genes [21-27]. Unlike the human genome, which adapts slowly, the microbiome evolves more rapidly in response to environmental changes associated with socio-economic development. The genetic material of all organisms forms the metagenome, and the carriers of this material are properly called metabiota. The diverse conditions in which many of them live do not allow them to be cultivated and typed using standard techniques. The human body has "formed" three lines of defense. The first is based on nutritional dependencies between members of the 5 kingdoms. The microbial ecosystem in different niches is a complex community as members compete for limited resources. The lack of free resources or "open niches" makes it difficult for new microbes to colonize, a phenomenon known as "colonization resistance". The "Black Queen" hypothesis helps us to explain the stabilization of positive interactions between organisms in complex habitats through gene loss and the resulting dependencies [28, 29]. Over phylogeny, they have become so complex that some strains cannot survive on their own. Dependencies on food type improve their vitality and relationships against stress, competitors, and cheaters. The sharing of primary metabolites is the basis of the existence of species in nature [30]. D'Souza traces two ways of supplying metabolites in cross-feeding. In the first, by sharing hydrolytic extracellular enzymes - proteases,

invertases, and lipases - the available substrates are broken down from the common set of molecules. In the second way, one microorganism/donor converts a primary substrate into a product used by another/acceptor [31].

The interaction of commensals with the mucosal immune system forms the second line of defense. Communication with immune cells expressing Toll-like receptors (TLRs) or GPR41/43 is mediated by microbe-associated molecular patterns (MAMPs)- SCFAs. They shape host immune responses by regulating the development of lymphoid tissue, maturation, and function of various immune cell types [32,33]. TLR signaling in the neonatal establishment of the gut microbiota has long-term effects on myelopoiesis. Innate, innate-like, and adaptive immune cells—tissue-resident memory T cells (TRM), effector memory T cells (TEM), regulatory T cells (TREG), mucosa-associated invariant cells (iMAIT), unconventional (invariant natural killer T cells iNKT and $\gamma\delta$ T cells), IgA-secreting plasma cells, NK cells, macrophages, dendritic cells (DCs), and others—underlie the innate and adaptive immune responses. They also regulate the composition and abundance of the microbiot [34-37]. Conventional $\alpha\beta$ T cells, recognizing peptides presented by the MHC (Major Histocompatibility Complex), are the main part of the T-cell community. Their differentiation is based on metabolic and antigenic dialogues. MAITs are the largest population of unconventional $\alpha\beta$ T cells. These innate-like cells reach 10% in peripheral blood and play an important role in barrier immunity. Their responses are similar to NK cells in viral infection. For the recognition of non-peptide antigens, they use mechanisms different from the standard MHC class I and II antigen presentation pathways.

MAITs, through invariant T-cell receptors (iTCRs), recognize bacterial and yeast antigens derived from riboflavin metabolites presented by the evolutionarily conserved MHC class I-related protein 1 (MR1). The response is of a rapid type and provokes the production of IFN γ , TNF, IL-17, and IL-22, a potent cytolytic response - apoptosis and keratinocyte death of infected cells and bacteria - mediated by perforin, granzymes, and granzysin. The profile of MAIT is determined by tissue localization. In the mucous membranes of the oral cavity, lungs, and female genitals, IL-17 is expressed more strongly, while in the blood, IFN γ and TNF dominate. Rapid MAIT activation also provides an adjuvant effect, generating stronger antiviral CD8 T-cell responses in mice. Their TCR-independent activation is provoked by virus-triggered inflammatory cytokines and engagement of TLRs. After binding to chemokines, they migrate to tissues or areas of inflammation. MAIT antigen-independent activation is observed in HIV-1, hepatitis viruses, influenza viruses, and SARS-CoV-2. Activation of MAITs during influenza infection of human lung epithelial cells in vitro triggers the expression of IFN γ and granzyme B. By recruiting other immune cells,

they provide direct or indirect antiviral protection, but can enhance inflammation and worsen immunopathology. Higher levels of MAITs in mouse models and humans are associated with better outcomes. Chronic viral infections alter host defenses. McSharry et al. reviewed the mechanisms by which some herpesviruses inhibit antigen presentation. HSV-1 suppresses cell surface expression of MR1 and, through proteosomal degradation of intracellular MR1, escapes HSV-1-dependent targeting and inhibits MAIT activation. HCMV inhibits surface expression of MR1 through the glycoprotein gpUS9. Conversely, increased expression of MR1 in cancer cells makes them a target for MAITs. In HIV-1 infection, peripheral MAITs also serve as a viral reservoir. In mouse models, they provide control of bacterial lung infections - *Francisella tularensis*, *Legionella longbeacheae* and *Klebsiella pneumoniae*. Infections with *F. tularensis* and *Vibrio cholerae*, in contrast to viral infections, cause the formation of antigens from riboflavin metabolites. In mice infected with *F. tularensis*, MAIT activation promotes monocyte differentiation in vivo with recruitment of CD4+ T cells, while in *V. cholerae*, B-cell differentiation and specific IgA responses are observed [38,39]. MAITs also play roles in the protection, maintenance, and repair of barrier tissues in an amphiregulin MR1-dependent manner. Their activation is determined by the type of virus and which cells and organs it infects. Their cytokine-mediated activation does not exclude the involvement of MR1-presented antigens derived from cellular metabolomes, microbiota, and co-infecting bacteria [40].

iNKTs are innate-like cells expressing an invariant T-cell receptor associated with MHC class I. As with MAITs, viruses do not express antigens that engage directly with TCRs of iNKTs. The cells can be activated in a TCR-independent manner by virus-induced cytokines. Other unconventional cells are $\gamma\delta$ T cells, which recognize partially characterized molecules from stressed, transformed, or infected cells. These include viral antigens that are not restricted by MHC, such as glycoprotein I produced by HSV-1. These T cells are found in peripheral tissues, including mucosal membranes. The different $\gamma\delta$ T cell subtypes, innate-like and adaptive-like, play heterogeneous roles [41,42]. Activation of TRM in the lungs requires the encounter of the lung microbiota with local antigens, as observed in the immune response against influenza viruses [43].

TREG populations have a nuanced role in activating or inhibiting antiviral mucosal T-cell immunity in infected tissues. The presence of IL-10-secreting T cells is a determinant of herpesvirus chronicity. Ann Campbell et al. have shown that depletion of TREG limits reactivation of chronic CMV mucosal infection. Inhibition of IL-10R signaling in the chronic phase reduces IL-10 levels from virus-specific IL-10+CD4+ T cells, reduces viral replication, and improves

control of MCMV. HCMV-induced TREGs suppress specific T-cell responses *ex vivo*, and iTREGs lead to reduced vascular pathology in adult subjects. Such an effect was not observed in the nasal mucosa. TREGs in HSV-2 infection in murine models promote DC traffic from the vaginal mucosa to draining lymph nodes, and their depletion and suppression of NK-DC signaling impair CD4+T-cell differentiation. In influenza infection, TREG immunity promotes the development of CD8+ TRM from T-bet-expressing regulatory Tr1. IL-10+ CD4+ T cells respond to latency-associated proteins in EBV infection. The first two lineages form our baseline resistance through a complex immune response.

The third line of defense is based on the principles of thermodynamics. Human homeostasis gravitates around a temperature of 36.6°C due to its association with the heat capacity of water, whose absolute minimum is in the range of 36.5°±0.5°C. This is the temperature at which cells in the human body require the least external energy to maintain thermal stability and minimize nutrient consumption at the cellular level. This raises the question of who is served by giving an antipyretic below 38.5°C. Beyond maintaining a stable metabolism, endothermy acts as a barrier/a thermal shield that prevents certain pathogens from proliferating.

Objectives: Until the end of the 20th century, infectious diseases were predominant, but since the beginning of the 21st century, the trend has reversed, and noncommunicable diseases have already prevailed. Our task is to determine when, how, and to what extent we can intervene to limit and restore the disturbed ratio. Knowledge of simple positive and competitive interactions between members of one kingdom and different kingdoms is important, but not sufficient. Establishing whether the combination of cytoskeletal structure, metabolism, humidity, oxygen concentration, temperature, pH, and/or resource availability determines the dominant relationships between representatives of the kingdoms and the preferences of microorganisms for the corresponding anatomical niches is important for us. The question we need to answer is how the qualities of microorganisms change when jumping to another niche, and whether this leads to a change in the composition of the microbiota and local or systemic suppression of the immune system.

Wild in 2005 reviewed the epidemiological aspect of environmental influences. Physical, chemical and non-chemical exposures throughout our lives, or exposome, are involved in modifying the microbiota before birth and from birth to adulthood and influence the associated microbial genomes and phenotype. All non-genetic factors include the impact of geographical location, uneven settlement, sanitation, diet, food supplements and drugs, hygiene products, air, soil and water pollution, physical and economic

activity, noise, radiation, socio-economic status - loneliness, education, marginalization, property status, discrimination, access to green spaces, and perception of the surrounding environment. They are also involved in biological processes such as inflammation, body morphology, aging, etc.

Exosome compounds direct their dysregulation through their effects on endogenous metabolites. Genomics has outlined their influence in chronic diseases. Vermeulen, et al. found that non-genetic factors, through phenotypic adaptation/disadaptation, influence the human genome in the short and long term in diseases, reflecting evolutionarily on human biology. The influence of the exposome sounds dry and abstract if not linked to specific epidemiological moments in our history. The second plague pandemic of 1346-1353, which led to 30-50% mortality among the population in Europe and North Africa, according to available archives, is a good example of this. Chronic famine after years of poor harvests, high urban population density for the time, lack of sanitation and waste treatment, poor hygiene habits, large populations of black rats (*Rattus rattus*) and fleas (*Xenopsylla cheopis*), expansion of European trade relations to Mongolia to compensate for grain shortages, and the "import" of rats infected with *Yersinia pestis* with food are the basis for this. If we examine the mortality rates in the cities along the Rhine by ethnicity, an interesting correlation emerges. The mortality rate of Jewish communities is 8-10% compared to approximately 40% in other communities. The relatively limited communication of these closed communities with others partly explains this, but the real reason lies in the implementation of a hygiene protocol based on the religious law of Halacha, a culinary protocol (kashrut), and measures in case of illness of a member of the community according to the book of Leviticus. The first includes mandatory washing of hands with running water up to the wrists after getting up, before eating, and after using the toilet; the mikvah - a facility with a constant flow of fresh water, used for ritual immersion - also performed a function of mechanical cleaning and reducing the population of external parasites such as fleas, the main vector of the bubonic plague. The second requires an examination of the organs of slaughtered animals, separation of used utensils, and a ban on the consumption of spoiled food. These rules contrast with the beliefs of other urban communities. Isolation and washing, removal or burning of the belongings and clothes of the sick person also played an important role. This gave the community a sanitary advantage in those times. Archaeopathology and Jennifer Klunk et al.'s studies of fossil DNA from medieval cemeteries have identified targeted genes related to immunity that confer increased protection or susceptibility to *Yersinia pestis*. In addition to sanitary advantages, genetic isolation or endogamy in these communities has been shown to explain the higher frequency of immune alleles that confer protection. The combination of these factors has provided an

almost fourfold reduction in morbidity and mortality, but not complete protection [44]. It is therefore time to assess how our actions or inactions and dietary habits determine our “health destiny” [45].

It is necessary to start with the formation of the prenatal microbiota, the fetal immune system and neonatal immune modulation. Permanent relationships in the holobiont between microorganisms and the host are formed during the first year of life, in later stages, their effect is limited. It is correct to divide colonization into: prenatal, neonatal, first trimester, and 1st year. The placenta during pregnancy is an interface between the mother and fetus, and the mucosal surfaces lining the respiratory, gastrointestinal, and genitourinary systems play a similar role between the environment and our immune system after birth. During pregnancy, the placenta acts both as a protective barrier and as a vehicle to facilitate the transfer of exposome components, noninfectious and infectious microbial fragments, and metabolites from the mother to the fetus, shaping the prenatal microbiota and the fetal immune system. Before birth and in early childhood, microbial colonization goes beyond passive transfer and actively directs the differentiation of immune cells through metabolic signaling, epigenetic modulation, and the inclusion and exclusion of pathogens. Eukaryotic viruses are capable of causing innate infections. By locally or systemically suppressing the activity and cytotoxic capacity of T-cell subsets, they “model” the niche environment and create conditions for different behavior of commensals and other transient exogenous pathogens.

The effects of herpes viruses - HCMV, EBV, and HSV-2 on immune programming in children and adults contribute to the “atypical” course of some infections. The expression of proteins helps to avoid the host immune response and facilitates the transition of the infection into a latent state. Cellular prion protein (PrP), positioned in various immune-privileged sites, protects cells from damage and immunopathology by modulating inflammation. Its effects are particularly pronounced in stress and viral infections. By binding to immune cells, PrP regulates their function, cytokine responses, and immune synapses. Its potential for “immune silencing” has been studied primarily in mouse models. HCMV infects up to 83% of the human population and is thought to be able to cross the placental barrier. Perinatal infection in 7 out of 1000 children results in permanent neurological and immune damage, while in adults the primary infection is often unnoticed. The ability to infect various mucosal surfaces explains its detection in breast milk, semen, cervical fluid, urine, and saliva. PrP in CMV infection weakens neonatal antiviral T-cell immunity and causes neurological damage. HCMV removes it from the plasma membrane by the metalloprotease ADAM10 and by suppressing the expression of the endogenous

tissue inhibitor (TIMP3). It may be partial, when some PrP remains in the cell pellet or newly synthesized PrP reaches the cell surface (stress-inducible). Cellular regulation upon in utero and postnatal exposure to exosomal components and pathogens such as HCMV has been established only in neonatal CD8+ T cells. In humans, studies of T cells from umbilical cord blood of newborns show expression of lower levels of inhibitory receptors compared to adults. Neonatal cells are characterized by increased proliferation, rapid accumulation during infection, lower diversity, expression of transcripts, and an all-or-none TCR response [46,47]. Such regulation is not observed in B lymphocytes, CD4+ and uncommitted T cells. By binding to cytotoxic CD8+ T lymphocytes, soluble PrP suppresses the production of IFN γ and TNF through negative effector regulation of the CD8+ T-cell immune response. Initially, conventional CD8+ virus-specific T cells are predominant, but later proinflammatory T cells predominate. A similar role of PrP has been observed with IAV, HIV, and HSV. In chronic infection, tolerance of viral replication without an excessive immune response limits tissue pathology [48]. In rhesus macaques, CD4+ T cells limit transplacental transmission of CMV. CMV-specific CD8+ T cells in peripheral blood, despite low levels of inhibitory receptors PD-1, retain their cytotoxic and proliferative potential. In the presence of strong CD4+ and CD8+ responses elicited by MCMV, only depletion of CD4+ T cells increases viral load in the infected area. HCMV-induced changes lead to an increased risk of EBV infection in children [49]. CMV colonization of the oral and respiratory mucosa is facilitated by suppression of CD4+ T cells by degradation of MHC class II by the M78 protein. Nasal contamination induces a strong TRM response in the mucosa and a weak one in the lung. HCMV CD4+ specific cells in peripheral blood have a TEM phenotype [50]. Upon reinfection, TRM subsets residing in nonlymphoid tissues (NLT) and the mucosa of the small intestine and lung elicit tissue-specific responses.

It is assumed that the primary colonization with bacteria, phages, archaea, fungi, and protists lasts for months, and the subsequent waves are shorter. While for the first ones the method and speed have been studied, for archaea and protists there is not enough data. Colonization is based on vertical and horizontal types of transmission. The first one includes the mode of birth - natural/vaginal or cesarean section. Vertical transmission between generations determines the evolution and adaptation of the human microbiota and the coevolution with the host. The baby's contact with the skin, vaginal mucosa, maternal intestinal microbiota (dominant), and breast milk are the basis of this transfer. In vaginal birth, Bifidobacterium, Escherichia, and Bacteroidetes predominate and are more stable during the first year. The composition of the newborn is similar to that of the maternal microbiota but enriched with Lactobacillus and Bifidobacterium. In caesarean section, Staphylococcus,

skin-associated, hospital strains, environmental taxa and, to a limited extent, *Corynebacterium* and *Dolosigranulum* predominate. Sources in the horizontal type are hospital staff, father, siblings, relatives, contact with objects and domestic animals. Breast milk is the first functional food, providing beneficial effects on the physiology of the newborn beyond its nutritional value, and in addition to dynamic microbial communities and prebiotic compounds, it contains IgA, lactoferrin, lysozyme, growth factors, and bioactive substances that shape the intestinal ecology of infants. The intestines after birth are free of microorganisms, but within just a few hours, microbial diversity increases. The first bacterial colonizers of the intestines introduce colonizing (induced) phages. Bifidobacteria transmitted during breastfeeding carry prophages known as bifidophages. The abundance of temperate phages is initially high due to a lack of potential hosts. As bacterial species expand, colonization by virulent phages from the crAss-like and Microviridae families increases. They regulate bacterial abundance through lysogenic transformation and horizontal gene transfer through plasmid exchange. Transduction of DNA by phages results in the silencing of bacterial genes or in the encoding of genes that enhance the ability of bacteria to expand their ecological niche, such as toxin production (Shiga toxin), antibiotic resistance, and lysis of related strains to reduce competition (kill relatives). Prophages are transmitted vertically to the host's progeny [51-67]. The predominant bacterial aerobes (Enterobacteriaceae) after the first month begin to be replaced by strict anaerobes (Bacteroides, Clostridiales, and Bifidobacterium). In the former, diversity increases, while in Bifidobacterium with the transition to solid food and the use of carbohydrates not included in the composition of HMO, diversity decreases. The microbiota of the child reaches the adult stage around three years of age, as the transition to solid food increases and stabilizes diversity. In full-term infants, the intestinal microenvironment is dominated by Bifidobacterium, which is rarely found in premature infants. Shorter gestational age is associated with greater variability, unpredictability, and uncertainty in the microbiota, with strict anaerobes such as *Staphylococcus*, *Klebsiella*, *Enterococcus*, or *Escherichia*, and fluctuations in the dominance of one or another genus. Diet is decisive for the composition of the microbiota in newborns [68, 69]. The genus Bifidobacterium (30 species) is involved in the microbial assembly of infants and the associated immune maturation, vaccine response, and metabolic programming. The strains Bifidobacterium breve, bifidum, longum subsp. longum and longum subsp. infantis serve as markers of GIT status. Glycans produced by humans are absorbed by B. bifidum - an example of coevolution.

Colonization with commensals in newborn mice in the postnatal period is facilitated by suppression of TGF- β and limited representation of NK cell receptors. By localizing

in the superficial mucus layer of the intestinal mucosa, commensals evade innate immunity, while pathogens that have entered the deep layer are lysed by the acquired immune response. Dr. Malesu's study is looking into the reasons for the reduced or absent representation of the genus Bifidobacterium in the US and the impact on health by tracking immune maturation-relevant amounts of thiamine and indole-3-lactate (ILA) in the feces of infants through gene sequencing. These are not just microorganisms; these are microorganisms involved in the future architecture of the microbial functional networks of the holobiont. Cesarean section, adapted milks, and early antibiotic therapy explain this in a large proportion of children, but the absence of the genus in normally born and breastfed infants may also be due to transplacental transfer of infectious microbial fragments and metabolites, and components of the exosomes. The abundance of B. breve alone is associated with a 4.8-fold lower risk of developing noncommunicable diseases (asthma, eczema, allergy, etc.), and the genus Bifidobacterium as a whole - 3.1 times. A marker for impaired immune maturation is the identification of genes for the synthesis of phage repressors (Proteobacteria) and lipopolysaccharides (LPS) in Firmicutes. Human milk oligosaccharides (HMO) have a prebiotic bifidogenic effect, determining the vertical transmission and stabilization of some of the early strains of Bifidobacterium in the next generation. They serve as decoy receptors for Bifidobacterium sp. and antimicrobial adhesive substances, preventing the adhesion of pathogens to the epithelium. Their heterogeneity characteristic of them is due to the secretion by each woman of structurally specific saccharides important for vertical transfer [70,71]. According to the 2017 ISAPP definition, prebiotics are a substrate selectively utilized by microorganisms that confers health benefits to the host. Modulation of the composition of the intestinal microbiota occurs by providing energy and selectively stimulating the growth of beneficial bacteria, producing metabolites for physiological regulation and improving the intestinal barrier.

The high amounts of oligosaccharides and fatty acids in human milk promote the Th1/Th2 balance and activate Tregs, provoking the growth of lactobacilli and bifidobacteria. Their importance is expressed in increased levels of acetate (C2), mediating improved intestinal barrier function, suppression of the inflammatory response, and prevention of respiratory infections by limiting Th17 in the intestine and lungs [72-77]. In mouse models, *L. johnsonii* modulates the gut microbiota profile of the mother and offspring, resulting in reduced pro-inflammatory metabolites in maternal plasma and breast milk, and in the circulation of the pups. Lactobacillus-driven modulation and metabolic reprogramming of the maternal microbiota are also associated with improved airway protection mechanisms in the newborn. Antibiotic administration

and adapted milks for infants disrupt the immune system, neuroendocrine, and metabolic maturation of the infant gut microbiota. Treatment with the former triggers increased phage-bacterial interactions, increased colonization with *Streptococcus*, *H. influenzae*, and *Moraxella*, and facilitates bacterial adaptation and growth [78,79]. Bacterial lysis, gene exchange, generation of new phage particles, and integration of the phage into the bacterial genome alter phenotype, virulence, vitality, antibiotic resistance, toxin-secreting capacity, tolerance to oxidative and acid stress, and energy utilization. In infants, a causal relationship between impaired microbial assembly, reduced diversity, and susceptibility to noncommunicable diseases (asthma, eczema, allergy, etc.) has been observed as early as 1 month after birth. Transient depletion of immunomodulatory taxa of the temporal microbiota (*Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia*) during the first 3 months after birth is associated with high risk for infants [80]. This induces the DNA repair system, or SOS response, which is a regulatory response of bacterial cells against the loss of diversity of the intestinal microbiota, pathogenic bacteria, and prophage induction. It is suggested that *L. reuteri* induces the SOS response by activating specific metabolic pathways in the GIT [81]. The possibility of using it as a Live biotherapeutic monoproduct (LBP) during the first year of life after antibiotic therapy will probably allow us to reduce the potential health risk in at least a part of patients, restoring the specificity of the microbiota. This is important because early colonization modulates the host immune system in a way that is not observed in later stages of life. *Bifidobacterium lactis* HN019 is known to modulate long-term immune responses, expressed in increased numbers of mononuclear leukocytes, increased phagocytic and lytic activity [82]. The intestinal component influences the physiology and function of cells through metabolites from tryptophan deamination, modulating energy pathways - glycolysis, tricarboxylic acid (TCA) cycle and fatty (FA) and amino acid (AA) metabolism. The intestinal autochthonous *Clostridium* spp. - *sporogenes* and *striatum*, *B. breve* and *Peptostreptococcus anaerobius* in healthy hosts produce indole-3-propionic acid (IPA) with functional selectivity documented in the intestine, liver, respiratory tract and brain. IPA circulates systemically in the plasma but does not have a specific receptor expressed in only one organ, which allows it to reach many tissues. It regulates mitochondrial respiration and energy metabolism of CD4+ T cells by enhancing fatty acid oxidation (FAO) and amino acid oxidation (AAO) both in vitro and in vivo. Through PPAR β/δ signaling, IPA reprograms the anti-inflammatory effects and differentiation of CD4+ cells towards Th1 and Th17, without affecting Treg activity. This effect is achieved after relatively short exposure and does not require constant presence. IPA is associated with limiting DNA damage and reducing ischemic neuronal damage, intestinal barrier resistance, antioxidant activity, lung cell maturation, preventing allergic

airway inflammation and the development of asthma. Patients with low IPA levels have insulin resistance, obesity, a tendency to low-grade inflammation, depression, and symptoms of metabolic syndrome, in contrast to those with high IPA. There is a negative relationship with polymorbidity. The taxonomic units (OTUs) *Ruminococcus*, *Alistipes*, *Butyrivibrio*, *Coprococcus* and *Akkermansia* correlate with high IPA, *Blautia* with lower levels, while the *Escherichia-Shigella* group, *Megasphaera* and the genus *Desulfovibrio* are associated with low IPA. [83] This shows how in dysbiosis, changing the levels of just one metabolite can disrupt homeostasis, and it is never just one. Both in eubiosis and in dysbiosis after a course of antibiotics, the microbiota can take on the functions of immune modulation, preventing damage to mucosal tissue. The composition of the intestinal microbiota is decisive for the development of the brain, lungs, immune function, and overall physical growth. Studies in mouse and human models confirm the results of Dr Malesu that impaired microbial assembly in the early postnatal period often causes irreversible metabolic disorders. Intestinal dysbiosis in early childhood, associated with the mode of birth, antibiotics, and diet, leads to an alteration of SCFA-mediated immune homeostasis, enhances Th2 inflammation, and impairs the function of alveolar macrophages.

Cataloging microbial taxa. The structure of commensal communities in the human body will allow us to understand the interactions in the holobiont through the prism of the dominant influence of some species on the immune system independently of other members. Mapping microbial taxa will shed light on microbial network architecture, functional relationships, secretory metabolic regulation, and the possibilities for their use in therapeutic interventions. Due to gaps in our knowledge, we must use results from animal models to reproduce interactions between kingdoms. The bacterial component of the microbiota is the best studied, with six phyla prevailing: Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, Fusobacteria and Proteobacteria. Its members constantly pass through the commensal-pathogen continuum during coevolution with the human host. In the upper respiratory tract of healthy individuals during the first year of life, the genera *Staphylococcus*, *Streptococcaceae*, *Corynebacteriaceae*, *Moraxella*, *Haemophilus*, and *Alloicoccus/ Dolosigranulum* are mainly found. After the third year, *Staphylococcus*, *Streptococcus*, *Corynebacteriaceae*, *Prevotella*, *Veillonella*, *Propionibacterium* and *Fusobacterium* are predominant. *Corynebacterium*, *Dolosigranulum*, *Streptococcus epidermidis* and *Staphylococcus lugdunensis* are associated with limiting the possibility of diseases caused by *S. pneumoniae*, *H. influenzae*, *S. aureus* and *M. catharralis*. The respiratory tract is characterized by uneven colonization. It is expressed in a combination of rich niches - nose, naso- and oropharynx- and poor - sinuses, lower respiratory tract

and middle ear, their composition including a transient and permanent component.

Their spatiotemporal framework is determined by

1. inhalation of microorganisms, microbial migration and mucus secretion.
2. sneezing (upper) and coughing (lower), mucociliary clearance and elimination capacity based on innate and acquired immunity.
3. opportunities for local growth - temperature, energy availability, competition, O₂ gradient, and activity of proinflammatory cells.

The microbiota of the nostrils is represented mainly by Actinobacteria - *Corynebacterium* and *Propionibacterium* spp., Moraxellaceae, and Neisseriaceae without significant differences, and representatives of the Firmicutes type - *Streptococcus* in children and *Staphylococcus* in adults. Strains of the genus *Propionibacterium*, metabolizing sebum lipids secreted by the sebaceous glands to SCFA, lower the pH and support the growth of *Corynebacterium* and *S. coagulans*. Additionally, the O₂ gradient, humidity, and coproporphyrin III ensure colonization with *S. aureus* and *Corynebacterium*. The dominance of the latter and *Staphylococcus* spp. in the nasal cavities is based on niche differentiation, and not on jumping from neighboring areas. The paranasal cavities are taxonomically poor and are infected mainly by *Streptococcus* spp. and *H. influenzae*. The nasopharyngeal microbiota is related to the mode of delivery and nutrition and evolves throughout life. *Staphylococcus* and *Corynebacterium* spp. predominate in cesarean section, while *Staphylococcus*, *Streptococcus*, and *Dolosigranulum* spp. predominate in vaginal delivery. Gram (+) aerobes overlapping with those in the nostrils and oropharynx include *Staphylococcus*, *Streptococcus* spp., and *Dolosigranulum* spp., and Gram (-) anaerobes include *Corynebacterium* spp., *Prevotella*, and *Veillonella* spp., identical to those in the oropharynx. *S. pneumoniae*, *H. influenzae*, and *S. aureus* are the most common pathobionts. *Moraxella* is rarely observed in adults. *S. pneumoniae* carriage in children is often asymptomatic, leading to a short but progressive colonization that leads to infection. When spread beyond the epipharynx, it causes pneumonia, meningitis, or sepsis. The middle ear is also a poor niche, and *S. pneumoniae*, *H. influenzae*, and *S. aureus* mainly cause otitis media [84-92].

The oral cavity is among the richest ecological niches in the human body. It is estimated to have between 800 and 1000 species due to the relatively constant conditions - temperature, pH, and nutrients. Some of them are individual-specific, while others depend on age, lifestyle, diet, and health status. The largest percentage (40-60%) is made up

of α -hemolytic streptococci from the *Streptococcus viridans* group (VGS) - *S. mutans*, *S. sanguis*, *S. salivarius*, *S. mitis*. They are also found in the gastrointestinal and genitourinary tract. With representatives of the genus *Neisseria* (*N. sicca*) and coagulase-negative staphylococci („inhibitor strains“), they suppress the development of potentially pathogenic *S. aureus*, *S. pyogenes*, *N. meningitidis*, *Mycobacterium tuberculosis*, and *Legionella pneumophila*, and prevent recurrences of otitis media caused by *Haemophilus* spp. and *S. pneumoniae*. Inhibitory strains increase with age. VGS are of low pathogenicity, but in immunocompromised and co-morbid individuals they can cause serious infections. The invasive infections caused by group A beta-hemolytic streptococci tend to be more severe and less common. The levels of antimicrobial resistance of pediatric VGS are higher than those in adults. Specific adhesion conditions determine the composition of the oral mucosal flora. The epithelium is covered with the protein fibronectin, which acts as a receptor for lipoteichoic acids on the walls of Gram (+) bacteria. In pathological conditions such as liver failure, cirrhosis, hypermetabolic conditions, sepsis, cellular aging (replicative), and malignant neoplasms, its synthesis decreases and changes the ratio in favor of Gram (-) representatives. In these patients, pneumonia caused by Gram (-) *Klebsiella*, *Coliforms*, *Pseudomonas*, *Haemophilus*, and *Moraxella* is more common. Increased fibronectin synthesis is observed in scleroderma, rheumatoid arthritis, Crohn's disease, ulcerative colitis, myelofibrosis, and systemic lupus erythematosus. VGS are also key members of the pharyngeal microbiota, in particular the Mitis group - *S. mitis*, *S. oralis* and *S. sanguinis* and the Salivarius group. They inhibit the colonization of pathogens by emitting bacteriocins and H₂O₂, causing α -hemolysis. The microbiota of the oropharynx is the most dynamic, due to its location between the nasopharynx, oral cavity, gastrointestinal tract, larynx, and lower respiratory tract. It includes microorganisms of endogenous and exogenous origin. In healthy individuals, *Streptococcus* spp., *Neisseria* spp., and *Haemophilus* predominate, and Gram-negative anaerobes include *Prevotella*, *Veillonella* spp., *Fusobacterium*, and *Leptotrichia*. Pathogenic strains of the genus *Streptococcus*, including *S. pyogenes* and *S. pneumoniae*, and group A and group B bacteria, including *S. agalactiae*, can cause serious and even life-threatening disease [93-99].

The bacterial load of the lower respiratory tract is 10³-10⁵ CFU/mg and exhibits spatiotemporal stratification. Its composition is determined by that of the upper respiratory tract, oropharynx, and gastrointestinal tract. The bacterial phyla Firmicutes and Bacteroidetes, followed by Proteobacteria and Actinobacteria in the lungs do not differ from those in the intestine [100]. Commensal bacteria reduce the production of Th2-associated cytokines in allergic predisposition in the lungs and induce TREG in early

life [101,102]. Fungal strains are mainly imported from the environment: Ascomycota (*Aspergillus*, *Cladosporium*, *Eremothecium*, and *Vanderwaltozyma*) and Microsporidia (*Systemostroma*) [103]. In mice, limited colonization leads to increased production of Th2-associated cytokines and IgE, promoting allergic airway inflammation [104].

The gastrointestinal microbiota is mainly anaerobic and is dominated by the phyla Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia. Mannose-containing receptors on the intestinal epithelium through bacterial lectins adhere to Gram-negative bacteria. Its diversity is estimated at 500-1000 bacterial species. The stomach is characterized by *H. pylori*, *Veillonella*, and *Lactobacillus*. In the small intestine, Bacilli, Streptococcaceae, Actinobacteria, and Corynebacteriaceae predominate, and in the colon and rectum, Lachnospiraceae and Bacteroidetes [105-109].

Knowledge of the modulating influence of the prokaryotic component of the microbiota does not allow us to reproduce the full complexity of our immune development. When tracking the likely dominant influence of the eukaryotic component - protists, viruses, and helminths - it is necessary to use results from studies in animal models to shed light on the role of members of different kingdoms in the secretory-immune regulatory network in the holobiont and their local and systemic effects in different areas of the human body. Protists are ectosymbionts, using the host for their spread, and endosymbionts - commensals, facultative, and obligate parasites - causing effects ranging from mild discomfort to death. The causative agents of toxoplasmosis, trypanosomiasis (African sleeping sickness), malaria, leishmaniasis, and amoebic dysentery are better known, but toxin-producing marine dinoflagellates can indirectly cause poisoning after consumption of shellfish. Commensal protists in the intestinal and urogenital tracts of mammals and humans are poorly understood. Segmented filamentous bacteria (SFB) colonizing the ileum of most animals and humans are involved in the development and modulation of the immune system. Of these, the genus *Parabasal* was isolated in 22% of samples in rural areas and 3.8% in urban areas. These unicellular organisms share specific morphological features. Protists possess the quality of "specialization", but when jumping to other departments they lose the criteria for specific adaptation, and from harmless or beneficial symbionts in animals they become parasites, and a change occurs in the profile of the immune response provoked by them. The most famous example is *Trichomonas vaginalis*. Of the amitochondrial protists, *Tritrichomonas arnoldi*, *Trichomonas vaginalis* and *Tritrichomonas foetus* of the phylum Parabasalia, *Dientamoeba fragilis* of the phylum Metamonada and *Blastocystis hominis* of the phylum Bigyra have a proven impact on human and livestock health.

Pentatrichomonas hominis has also been identified in the human intestine. The biology of commensal *Tritrichomonas* species has been studied in the urogenital pathogens *Trichomonas vaginalis* and *Tritrichomonas foetus*. Strains of *T. foetus* from the order Tritrichomonadida use the succinate-fermentative pathway to convert malate to succinate via fumarase and fumarate reductase. *T. vaginalis* from the order Trichomonadida uses the lactate pathway to convert pyruvate to lactate via lactate dehydrogenase. Lactate and succinate are waste products, but in SI they provoke different immune responses. Commensal protists in the gut of healthy mice are considered architects of the intestinal ecosystem and an opportunity to trace their dominant effect on host immunity. Their epithelial and immune effects determine the severity of diseases in the gastrointestinal tract and in other parts of the human body. Plant polysaccharides in dietary fiber are the most accessible source of carbon and mucus glycans for parabasalids and may be a determining factor in their composition.

Competition with bacteria for fiber is the basis of trans-kingdom food-type dependencies, and the metabolites emitted determine their interactions with other microbes and the host. Some bacteria metabolize emitted succinate to SCFAs - C3-propionate and C4-butyrate. The metabolic products of *Tritrichomonas casperi* (Tc) and *Tritrichomonas muris* (Tmu) strains induce different immune responses depending on the niche. In the duodenum and jejunum of the small intestine, murine *Tritrichomonas* from the order Tritrichomonadida, by producing succinate, provoke a Th2 adaptive immune response. By activating innate lymphoid cells ILC2, they stimulate the production of IL-25 and the Th2 cytokines - IL-4, IL-5, and IL-13. In the distal end/ileum of the SI, Tmu and Tc provoke different immune responses. In the ileum, Tmu is dominant for the mucosal immune response, and the reason that Tc does not induce type 2 immunity and Th17 is not due to a deficiency in colonization. In the colon, by activating the inflammasome, Tmu promotes Th1 and Th17 immunity and increases CD4+Th1 and Th17 cells in the cecum and colon. In contrast, *Bacteroides fragilis* stimulates TREG in the colon. Induction of Th1 and Th17 is a common immune response in tritrichomonads. Provoking Th2 immunity in the SI allows the gastrointestinal tract to distinguish "self" from "foreign" in the intestinal contents, and through PRRs - TLRs, C-type lectin phage receptors, RLRs-retinoic acid inducible gene(RIG)-I-like receptors and NOD like receptors, intestinal cells distinguish pathogens from non-pathogens, which is the basis of tolerance to commensal microorganisms and control of the composition of the intestinal microbiota. Every day we take in various nutrients and about $\sim 1.10^9$ microbes through the mouth. The "oral tolerance" function does not allow our immune system to react to orally ingested antigens, which are mainly nutritional. It is generated in the mesenteric lymph nodes

(mLN). When the gastrointestinal tract is in homeostasis, DCs present antigens to naive T lymphocytes and induce TREG, responsible for oral tolerance. When the composition of the eukaryotic microbiota changes, DC acquire an inflammatory phenotype, leading to an inflammatory Th1 response against food antigens and loss of oral tolerance. An example of this is celiac disease, a chronic immune-mediated enteropathy due to sensitivity to proteins in cereals collectively called “gluten”. Factors in its pathogenesis are genetic predisposition (alleles HLA-DQ2, HLA-DQ8, and HLA-DQ7 on chromosome 6) and exposure to dietary gluten, but these are not sufficient by themselves to cause the disease. Cofactors include viral infections, proteolysis of gluten by the intestinal microbiota, and modification of the severity of tissue damage. Dr. Reinhard Hinterleitner et al. have identified a gluten intolerance-inducing reovirus. Its mechanism of action is expressed in the activation of tissue transglutaminase 2, modifying gluten peptides and enhancing their affinity for antigen-presenting cells in mouse models. The protist *Tritrichomonas arnoldi*, through unidentified metabolites, suppresses viral gene induction regulated by transcription factors IRF1 and NF- κ B and counteracts the activation of pro-inflammatory DCs. It induces anti-inflammatory/tolerogenic DCs and the generation of Tregs that prevent the loss of gluten tolerance. For the colonization of *T. arnoldi* in mice, an important condition is a diet rich in soluble fiber.

Gluten-free diets in animals are associated with longer lifespan and lower incidence of spontaneous cancer, but are more susceptible to infections. Gerrick et al. believe that information on the metabolites secreted by parabasalides could in the future be used to predict possible immune responses in humans. Dietary fiber composition is among the determinants of protist-induced type 2 immunity. The cytoskeleton in different compartments, rather than the level of colonization, is another possible factor determining immune modulation by *Tritrichomonads* in mouse models. They underlie the Th2 adaptive immune response in the ileum and the stimulation of IFN γ -producing Th1, IL-17-producing Th17, and double-positive IFN γ -IL-17 T cells in the colon. The IL-23/IL-17 axis is used by SFB to polarize Th17. In commensal *Tritrichomonads* in mouse models, “colonization resistance” is absent. Gerrick et al. suggest that it involves the “outcome” of other microbes in occupying their preferred niche. In all three small intestinal compartments, Tmu “outcompetes” the fiber-degrading *B. pseudolongum* and *Turicibacter sanguinis* for food MACs, reducing their abundance. It is found both on the mucosal surface and in the lumen of the colon. The mucus network formed in the colon binds to the epithelium and serves as a barrier against microbial invasion. Tc, together with *Akkermansia muciniphila*, a mucolytic, mucin-consuming bacterium, colonizes the mucus layer of the colon. Tc preferentially consumes glycans from the host’s mucus and reduces A.

muciniphila to undetectable levels. Gerrick et al. found that in food-type competition for glycans, Tmu and Tc, unlike their bacterial competitors *Bifidobacterium* (*B. pseudolongum*), *Turicibacter* (*T. sanguinis*), and *A. Muciniphila*, secrete carbohydrate-active enzymes (CAZymes) to cleave sugar subunits in mucus glycans and glycoside hydrolases (GH) that degrade mucus. On a diet low in plant polysaccharides, the protists limit their numbers and colocalize in the mucus layer, switching to mucolytic metabolism. Only *Bacteroidetes* directly compete with Tmu for mucus glycans. Identification of Tmu and Tc genes in human fecal bacteria eliminated by murine *Tritrichomonads* will help us to define their preferred nutritional niches. This will facilitate the study of human-colonizing parabasalids related to them [110-115].

Infection of epithelial cells expressing specific receptors by eukaryotic respiratory viruses demonstrates their niche “specialization”. IAV(H1N1) binds to the α 2,6 receptors of non-ciliated cells of the upper respiratory tract, and avian influenza H5N1 and H7N9 bind to the α 2,3 receptors of ciliated epithelial cells of the lower respiratory tract. SARS-CoV and SARS-CoV-2 primarily attack type II pneumocytes, and infection of alveolar macrophages supports viral replication. SARS-CoV-2 also replicates in the epithelium of the upper respiratory tract, allowing for its efficient transmission. This requires knowledge of the cytoskeleton. The upper respiratory tract and trachea are predominantly lined by pseudostratified epithelium, while cuboidal epithelium lines the lower respiratory tract. Squamous alveolar cells of type I, involved in the process of gas exchange, together with cuboidal alveolar cells of type II, form the alveoli [116-122]. Mucosal immunity underlies the pathogenesis and immune response of eukaryotic respiratory viruses. Exogenous pathogens, when attempting colonization, elicit a clearance response involving antimicrobial peptides secreted by commensal strains and immune cells of the age-related local immunity. The repertoire of virus-mediated immune evasion mechanisms of eukaryotic viruses includes active targeting and restriction of MHC class I molecules, non-classical CD1d molecules - MHC class I-like glycoproteins, binding and presenting lipid and glycolipid antigens to iNKTs, and mechanisms preventing antigen presentation to T cells. The balance between proinflammatory (Th1, Th2, and Th3/Th17) and anti-inflammatory (Treg) cells shapes the homeostasis of mucosal surfaces. Accumulating evidence suggests that responses to viral infections are driven primarily by innate cytokines produced by other cells, with little or no direct contribution from MR1.

Individually, the effector profiles of IL-12, IL-15, IL-18, IL-7, and IFN α/β are limited, but when combined, they are much more potent [123,124]. During infection, these cytokines can act sequentially and activate different cells. Infection alters the components of the extracellular matrix,

facilitates adhesion, and damages the epithelial cytoskeletal complex, disrupting its barrier function and its interaction with the human immune system. Disruption of epithelial integrity impairs the mechanical removal of pathogens and facilitates secondary infection. Damaged cells or cells in an intermediate state of differentiation express apical $\alpha 5\beta 1$ integrin receptors to which bacterial and fungal pathogens attach [125,126]. Glycolysis and lipid metabolism of the airways are the basis of the immune response. In the former, the amount of oxygen is decisive. According to the “Pasteur effect”, its availability has an inversely proportional effect on it, with reduced availability accelerating it, at least initially. Changes in the oxygen pressure in the mucosa are observed in all forms of inflammation. Lipid metabolism is involved in the regulation of cellular function, particularly of immune cells, determining metabolic pathways, cellular phenotypes, immune responses, and cytokine levels in health and disease. Glycolysis and lipid metabolism direct the proliferation, differentiation, and activation of lung macrophages, their metabolic susceptibility/responsiveness, and response to type 1 and type 2 cytokines. The Embden-Meyerhof pathway is more typical of proinflammatory type 1 macrophages (M1). Lipid metabolites, through genetic, epigenetic, posttranscriptional, and posttranslational regulation, alternatively modulate type 2 macrophages (M2), T cells, B cells, and neutrophils, and direct innate and adaptive immune responses [127]. Studies have shown that the tissue environment is a determinant of function, cell fate, and metabolic response. The constant dialogue between niches is based on physical interactions, quorum sensing molecules, antimicrobial agents, immune cells, and nutrients [128]. The gut microbiota exerts local and transorgan immune regulation through the mesenteric lymphatic system. After overcoming the intestinal barrier, the translocation of microbes, their fragments, and metabolites (SCFAs) exerts constant signaling between different systems in the human body through the systemic circulation and maintains homeostasis.

Protists and fungi also produce SCFAs [129-131]. Circulating microbial metabolites and trained immune cells mediate transorgan immunity. The consideration of the oral cavity-gut-respiratory tract triangle is correct, since the oral cavity connects the environment with the respiratory and gastrointestinal tracts. In the GIT, PRRs identify specific molecular patterns and, by activating the antigen-presenting capacity, initiate immune responses through cytokines and chemokines, through activation, maturation, and migration of immune cells. Ligands are the basis of communication between cells and within cells. By binding to the receptor, they change its activity, triggering a complex cascade of changes in cellular structure and signaling. Receptors and ligands form pairs, with each receptor recognizing only one or a few specific ligands, and the ligand binds to only one

or a few receptors. This specificity explains the number of cascades triggering metabolic pathways. DCs activate T cell subpopulations in the MLN and gastrointestinal lymphoid tissue (GALT) and produce regulatory cytokines. Following stimulation in the GALT and MLN, T cells migrate to the respiratory epithelium. The gut and lung microbiota form a bidirectional, unified network from birth [132-134]. The concept of GLA considers host-microbe and microbe-microbe interactions and the local and long-term effects they cause. Childhood immune ontogeny underlies their coevolution. Colonization in these niches forms a systemic “immune set point,” the dysregulation of which determines susceptibility to infectious and noninfectious diseases. The gut microbiota modulates lung immune activity. Binding of TLRs on neurons, microglia, and immune cells to microbial cell wall components, LPS and peptidoglycans, provokes cytokine release. LPS, by binding to TLRs on the intestinal mucosa, activates dendritic cells and favors the effector regulation of Treg, Th17, Th1, CD4, and the ability of neutrophils to extravasate from the blood [135]. In dysbiosis through IL-23 signaling, intestinal Th17 cells, reaching the lungs, exacerbate neutrophilic inflammation in asthma. The genera *Blautia*, *Lachnospira*, *Roseburia*, and *Coprococcus* of the *Lachnospiraceae* family, class *Clostridia*, play an important role in maintaining homeostasis of the holobiont. Through bacteriocins and acid production, which modulates local pH, they determine the colonization resistance of the niche against pathogens. Their members are among the most abundant bacterial taxa in the “healthy gut microbiota” and constitute 10 to 45% of the bacterial population of feces [136]. In the fermentation of a wide range of carbohydrates, including complex polysaccharides such as starch and inulin, they produce, in addition to energy, essential metabolites, SCFAs: C2, C3, and C4. These metabolites, together with indoles, serve as endocrine-like messengers and a systemic immune rheostat for pulmonary immunity. SCFAs serve as signaling molecules to resident antigen-presenting cells, reducing inflammatory and allergic responses in the lungs [137,138]. Upon reaching the lungs, they suppress inflammation and enhance the effector function of CD8⁺ T cells in mice fed an HFD [139]. Reduced abundance of the genera *Lachnospira* and *Blautia* compromises the intestinal barrier and facilitates translocation of pathogens and/or their metabolites. C4 maintains the integrity of the intestinal barrier, regulates the inflammatory response, and limits the induction of a cytokine storm [140]. Dysbiosis of the intestinal microbiota (*Bifidobacterium*↓) impairs the phagocytic function of alveolar macrophages. Their effects are mediated through G-protein-coupled receptors on various subsets of epithelial, immune, and endocrine cells. SCFA receptor deficiency in mice results in an increased inflammatory response. Innate lymphoid cells (ILCs) and gut-primed Tregs migrate to lung tissues under chemokine control via the mesenteric lymphatic system upon inflammatory signals.

Reduced levels of C3 released by *Bacteroides* compromise GPR41 signaling and impair neutrophil phagocytic function. SCFAs exert systemic anti-inflammatory effects by promoting Treg differentiation (HDAC inhibition) and suppressing Th2/Th17 polarization (GPR41/43 signaling).

Fecal C3 levels are inversely correlated with the risk of asthma in infants. Omega-3 polyunsaturated fatty acids (PUFAs) are involved in the regulation of immune cells, attenuate inflammation, and enhance antiviral immune responses in childhood lung diseases. Intestinal TLR activation, required for NF- κ B-dependent pathways of innate immunity and inflammation, induces an increased pulmonary response in mice with influenza. SFB, by inducing the Th17 cytokine IL-22, increases the number of neutrophils in the lungs in pneumonia caused by *Staphylococcus aureus* and limits bacterial infection [141-143]. The participation of protists in the immune regulation of the respiratory tract is expressed in the polarization of CD4+ T-cells into Th17 in pulmonary fungal infections and autoimmune manifestations. In the presence of a poor intestinal microbiota, inflammatory lung diseases are more severe, and enrichment with strains of *Lactobacillus*, *Clostridium*, and *Bifidobacterium* leads to an increase in Treg. Fecal metabolite profiling can be used as a noninvasive biomarker for predicting treatment response in precision medicine. The lung microbiota also influences the composition of the gut microbiota through the GLA secretory-immune regulatory network. Influenza infection modulates the composition of the gut microbiota not through intestinal tropism of the virus but through the migration of Th17 cells. This leads to an increase in the proportion of Enterobacteriaceae as well as endotoxins (LPS) and a decrease in the amount of Lactobacilli and Lactococci in the gut. Transorgan regulation of lung immunity by the gut microbiota occurs through three main mechanisms:

- 1) production of bacterial ligands (LPS) that activate alveolar macrophages via TLR4.
- 2) trafficking of SCFAs:
 - a) mainly C3 and C4 released in the gut suppress IL-13-induced eosinophilia, improving the integrity of the airway epithelial barrier;
 - c) when SCFAs reach the lung, they suppress PRRs, leading to a decrease in the production of inflammatory cytokines (IL-1, IL-12, IL-18), TNF- α , IFN γ , and granulocyte-macrophage colony-stimulating factor (GM-CSF).
- 3) migration of immune cells through the lymphatic flow [144-146].

The connection between the microbiota in both niches is also established indirectly through modulation of the host immune system. The lung microbiota independently protects us against *S. pneumoniae* and *Klebsiella pneumoniae* through the production of GM-CSF upon stimulation with IL-17 and Nod2 [147-149].

HPV is among the most common human viruses, but most infections are transient and clinically insignificant. Infection occurs through the interaction of receptors on the surface of the mucosa and the capsid proteins L1 and L2. Chronic viral infections with oncogenic potential, RRP and HPV-related diseases - head, neck, and cervical cancer - are considered possible primary "microbial-selective" immunodeficiency diseases, but patients with RRP have normal immune responses to other infectious agents. The excessive inflammatory reaction of the tissues provoked by HPV and EBV, due to an overreactive immune response during the latent course of the infection, provokes the formation of tumors. A small part of these formations can undergo malignant transformation. The reason for this is considered to be HPVs of the α genus and reactivation of other latent infections. HPV is an interesting example of the "resourcefulness" of microorganisms to take maximum advantage of the conditions provided to them. For us otolaryngologists, recurrent respiratory papillomatosis (RRP) is of interest, a rare disease manifested by recurrent proliferation of benign squamous cell papillomas both in the larynx and in other parts of the aerodigestive tract. In 5% of patients, involvement of the trachea and proximal bronchi may occur, and in less than 1%, involvement of the lung parenchyma. In aggressive forms, the interval from involvement of the larynx to spread to the lower respiratory tract is up to 12 years, but there are also patients in whom the period is greatly shortened. This entity represents a serious clinical problem due to its localization, resistance to the therapies performed, frequent relapses, spread to the lower respiratory tract and esophagus, and the possibility of malignant transformation into squamous cell carcinoma. The presumed mechanisms of infection in juvenile RRP are several:

1. "Genetic locking." This blocks key morphogenetic pathways—BMP, TGF- β , FGF/ERK, and WNT, which are responsible for coordinating embryogenesis, tissue homeostasis, stem cell differentiation, and the regulation of cell polarity and fate (via canonical β -catenin-dependent or non-canonical mechanisms), as well as disease progression. This causes the closure of information channels for cell lineage differentiation at a specific stage/day of embryonic development, acting at the epigenetic level, thereby inducing congenital anomalies and other diseases. This is likely attributable to:
 - a. Genetic variation
 - b. A viral vector crossing the placental barrier; through epigenetic modulation, it locks/blocks specific gene(s) and unlocks/triggers others.

The hypothesis regarding disrupted embryogenesis in immature iLC precursors is based on research conducted by Kyle Loh at Stanford University using human pluripotent

stem cells and mouse embryos to study human brain embryogenesis during the formation of the forebrain and midbrain (anterior neuroectoderm) and the hindbrain (posterior neuroectoderm).

Tissue-resident lymphoid cells (TRiLCs) are innate immune cells. During embryogenesis, their immature progenitors migrate to the epithelial surfaces of the airways and lungs, becoming long-lived iLCs and the first line of defense against microbes and injury [150-153]. They are divided into ILC1, ILC2, and ILC3 and carry out different types of defense responses. They associate with keratinocytes through tight junctions and do not circulate en masse in the blood. They are distinguished from iLCs derived from bone marrow monocytes, which are representatives of adaptive immunity, because they respond differently to activating stimuli [154, 155]. Cytokines and chemokines produced by keratinocytes and TRiLC influence the maturation and migration of monocyte-derived iLCs, and their balance polarizes adaptive immunity toward Th1 or Th2 responses [156-158]. Langerhans cells (LCs) are DCs specialized in the uptake, processing, transport, and presentation of antigens to T cells directly or via myeloid Langerhans+DCs [159-161]. The variety alone, or in combination with exosomal factors and infectious microbial fragments and metabolites, may account for the lack or impaired migration of progenitors, disabling their protective function, and disrupting the link between innate and adaptive immunity.

2. Trauma to the epithelium allows HPV to reach the keratinocytes in the basal layer, the only mitotically active cells. In juvenile RRP, rinsing is theoretically possible to cause this, but practically it is extremely unlikely.

3. HCMV, crossing the placental barrier, attacks the immune system of infected children and leads to an increased risk of infection with both EBV and HPV.

4. Crossing the placental barrier of viral fragments/proteins, allowing evasion of the host immune response or "immune silencing". Viral replication and assembly in the differentiated keratinocyte is far from sites of immune activity; therefore, cytokine release and activation of antigen-presenting cells are unlikely.

5. Exploitation of the phenomenon of "immune evasion" expressed in a highly prolonged infectious cycle that does not allow cytolysis or cytopathic death.

6. Abrogation of cell cycle checkpoints, allowing replication of viral DNA in mitotically inactive cells. The impaired growth control of the infected cell allows the formation of papillomatous formations and, at a later stage, even

malignant transformation [162].

7. Contact of the baby with the maternal intestinal microbiota (dominant) during birth and contamination with helminth eggs.

In the infant's GIT, PRRs respond to molecular patterns and, through antigen-presenting capacity and cytokine- and chemokine-mediated immune responses, lead to activation, maturation, and migration of immune cells. If dysbiosis is present in early childhood due to birth, antibiotics, and diet, this alters SCFA-mediated immune homeostasis, enhances Th2 inflammation, and impairs alveolar macrophage function. Local and transorgan immune regulation via the mesenteric lymphatic system creates conditions for HPV infection. The mechanisms presented may be elements of a single process. The study of microbial functional networks is important in clarifying whether the calibration of local and systemic immunity through endocrine and metabolic interactions, the properties of the local niche, the exosomes, and epigenetic modulation are responsible for the maximally comfortable immunosuppressive Th2 microenvironment and the suppression of the Th1 response, responsible for the frequent relapses of RRP. They will also show us the presence or absence of synergistic interactions with other members of the microbiota. Our colonizing helminths and protists are found in one third of the Earth's population and can manipulate the immune response. Archaeopathology provides us with the first data on fecal-oral transmitted helminths in Roman Britain. By microscopy and ELISA, eggs of *Ascaris lumbricoides* (roundworm) and *Trichuris trichiura* (whipworm) have been identified in sedimentary deposits of Roman garrisons.

These nematodes have caused intestinal disorders, hemorrhages, anemia, and exhaustion of the body, but more important is the local and transorgan immune regulation carried out by these organisms. In ulcerative colitis, local immune regulation during infection with the pork tapeworm limits inflammation in some patients. A study conducted in Peru linked parasites to increased HPV infection in women. They induce a Th2 intestinal immune response, leading to activation of DC, M2, Treg, Breg, Eo, Ba, and MC, release of cytokines (IL-4, IL-5, IL-9, IL-10, IL-13, IL-21, IL-25, IL-33), and TGF- β signaling to CD4+ and CD8+ T cells of the adaptive immune system [163-167]. Transorgan immune regulation of the respiratory tract may occur alone or in combination with protists. Intestinal helminths induce IL-4-enhanced viral replication and block the antiviral effects of IFN- γ by upregulating the viral latent-to-lytic switch gene. Chronic intestinal carriage favors the pathogenesis of most viruses through strong Th2 cytokine responses that counteract IFN- γ in the Th1 response and direct polarization from a proinflammatory M1 to a regulatory M2 type. Reduced

C3 levels impair neutrophil phagocytic function. Whether nematodes are the basis for transorgan immune regulation of the airways individually or in combination remains to be elucidated. SFB, by inducing the Th17 cytokine IL-22 in *Staphylococcus aureus* pneumonia, increases neutrophil numbers in the lungs and limits bacterial infection, but their role in viral infections is not well understood [168]. A synergistic interaction with bacteria and fungi cannot be ruled out, as SCFAs promote Treg differentiation (HDAC inhibition) and suppress Th2/Th17 polarization (GPR41/43 signaling), leading to systemic anti-inflammatory effects.

If protist jumping to another anatomical niche is the cause, is the rare occurrence of RRP related to the local conditions of the niche? Helminths demonstrate how a pathogen modifies the immune response to a related or unrelated pathogen, resulting in increased or decreased tolerance, local immunity, and immunopathology. Heterologous immunity has been observed in protists, parasites, bacteria, and viruses. Studies by Mohd Israr et al. have shown that the papilloma microenvironment is characterized by, in addition to a sustained Th2-like/Treg HPV-specific adaptive immunity, overexpression of cyclooxygenase-2/prostaglandin E2 (PGE2) in the upper respiratory tract [169]. Granzyme-expressing CD8⁺/CD28⁻ T cells in papillomas do not function as mature cytotoxic T lymphocytes (CTL). The authors believe that innate immune dysregulation in patients with RRP is the cause of the generation of fewer iLC due to the reduction of the subpopulation of classical Mo. Their percentage (CD14^{bright}, CD16⁻) is lower, and PGE2 limits their differentiation into iLC. The average concentration of PGE2 in the plasma of patients with RRP is significantly higher than that in healthy subjects. The increased amount of PGE2 in the plasma of patients is responsible for the reduction of Mo-iLC differentiation. The suppressive effect of PGE2 on the differentiation of monocytes into iLC is difficult to reverse; monocytes do not recover over time. It is assumed that they are "locked" at a lower level of differentiation [170]. The balance of pro-inflammatory versus anti-inflammatory immune mediators and cells in the papilloma microenvironment is disrupted [171-174]. A similar Th2-like/Treg-specific adaptive immunity and iLC response is also observed in PIV infection [175]. A variety of TRiLCs cannot explain the behavior of NK cells and high levels of the immunosuppressive cytokine TGF- β . Distortion of TREG function due to local tissue-specific immune response leads to IL-27 suppression of effector or regulatory immune cells. The amino acids arginine, leucine, and glutamine determine the differentiation of different CTL and NK lineages, and the cytotoxic and proliferative potential of the latter depends on the bioavailability of arginine. Perhaps it is also responsible for MHC-I deficiency and suppression of the activating receptors NKp30 and NKp46, reducing their activity and cytotoxic capacity. Arginase-1 (Arg1) degrading L-arginine

limits T-cell proliferation and facilitates the persistence of MCMV. In the growth medium of HPV, conversely, the lack of arginine limits viral replication units (RFU). TGF- β secreted in RRP suppresses cell division in epithelial and lymphoid tissues through cyclin-dependent kinase inhibitors p15 and p27, NK and white blood cell function, controls excessive inflammation, and promotes Treg. The number of iLCs in the peripheral blood is increased, but for papilloma LCs to be activated and leave the tissues, neutrophil elastase is required to convert the precursor IL-36g into the active proinflammatory cytokine IL-36 through extracellular proteolysis. Tregs block the activation, maturation, and migration of LCs from the papilloma epithelium to the regional lymph nodes, where they would transfer HPV antigens to myeloid DCs or present them directly to T cells.

Cytokines and chemokines produced by keratinocytes and TRiLCs influence the maturation and migration of monocyte-derived iLCs, and their balance directs the polarization of adaptive immunity toward Th1 or Th2 responses [176]. The expression of C-C chemokine ligand 1 by monocyte-derived iLCs in patients with RRP is almost undetectable. It is responsible for attracting monocytes, Th2 cells, and Tregs to sites of active inflammation after binding to the cell receptor CCR8, as well as activating TRiLCs. CCL20, abundantly expressed in papillomas, would conversely maintain these lesions [177-179]. The lack of CCL1 expression by iLCs in papillomas could be due to the presence of Tregs in the lesions. Disruption of the relationship between Tregs and iLCs could reverse the immunosuppressive TH2-like/Treg adaptive microenvironment in the tissues. T-cell responses to early proteins of HPV6/11 and autologous papilloma tissue are far from effective viral control [180]. In chronic viral infections with oncogenic potential, RRP and HPV-related diseases - head, neck, and cervical cancer - TREG biology is well expressed. The E5, E6, and E7 proteins are responsible for the integration of viral DNA into the genome and possible malignant transformation.

Tregs accumulate more often in larger formations, and depletion of FoxP3⁺ T-cells increases the activity of infiltrating effector T-cells. Increased expression of FoxP3 is observed in the progression of cervical intraepithelial precancer to invasive squamous cell carcinoma. This supports the theory of a putative role for TREG in promoting carcinogenesis in latent HPV infection. Depending on the anatomical site, it has a positive or negative prognostic value in HPV-associated squamous cell carcinoma of the head and neck. TGF- β suppresses tumor growth and causes cell death in early stages of carcinoma, but in later stages promotes growth, immune evasion, and metastasis through epithelial-mesenchymal transition (EMT). Studies by Papagiannakopoulos et al. on the causes of metabolic exhaustion/cachexia, although unrelated to RRP, may help us

to clarify why none of the therapies used have the desired effect. They found that a subtype of lung carcinoma uses the pulmonary sensory innervation to send a direct signal to the brain through abnormally high levels of PGE2 released from it. This lipid signaling molecule, mainly associated with mediating acute inflammation and thermoregulation in the hypothalamus, forms a neuroimmune axis, transforming the tumor process (perhaps HPV-related diseases) into a systemic administrator. PGE2, captured by local afferent fibers of the vagus nerve and lung parenchyma, acts as a neurotransmitter of the CNS. When blocking the pulmonary nerves, the manifestations of cachexia are reduced, without affecting the tumor. In premalignant tumors (RRP), lung-brain signaling may be critical. PGE2 levels are related to our diet. The molecule is synthesized from arachidonic acid, a derivative of omega-6 fatty acids found in fats of animal origin. High-calorie, fat-rich foods worsen the condition of experimental models and accelerate the lethal outcome, as also observed in pneumonia in mouse models. Switching to a diet rich in omega-3 polyunsaturated fatty acids (PUFAs), docosahexaenoic (DHA) and eicosapentaenoic (EPA), normalizes PGE2 levels because these acids are competitive inhibitors, limiting the synthesis of cyclooxygenase products. Separately, they participate in the regulation of immune cells, weaken inflammation, and enhance antiviral immune responses. The use of NSAIDs - aspirin, ibuprofen, etc. blocks COX/PGE2 and prevents the manifestations of cachexia, and in reports in RRP, a prolongation of the remission period is observed. The use of neuro-oncology principles to suppress the peripheral and central nervous system from the tumor process of proliferation and survival transferred to RRP can be used as an example of how complex neuroimmune circuits connecting the respiratory system with the central nervous system suppress the systemic immune response. Another element of the exposome, stress, is also involved, seemingly unnoticed. Its biological determinant, the cortisol pathway, is responsible for this. High levels of cortisol and adrenaline suppress the activity of the telomerase present in T-lymphocytes and increase the levels of pro-inflammatory cytokines (IL-6, TNF- α). They generate oxidative stress, attack the cyanine-rich telomere chains, and make them susceptible to breakage. Stress hormones attack receptors on the cell membrane, interrupt DNA maintenance, and this leads to a transition to a short-term adaptation mode used by the virus.

Results

Since the beginning of the 21st century, non-communicable diseases have prevailed over infectious diseases. The influence of the environment on biological processes helps in understanding the etiology and consequences of non-communicable diseases or „lifestyle diseases“. They are increasingly common worldwide.

Pregnancy occurring in an environment with unfavorable factors and feeding with adapted milk are among the causes. In low-income countries, an increase in the number of deaths from food-related diseases is observed every year. But this is only one side of the problem. Our dreams of a better life and realization sometimes cause us to migrate thousands of kilometers from our birthplaces. By eating, we also feed our microbiota. Diet is the most ancient means of modifying the microbiota. Our individual variability is shaped by gene-environment-diet interactions [136,181,182]. A rapid transition from a Mediterranean or similar diet to a High-fat diet (HFD) results in reduced diversity and imbalance in gut bacteria - an increase in „bad“ bacteria (Firmicutes, Proteobacteria, Enterobacteriaceae), a decrease in „good“ bacteria (Bacteroidetes, Bifidobacterium) and increased intestinal permeability (metabolic endotoxemia), which can lead to chronic low-grade inflammation of adipose tissue, the colon and metabolic problems such as obesity, insulin resistance and liver disease (NAFLD / NASH). No one doubts the usefulness of different diets, but given that up to 50% of the microbiota is individually unique, no one can answer whether they cover the food type dependencies in it when changing residence. The nutritional regime determines which microorganisms will be preserved or disappear, as impaired dietary diversity provokes loss of the microbial community, which in turn affects the phenotype. Diet is the connection with our roots. Loss of diversity limits self-regulation (autobionts↓ and pathobionts↑), signaling with the host, and defensive competition against pathogens. Malnutrition or overnutrition, metabolic stress, exposure to pollutants - heavy metals, pesticides, drugs, pharmaceuticals, and lifestyle play an important role in shaping the composition of the microbiota and determining our predisposition to non-communicable, infectious, and other diseases.

Managing the intake of medicines and pharmaceuticals will help us to limit misuse, prevent infections, reduce the need for use, and develop new antimicrobial agents. Antibiotic resistance has not emerged in the last century. Microorganisms have developed this survival mechanism over the billions of years since the emergence of life on the planet to maintain balance. The group of antibiotics has proven its role in maintaining health, but has an effectiveness of less than 100%, despite the fact that up to 50% of them are natural products. It makes sense that when a microorganism causes disease, we should try to eliminate it.

It sounds tempting, but each of them is part of the food chain, and its removal disrupts it. Our intervention eliminates the mechanism of administration and leaves the ecosystem without protection from overpopulation. The use of antibiotics also increases the risk of impaired perception of self and others, with the potential to trigger autoimmune and allergic disorders in childhood and adolescence [183-

186]. The concept of “good” and “bad” microorganisms is incorrect. Under certain conditions, any microorganism can cause severe illness and even death. But can we replace antibiotic use with the intake of antibacterial substances in certain cases? Bacteriocins are ribosomally produced small antibacterial peptides, including by commensals in the gut, and act as quorum sensing molecules. They play an essential role in the dialogues between members of the kingdoms. Some bacteria produce several types to protect their ecological niche, which allows them to survive by suppressing competitors, including pathogens [187]. Bacteriocins can be used as “smart” antimicrobial agents to edit the microbiota, which will help us to limit AMR.

Our task is to define how probiotic strains can be used to restore the composition of the microbiota, inhibit or inactivate other organisms through bacteriocins and other mechanisms, limit the spread and manifestations of non-communicable diseases (eczema, allergy, or asthma), strategies for protection against cancer and for the prevention and treatment of infectious diseases. Each strain can play a role in solving one or more of these tasks. The term “probiotic” is used when three criteria are met: it must be alive, in sufficient quantities, and have a health benefit. Since in many cases the claim is based only on in vitro or preclinical data, it is necessary to have a proven origin (without genetically modified bacteria and fungi), purity, adequate quantity, clarity on whether they are transient or permanent members, and carrier of phages. It is necessary to take them out of the comfortable environment of food supplements and meet the criteria of a medicinal product. This is especially true for preparations containing *L. reuteri*, *Clostridium* spp. - *sporogenes* and *striatum*, *B. breve*, *Peptostreptococcus anaerobius*, *Saccharomyces cerevisiae*, *Saccharomyces boulardii*, etc. Compared to broad-spectrum antibiotics, which do not distinguish between commensal and pathogenic bacteria and can reduce the microbiota by up to 30%, their first advantage is that probiotic strains inhibit or inactivate other organisms through bacteriocins and other mechanisms without reducing permanent members. The second advantage is in the loading of the limited resources of anatomical niches. The lack of “open niches” hinders the expansion of exogenous pathogens and pathobionts and strengthens “colonization resistance”. Their third advantage is increased competition for adhesion with those with pathogenic potential. Applied in “sufficient” quantities, they create a maximally hostile environment for colonization by pathogens - they limit invasion, overgrowth of the latter, and even return them to the orbit of commensalism (*Corynebacterium* spp. → *Staphylococcus aureus*) [188,189]. Since we ingest about $\sim 1.10^9$ microbes daily through the mouth without disturbing the ecosystem, the effective amount is above this number. A fourth advantage, but still untapped, is their use as Live biotherapeutic products (LBPs)

or their metabolites (ILA, IPA, β -glucans, etc.) to prevent, treat, or cure a disease or condition in humans. (US FDA) The fifth advantage is the regulation of primary and total fecal bile acid excretion levels (particularly chenodeoxycholic acid), thereby reducing elevated permeability of the small and large intestines and accelerated intestinal transit, as well as correcting the composition of the microbiota.

Prebiotics will probably find their place in the near future in immunocompromised and oncological patients. They serve as a source of energy and selectively stimulate the growth of beneficial bacteria for the production of metabolites for physiological regulation and improvement of the intestinal barrier, decoy receptors for commensals, and antimicrobial adhesive substances that prevent pathogens from adhering to the epithelium. In oncology, by restoring the composition of the intestinal microbiota, we will be able to modulate the response to inhibitors of immune checkpoints.

The use of bacteriophages in the treatment of multidrug-resistant strains will help us in our daily practice. However, like antibiotic and probiotic therapy, we will not be able to count on a 100% success rate. This is due to the evolutionarily developed defense mechanisms of archaea and bacterial cells, or phage resistance. The first is expressed in duplicated sequences in the genome of some bacteria and archaea, discovered by Yoshizumi Ishino in 1987, first in the *E. coli* genome. In 1993, Francisco J M. Mojica, while studying archaea, officially introduced the term CRISPR-Cas (Clustered Regularly Interspaced Short Palindromic Repeats) for the repetitive DNA sequences in their genome. They are divided into three main types of CRISPR-Cas systems, with a further division into several subtypes. They have a complex genomic architecture and extremely dynamic evolution. There are three main types of CRISPR-Cas systems, with several subtypes further subdivided. They have a complex genomic architecture and dynamic evolution.

In 2005, he and his team demonstrated that these repetitive regions are part of the adaptive immune system of archaea and bacteria, which helps them recognize and neutralize viral attacks. CRISPR spacers are derived from pre-existing sequences, either chromosomal or on transferable genetic elements such as bacteriophages and conjugative plasmids. These extrachromosomal elements fail to infect the specific spacer-carrying strain, suggesting a link between CRISPR and immunity against target DNA. Bacteriophages and conjugative plasmids are involved in population control, evolution, and pathogenicity of prokaryotes. After injection of the phage nucleic acid into a bacterium, it begins to cleave the chromosomal DNA into nucleotide fragments by nucleases. In another mechanism used, the attacked bacterium detects the fragments and the bacterial colony to block the expansion of the phage by releasing replicases (progeny phages),

and triggers mechanisms to destroy NAD⁺ or synthesize a toxic transmembrane protein that disrupts the electrical ion gradient of the cell. This causes the biological death of the infected cell. By killing the bacterial cell, the phages are prevented from infecting other cells in the bacterial biofilm. In turn, phages, through mutant strains, circumvent the mechanisms of evasion of recognition by synthesizing their sequences without degrading bacterial DNA [190].

Reports of experimental models using methanogenic archaea indicate a more pronounced immune response and weaker cytotoxicity in cancer patients [136]. Protists may also be used in practice in the future. Helminths are considered potential candidates for our interventions because of the possibility of altering local immune regulation. In ulcerative colitis, infection with the pork tapeworm reduces inflammation in some patients [191,192].

Several obstacles must be overcome before members of the 5 kingdoms can be used in the near or distant future to modify the microbiota and prevent or treat diseases as primary or adjunctive therapy to conventional medications. Direct and indirect interactions between drugs and the microbiota are bidirectional - the microbiota modifies (activates or inactivates) many drugs, as some drugs are associated with changes in their composition. Changing its composition and (phenotype) through indirect effects on the immune system alters the response to immunotherapy in patients with cancer and chronic inflammatory diseases. It can also indirectly modify drug metabolism by affecting the expression of hepatic enzymes of the cytochrome P450 family. Multiple studies have found drug-microbe interactions up to 50% for proton pump inhibitors (PPIs), metformin, laxatives, antibiotics, statins, β -blockers, ACE inhibitors, selective serotonin reuptake inhibitors, antidepressants, and other psychotropic drugs [136]. Some cancer drugs inhibit microbial growth. Most drug-microbe interactions are poorly understood. In particular, within the microbiota, some species have a dominant influence independent of others. Protists lack "colonization resistance," and their ability to "outcompete" other microbes in occupying their preferred niche limits the potential for probiotics and LBP. This is due to the evolutionary advantage of their enzyme systems, which minimize bacterial colonizers to undetectable levels and, probably indirectly, bacteriophages and archaea. DNA is the "densest" information carrier in nature. If you use the metric system, 1 gram of DNA probably stores several hundred petabytes (PB) of data. 1 PB = 1024 terabytes. If we conditionally take the 20,000 genes of the human genome as a framework, their interactions with > 33 million genes in the hologenome allow for its drastic expansion. The eukaryotic viral vector activates transcription factors, leading to gene induction. At the core of life on Earth are about 10^{130} protein molecules/genes, 10^{700} signaling cascades, and 10^{1000}

metabolic pathways, allowing us to respond to any scenario for which we carry genetic information, but not to all of them, as the survival of the species, not the individual, is the main concern. Like predators, microorganisms look for the weak spots of the weak. It is true that telomerase is considered an elixir of youth, but it is very likely that IPA and some other metabolites will turn out to be an elixir of "healthy" aging.

Conclusion

Microorganisms alone or in symbiosis can remodel the specific microenvironment and provoke susceptibility to other unrelated exogenous pathogens. Knowledge-based interventions could help limit the redirection of T-cell subsets during the transition from acute to chronic infection and limit the occurrence of diseases such as primary and secondary chronic rhinosinusitis with or without nasal polyposis, recurrent respiratory papillomatosis, and others. Nature does not tolerate absolute winners/dominators; therefore, the use of members of the 5 kingdoms alone or in combination with conventional drugs will have a less than 100% success rate. This limits our ability to influence the relationships in the holobiont.

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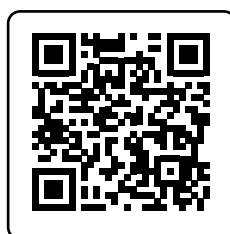
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