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Trends in Microbiology

Forum

How human endogenous retroviruses interact with the microbiota in health and disease

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The microbiota is a collective of microorganisms whose composition is intimately linked with human health and disease. Emerging evidence demonstrates that endogenous retroviruses facilitate crosstalk between the host and microbiota to fundamentally shape immunity.

The microbiota is a collective of host-associated microorganisms which reside along the skin and mucosal barriers of the gastrointestinal (GI) tract, reproductive tract, and pulmonary system to form a dynamic ecosystem that safeguards host health by promoting wound healing, regulating inflammation, outcompeting opportunistic pathogens, and providing key metabolites [1]. The benefit of this microbial flora is lost during dysbiosis when the ecological balance is disrupted by an overabundance of pathogenic microorganisms [1]. Microbial dysbiosis disrupts mucosal homeostasis by dysregulating host immunity and metabolism [1]. There are still many unanswered questions as to how exactly this balance of microorganisms affect host health.

Recently, emerging evidence has characterized a novel axis by which bacteria modulate endogenous retrovirus (ERV) expression, and vice versa [2,3]. This link between the microbiota and ERVs suggests a novel control of immunity and host health in which these ecosystems work together to create an immune environment favorable to them and the host. Conversely, when this ecological balance goes awry there is a consequential development of pathogenic inflammation. In this forum article, we discuss new evidence for the interaction of the microbiota and human ERVs (HERVs) and how these untapped interventional opportunities could be exploited in future therapies.

What are ERVs?

HERVs are the noninfectious remnants of ancient retroviruses that integrated into the genome during infection of the germ cells of human predecessor species [4]. Roughly 8% of the human genome is derived from HERV elements that dictate global transcription patterns and encode functional protein products [4,5]. HERVs provide diverse physiological functions, among which is an emerging appreciation of their role in inflammation. Briefly, HERVs influence inflammation through their involvement in the signaling pathways that propagate immunological processes [6] and by producing viral motifs that directly agonize antiviral immune receptors [7,8] (Figure 1). While ERVs facilitate critical processes, such as inflammation and cell-surface interactions under normal conditions, their presence is a double-edged sword that, when dysregulated, they can drive pathogenic inflammation [9] and oncogenesis [5,10]. Our current understanding of how HERVs influence human health is complicated further by potential interindividual discrepancies. HERV elements are stable in their locus-confinement within the genome and there is no evidence for active retrotransposition; however, recently mobile (<1 million years ago) HERV families possess interindividual disparities in genotype [11].

Collectively, HERVs play an important role in maintaining homeostasis, while their aberrant expression instead drives detrimental immunity in cancers [7] and inflammatory disorders [9]. This intricate balance between HERVs and immunity is attributable to the diverse roles HERVs possess in suppressing or promoting specific inflammatory cascades. Akin to other mediators of inflammation, the relative expression of specific immunomodulatory HERV elements can either be a benefit or detriment to the host, depending on the context of the local immune environment.

The microbiota influences endogenous retrovirus expression via innate immunity

Pattern-recognition receptors (PRRs) are innate immune receptors that identify motifs characteristic of infection or cell damage [12]. PRRs that recognize bacterial motifs include Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-containing protein (NOD) receptors. During infection and dysbiosis the increased abundance of pathogenic microorganisms activates these PRRs to drive inflammation [1,12]. Common motifs that drive inflammation under these conditions include lipopolysaccharide (LPS), a cell-wall component of Gram-negative bacteria. Under dysbiotic conditions, excess LPS agonizes TLR4 to promote a strong inflammatory response that disrupts host–microbe interactions by driving excess inflammation [1].

Emerging evidence has demonstrated that PRR stimulation by bacterial motifs also drives the differential expression of HERV elements [2,3]. Models of TLR4 activation demonstrate that global dysregulations in leukocyte-specific HERV expression is concurrent with the excessive inflammatory response [13]. Associations between global HERV expression and PRR stimulation suggest that HERVs have been co-opted to participate in the immune response to exogenous pathogens by mediating the expression of inflammatory response genes [6]. While

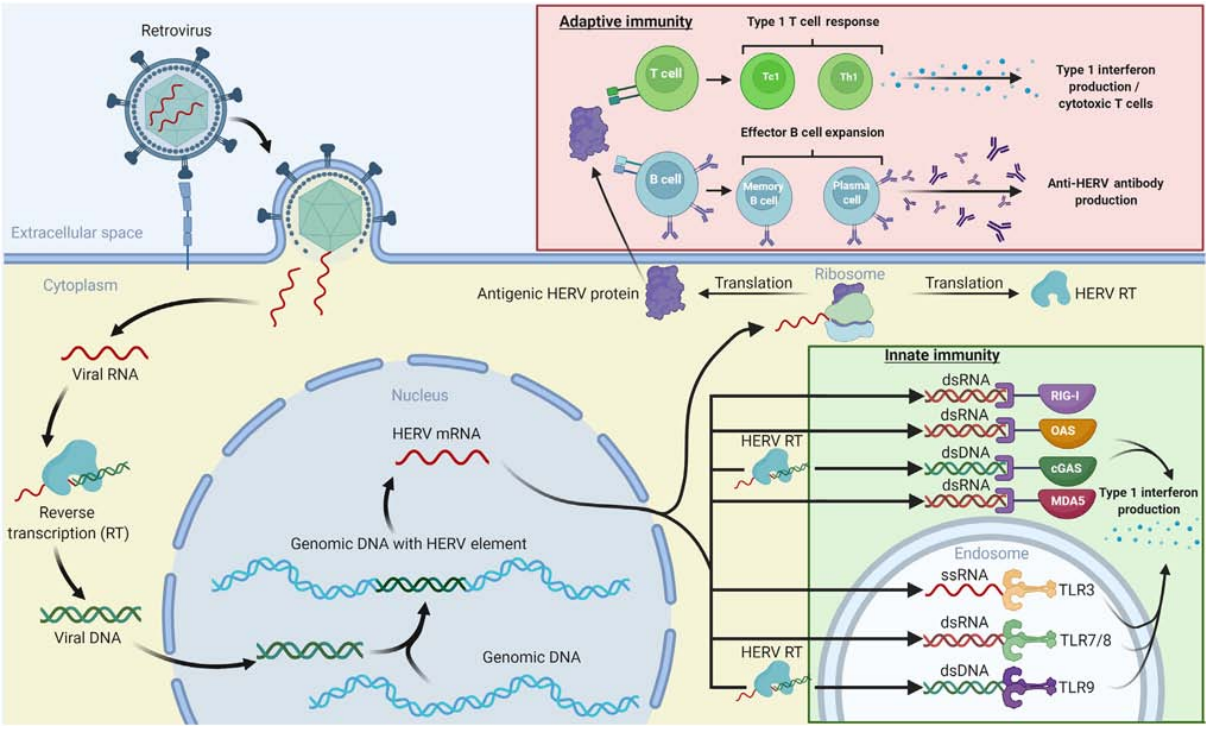

Figure 1. Human endogenous retroviral (HERV) elements activate adaptive and innate immunity. HERV elements are the product of viral RNA going through reverse transcription (RT) and subsequently integrating into the human genome. HERV elements can be transcribed to form double-stranded DNA (dsDNA), or single-/double-stranded RNA (ssRNA/dsRNA) molecules in the cytosol and endosomes. Within these sites the accumulation of transcribed HERV elements activates retinoic acid-inducible gene I (RIG-I), oligoadenylate synthase (OAS), cyclic GMP-AMP synthase (cGAS), and melanoma differentiation-associated protein 5 (MDA5) to promote the expression of type 1 interferons. HERV mRNAs, when translated, can promote adaptive immune processes by promoting effector B cell and type 1 T cell activation.

PRRs recognize pathogenic microorganisms, commensal microorganisms have also been shown to confer beneficial effects to the host by inducing endogenous reverse transcription through activation of these receptors [2,3]. Murine models comparing germ-free (GF) to specific-pathogen-free (SPF) mice demonstrate that bacterial colonization of the mucosa is a major determinant of host ERV expression in the GI mucosa *in vivo* and dendritic cells *in vitro* [3]. Furthermore, microbiota-induced ERV expression is lost in ulcerative colitis and is associated with microbial dysbiosis [3]. Collectively, these studies demonstrate that bacterial stimulation of PRRs is a major determinant of ERV expression.

Recent discoveries have shown that the expression of microbe-induced ERVs is critical to the development of homeostatic immunity along mucosal surfaces [2]. Briefly, TLR2 stimulation by *Staphylococcus epidermidis* induces the expression of ERV elements to agonize the cytosolic nucleic acid sensing cGAS-STING complex, which then promotes accumulation of innate-like lymphocytes, $CD4^+$ and $CD8^+$ T cells, to promote homeostatic immunity and wound healing [2]. This complex interaction is dependent on keratinocytes and leukocytes, and organisms stemming from eukaryotic, viral, and bacterial origin. Pattern recognition by the innate immune system collectively appears to be a major determining factor in ERV expression with implicit effects on host immunity (Figure 2).

Future studies

It has been a major surprise to learn that the microbiota impacts human health via their effect on HERVs. It is also a shock to realize that important immune decisions are being taken outside of what we have considered canonical signaling pathways – and that a side 'conversation' between two microbial ecosystems are in some senses orchestrating immunity and inflammation in a most unexpected way. As this fresh view is incorporated, new mechanisms are revealed, and new therapeutic opportunities presented. For example, there are diseases associated with both

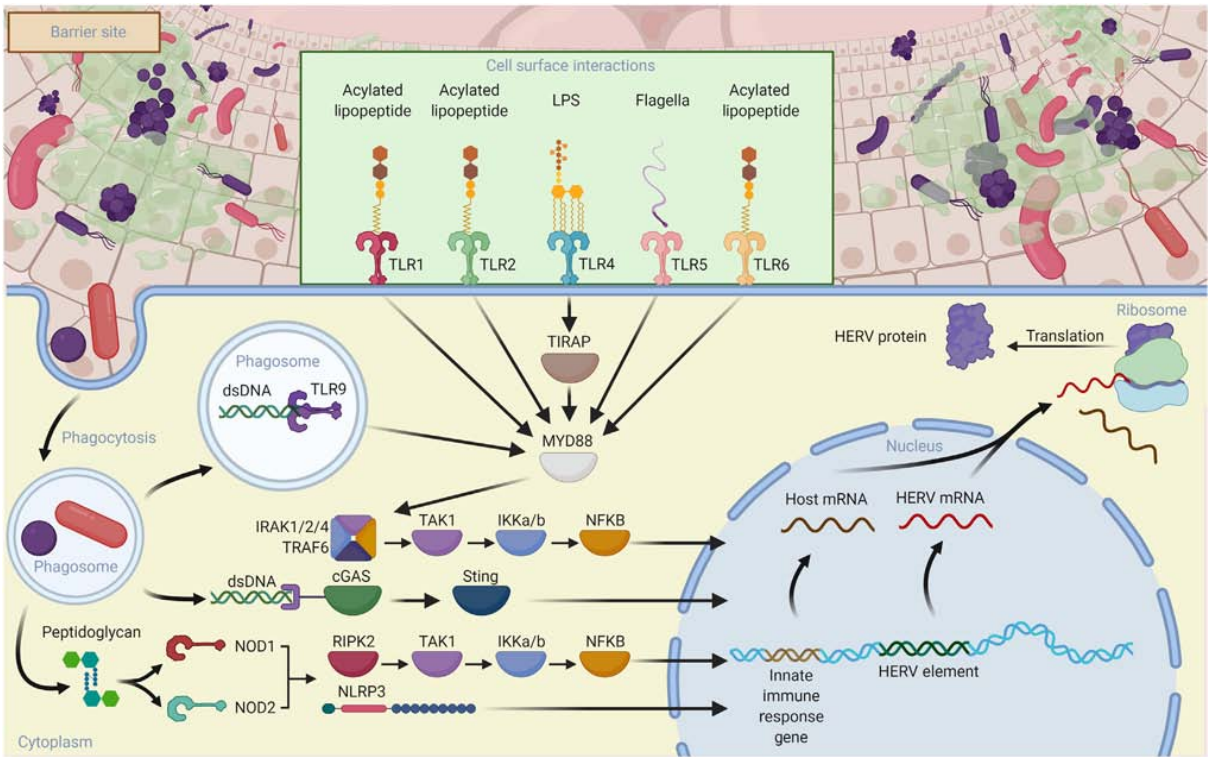

Figure 2. Bacterial by-products can alter the expression of human endogenous retroviral (HERV) elements via innate immune signaling pathways. Commensal and pathogenic prokaryotic organisms trigger innate immunity via the activation of pattern-recognition receptors (PRRs) which recognize motifs characteristic of infection. PRRs involved in the detection of microbial constituents at barrier sites include Toll-like receptors (TLRs), nucleic acid sensors, and nucleotide-binding oligomerization domain (NOD) receptors. The diverse repertoire of innate immune signaling pathways activated by microbial motifs results in the activation of specified antimicrobial response genes, such as TIR domain-containing adaptor protein (TIRAP) and myeloid differentiation primary response 88 (MYD88), within the host cell. The widespread changes in chromatin structure required to promote the expression of innate immune response genes promote the expression of proximal HERV elements. Common ligands that agonize PRRs include: acylated lipopeptides, lipopolysaccharide (LPS), peptidoglycan, flagella, and bacterial DNA.

abnormal HERV expression and microbial dysbiosis alike, such as multiple sclerosis (MS) [9,14]. Emphasizing how the microbiota and HERVs, instead of or, impact neuroinflammatory cascades may finally describe the elusive conditions that initiate unchecked autoimmune inflammation in MS. Recent bioinformatic pipelines that give accurate characterization of HERV transcripts with locus-specificity from bulk [15] and long-read single-cell [16] RNA sequencing datasets make this daunting task manageable. The analytic capabilities of these bioinformatic pipelines provide locus-specific definition when exploring the expression profiles of HERVs identifiable from RNA-sequencing strategies that have become a standard practice in biomedical research.

While our current understanding of HERV–bacteria interactions is derived from how commensal bacteria promote beneficial immunity through inducing expression of co-opted ERVs, this crosstalk may also be exploited by virulent bacteria that aim to sustain infection via immune evasion or activation. It is therefore important for future studies to consider HERVs as a potential underlying mechanism by which bacterial virulence factors could facilitate immune evasion or activation to the host's detriment.

In summary, the microbiota and HERVs are shown to be complex determinants of human health that provide potent regulation over host immunity. Communication between the two have recently been appreciated to be a determinant of host immunity and health. Due to the advancement and rapid adoption of '-omics'-based technologies dedicated to their study, in coordination with a growing emphasis on the development of novel therapeutics, we emphasize developing future studies that investigate this crosstalk. This novel microbiota–ERV–immune axis remains a vast untapped reservoir of immunoregulation that may provide novel

classes of prophylactic medications and immunotherapies.

Declaration of interests

No interests are declared.

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