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Short communication,

The Trespassing Bugs: Microbial Translocation Disorders

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"All disease begins in the gut"

Hippocrates:

The Human Microbiome Project, launched in in 2007, and the discovery of innate lymphoid cells (ILCs) in 2008 are major advances that have begun to shed light on the pathogenesis of some disorders of uncertain etiology, including autoimmune, fibrotic, and neuropsychiatric illnesses, as well as the potential interaction of systemic infections with the gut-brain axis.

The gut microbial community is immunologically "tolerated" in the gastrointestinal (GI) tract but may elicit immunogenicity and pathology upon translocation into host tissues (1) (2). Indeed, in the former case long-term, low-grade inflammation may eventually lead to disease (3), while in the latter case, numerous studies have reported the presence of intestinal microbes and/or their molecules as part of observed pathology within host tissues, such as the circulatory system and the brain (4) (5).

A better understanding of oral and gut tolerance, immune unresponsiveness to food proteins and gut microbiota, has led to the reconceptualization of some idiopathic diseases as microbial translocation disorders (MTDs) (6). Ironically, disease caused by viruses that were originally considered unrelated, such as human immunodeficiency virus (HIV) and severe acute respiratory syndrome coronaviruses (SARS and SARS-CoV-2) have contributed to a more complete understanding of the molecular underpinnings of oral/gut tolerance and immunogenicity (7)(8). As both HIV and SARS-CoV-2 viruses target ILC type 3 (ILC3), they disrupt the intestinal barrier and the immunological tolerance of oral and gut microbiome (9)(10)(11)(12). Indeed, ILC3-generated interleukin 22 (IL22) functions as a guardian of the intestinal barrier as it upregulates the antimicrobial peptides and luminal mucus, opposing microbial translocation (13)(14) (Fig. 1).

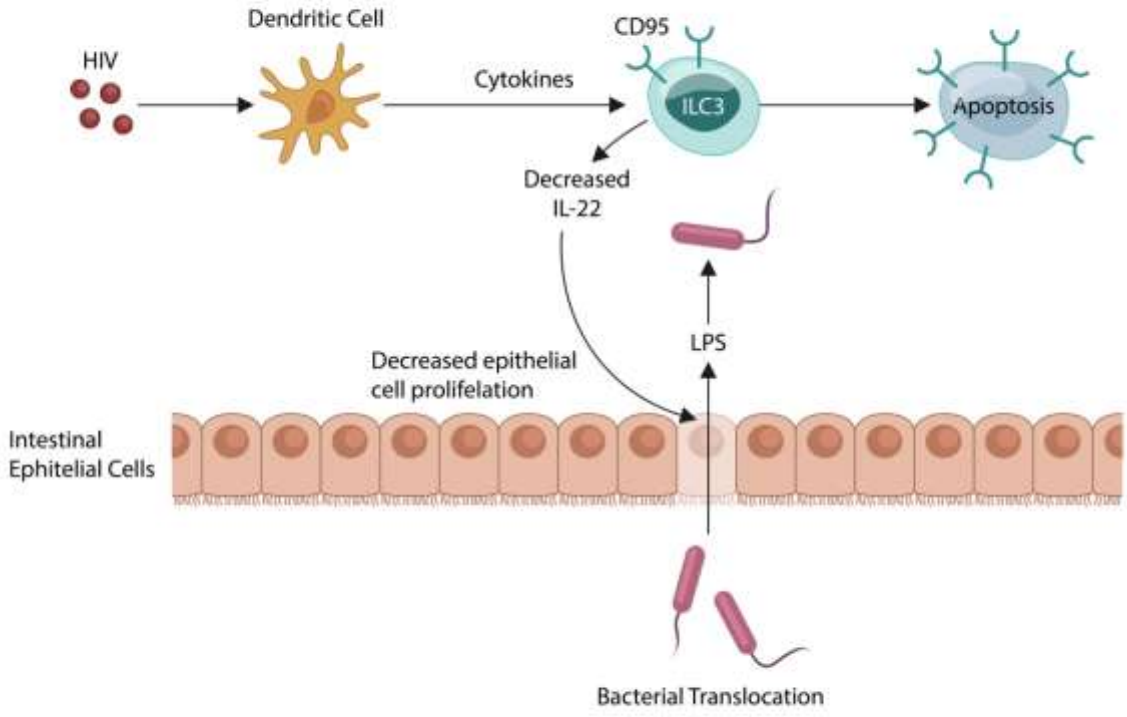

Fig. 1 HIV induces apoptotic loss of ILC3, lowering IL22, the guardian of gut barrier, allowing translocation of intestinal microbes and their molecules into the systemic circulation. Activated host immunity maintains a state of low-grade inflammation that characterizes many chronic diseases of uncertain etiology.

Innate lymphoid cells

ILCs are non-T and non-B lymphocytes, consisting of natural killer cells (NKCs), ILC-1, ILC-2, ILC-3, that reside in various tissues, including the central nervous system (CNS) and the GI tract (15)(Fig. 1). These cells play a key role in gut immunological tolerance as they maintain the barrier integrity and homeostasis, increasing antimicrobial peptides and intestinal mucus (16)(17).

Unlike the B and T cells, ILCs do not possess specific antigen receptors but express transcription factors and synthesize cytokines (18). For example, NKCs and ILC1, activated by IL12, IL15, and IL18 release interferon γ (IFN-γ), participating in antiviral defenses (Fig. 1). ILC-2 express GATA-3, are activated by IL-25 and IL33, and release IL5 and IL13; ILC3, expressing RORγt, are activated by IL23 and IL1 beta (IL-1β), while their output consists of IL22 and IL17 (Fig.2). Dysfunctional signaling in these lymphoid systems can trigger MTDs, though the full range of interactions remains to be determined.

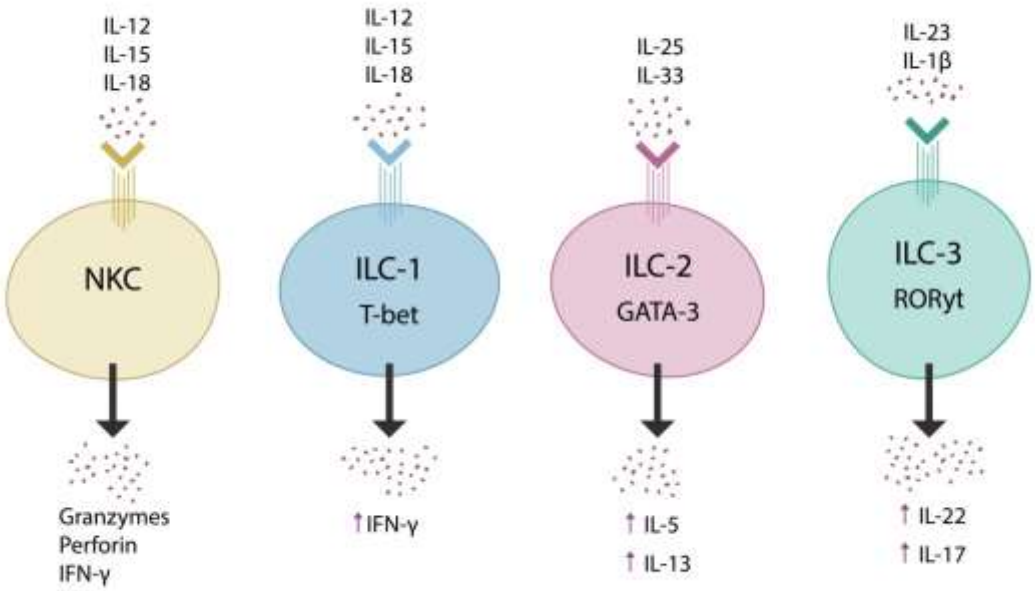

Fig. 2 Innate lymphoid cells are comprised of NKCs, ILC1, ILC2, and ILC3. They are activated by various cytokines (top), release other cytokines (bottom), and express transcription factors, including T-bet, GATA-3 and RORγt. When dysregulated, these lymphoid systems may trigger autoimmunity, fibrotic and neuropsychiatric illnesses.

In the following sections, we highlight several mechanisms that may connect ILCs with the disorders of unknown etiology, especially autoimmune, fibrotic, and neuropsychiatric illnesses

Autoimmune disorders:

Autoimmune disorders are believed to reflect an immune system dysfunction characterized by the generation of autoantibodies against self-proteins. However, improved understanding of the microbiome and ILCs has contributed to the emergence of noncanonical views in which autoantibodies can be conceptualized as conventional immunoglobulins directed at the translocated gut microbes and/or their antigens that resemble human proteins. As gut commensals express receptors similar to those of the human host, translocated microbes may elicit antibodies against these proteins, triggering pathology. For example, lupus-associated autoantigen Ro60, expressed by numerous gut commensal species, may elicit conventional immune responses when these microbes migrate into the host systemic circulation (19)(20). In another example, the gut resident *Escherichia coli*, expressing succinate dehydrogenase, a molecule that mimics the human mitochondrial enzyme, may elicit the formation of antimitochondrial antibodies documented in several autoimmune disorders (21)(22). Interestingly, elevated plasma succinate levels were associated with cardiovascular disease, hypertension, and diabetes type 2 (T2D), connecting these diseases of uncertain/multiple etiology to microbial translocation (23)(24). Along this line, a recent study has associated suicidal behavior in young adults with the depletion of succinate producing *Alloprevotella rava*, linking this condition to MTD (25). This is not the first time that suicidal behavior has been linked to potential enzymatic imbalance (26)(27), however it is one of the first linking directly to a specific species within the microbiome. Furthermore, diabetes type 1 (T1D) was associated with *Citrobacter rodentium*, suggesting a probable MTD etiology (28). Indeed, several studies have linked both T1D and suicidal behavior to increased levels of intestinal fatty acid binding protein (I-FABP), a serological biomarker of dysfunctional intestinal barrier, further emphasizing the likely MST etiology (29)(30). Moreover, succinate dehydrogenase was implicated in lung fibrosis, and a number of cancers, highlighting the interconnectedness of several diseases of unknown etiology (31)(32).

Neuropsychiatric disorders:

Upregulated translocation markers, I-FABP and lipopolysaccharide (LPS) were reported in several neuropsychiatric conditions, including major depressive disorder (MDD) and Alzheimer's disease (AD), linking these pathologies to MTDs (33)(34)(35)(36). This common biological foundation is further substantiated by the higher prevalence of several neuropsychiatric conditions, such as MDD and schizophrenia, in patients with inflammatory bowel disease (IBD), a disorder marked by impaired gut barrier (37)(38)(39). Moreover, CNS-resident ILCs have been implicated in MDD, neurodegeneration, multiple sclerosis (MS), and suicidal behavior, connecting these pathologies to MTDs (40)(41)(42)(43). Indeed, dysfunctional ILC2 and IL15 and IL13 mark autoimmune disorders as well as schizophrenia and AD, linking these neuropsychiatric conditions to autoantibodies (44)(45)(46)(47)(48). This is significant as autoantibodies against neuronal adhesion molecule (NCAM1) were recently detected in patients with Guillan-Barre Syndrome (49) and schizophrenia, emphasizing that inflammation in these conditions may be autoimmune in nature (50). As NCAM1 has been associated with several viruses, including COVID-19, rabies, and Zika, non-familial schizophrenia may be the result of prenatal exposure to those and similar pathogens as demonstrated in the aftermath of the 1957 influenza A2 epidemic (51)(52)(53)(54). In addition, as IL-13 attachment to its α1 receptor (IL13R α1) can trigger loss of dopaminergic neurons in substantia nigra, ILC3 may be implicated in Parkinson's disease (55)(56). Moreover, IL13 was reported to differentiate between MDD patients with and without suicidal intent, suggesting that for a portion of neuropsychiatric patients this cytokine could become a biomarker of suicidality (57)(58).

Various gut microbes produce molecules mimicking gamma-aminobutyric acid (GABA) and glutamic acid decarboxylase (GAD or GAD65), suggesting that microbiota translocation may elicit autoantibodies directed at these proteins (59). Indeed, anti-GAD antibodies were demonstrated in schizophrenia, bipolar disorder, T1D, and autoimmune thyroiditis, further emphasizing the intertwined nature of the idiopathic disorders (60). Interestingly, the protozoan *Toxoplasma gondii* (*T. gondii)*, previously associated with schizophrenia, utilizes GABA as a carbon source, depleting this neurotransmitter, likely contributing to neuropathology (61)(62). Moreover, *T. gondii* was found to induce immunosuppression via IL-10, NKCs and ILC1, implicating both immunodeficiency and autoimmunity in *T. gondii* psychopathology (63)(64). This is significant as several studies have demonstrated a high rate of latent T. gondii infection among COVID-19 patients, indicating a possible opportunistic symbiosis for disruption of host immunity (65).

Human fibrotic diseases:

Fibrotic diseases, marked by the accumulation of excessive extracellular matrix proteins (EMPs), encompass both generalized and organ-specific disorders, including systemic sclerosis, pulmonary, cardiac, intestinal, liver, and kidney fibrosis (66). Transforming growth factor-β (TGF-β), upregulated in fibrotic illness, is a key regulator of ILCs, linking excessive fibrosis to MTDs (67)(68)(69)(70)(71). Indeed, fibrosis has been associated with autoantibodies and the breakdown of gut immunological tolerance. For example, microbiota-generated curli amyloid fibrils were reported to disrupt ILC3, IL17, and IL22, promoting both autoimmunity and intestinal fibrosis (72)(73)(74)(75)(76). Furthermore, fibroblast growth factors play a key role in GI barrier integrity, while loss of fibroblast growth factor 9 (FGF9) was associated with pulmonary fibrosis, further linking this pathology to MTDs (77)(78)(79). This is significant as FGF9 possesses antiviral properties, probably regulating the gut virome, an intestinal viral community associated with various pathologies, including fibrosis, autoimmunity, and neuropsychiatric illness (80)(81)(82)(83)(84). Indeed, FGF9 has been implicated in MS, seizure disorder, and schizophrenia, emphasizing once more the interconnectedness of these poorly understood disorders (85)(86)(87).

While this overview provides a first indication of the potential links between MTDs, auto-immune and neuro-psychiatric disorders, it should be noted that a number of these investigations remain in their early stage. Additionally, these conditions have been presented here as being well-distinct, though in practice there are observed areas of etiological overlap. Therefore, caution would need to be exercised in inferring causation from apparent correlation. While there is no doubt that the discovery of ILCs and the improved understanding of the gut-brain axis will contribute to the in-depth knowledge of conditions and pathologies of as yet unknown etiology (and eventually lead to novel treatments), there exist profound gaps in the

current scientific knowledge that require to be addressed by further molecular and population-based studies on the subject.

Conclusions:

The discovery of ILCs contributed to a better understanding of microbial translocation outside the GI tract. The host-microbiota interaction may elucidate the etiology of some poorly understood disorders, including autoimmunity, fibrotic illness, and neuropsychiatric conditions. Restoring ILCs homeostasis and intestinal barrier integrity to oppose microbial translocation will, eventually lead to the development of novel therapeutic strategies for chronic illnesses.

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