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The Immunology of Suicidal Behavior

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Introduction

A recent study by Ahrens AP, et al. on university students with suicidal ideation has highlighted the connection between immunity and psychopathology, especially major depressive disorder (MDD) and suicidality [1-3]. This study has found that four major histocompatibility complex (MHC) alleles and the absence of oral microbe *Alloprevotella rava* increase the risk of suicidal behavior, emphasizing a microbial-genetic link in this pathology. Suicide is the second leading cause of mortality in young adults, contributing to more than 40,000 deaths per year in the US alone [4]. Previous studies have associated suicidal behavior with several alleles of the MHC, a network of genes encoding for the human leukocyte antigen (HLA). For example, the presence of DQB1*02 allele was reported to increase, while HLA-DQB1*05 to lower the odds of suicidal behavior, suggesting that genetics and immunity play a major role in the pathogenesis of this disorder [5].

Altered human microbiome, the microbial community living in symbiosis with the host, was previously linked to suicidal behavior, suggesting that microbiota could be involved in this pathology [6]. Indeed, the markers of bacterial translocation into the host circulatory system, including lipopolysaccharide (LPS) and intestinal fatty-acid binding protein (I-FABP), were reported to be elevated in individuals with recent suicide attempts, connecting this pathology with dysfunctional gut barrier [7]. This is further

substantiated by the earlier studies which reported increased suicide rates in patients with inflammatory bowel disease (IBS), further connecting microbial translocation outside the gastrointestinal (GI) tract with this behavior [8,9].

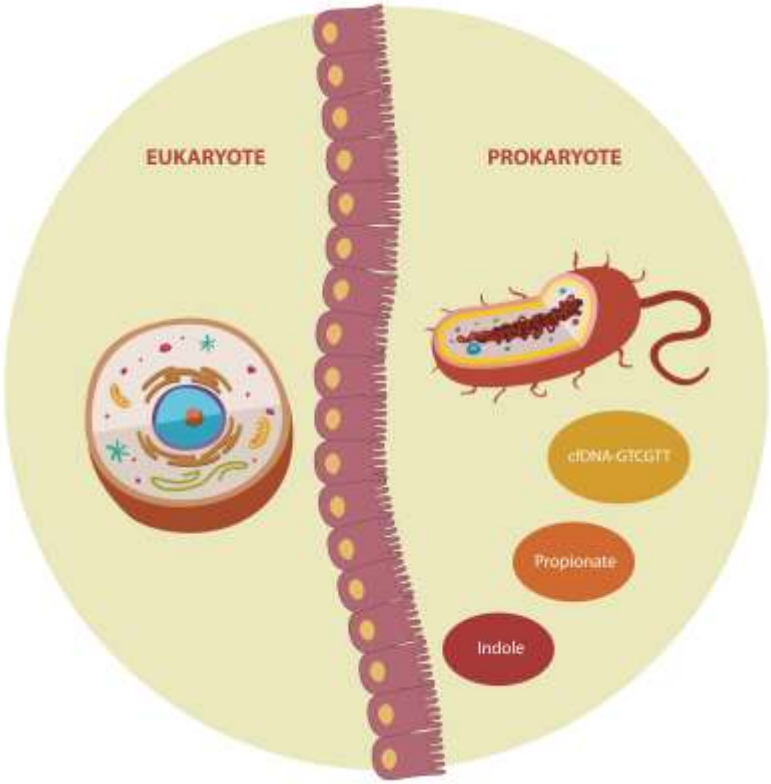

Figure 1: Two kingdoms, the eukaryotic host and prokaryotic gut microbes, are separated by a single layer of intestinal epithelial cells (IECs), highlighting the vulnerability of this biological barrier. Elevated circulatory LPS and I-FABP are established biomarkers of increased intestinal permeability, however, plasma levels of indole, short chain fatty acids, such as propionate, and cell free bacterial DNA, especially the one with abundant TLR9-activating GTC-GTT codons, may comprise novel markers of microbial translocation outside the GI tract.

Commensal microbes express proteins identical or similar to those of the human host, likely activating the immune system upon translocation, causing pathology. Due to molecular mimicry, antibodies against microbial antigens can interact with host proteins, giving the impression of auto antibodies. For example, *Bacteroides species* and *Pseudomonas fluorescens* produce γ-amino butyric acid (GABA) and GABA-binding proteins that may elicit the formation of antibodies, probably explaining the pathogenesis of anti-GABA-B receptor encephalitis [10,11]. This is significant as a recent study has associated elevated anti-GABA-B receptor antibodies in the cerebrospinal fluid (CSF) with suicidality, linking this behavior to autoimmune pathology [12]. In addition, Escherichia coli (E. coli), expressing glutamate receptor (GluR)-B and GluR-D, can, upon translocation, elicit the production of anti-N-methyl-d-aspartate-receptor (NMDAR) antibodies, immune globulins strongly correlated with suicidal behavior [13,14]. The study of microbiome and microbial translocation has blurred the concept of autoimmunity, begging the question: are human auto antibodies generated spontaneously, or are they conventional antibodies against

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microbial proteins translocated outside the GI tract? The answer to this question is significant as methotrexate, a major therapy for autoimmune disorders, may be counterproductive as it was shown to increase the permeability of gut barrier, and as such, it could facilitate microbial translocation further [15-16]. Moreover, enhancing the gut barrier may be a potential therapeutic strategy for patients with autoimmune disorders.

Discussion

Putting the above information together, Ahrens AP, et al. is the first study to examine the interface between commensal microbes and the MHC, a system which undergoes gene diversification by interacting with the human microbiome [17,18]. *Alloprevotella rava,* asuccinate-producing, Gram-negative bacillus, belongs to the*Prevotellaceae* family and resides in the oral cavity [19]. *Prevotellaceae* have been associated with the up regulation of Th17 cells known for generating interleukin [13] a recently identified marker of suicidal behavior in patients with MDD [20,21]. In addition, *Prevotellaceae* were implicated in other psychiatric disorders, including schizophrenia, probably accounting for the significant number of patients with this disorder who engage in suicidal behavior [22-24]. Indeed, activation of IL13 alpha 1 receptor (IL-13Rα1) in the dopaminergic neurons of *substantia nigra* was found to increase the vulnerability of these cells to oxidative damage, likely predisposing to Parkinson's disease (PD) [25]. The human saliva and gut microbiomes were reported to undergo diurnal, seasonal as well as geographical variations that affect gene expression, including those of the MHC [26-29]. This is significant, as numerous epidemiological studies have reported a seasonal pattern of suicidal behavior (with counts peaking in the spring and declining in winter) probably coinciding with viral infections [30,31]. As many viruses, including SARS-CoV-2, may activate oral and gut bacteriophages (bacteria-infecting viruses), it is tempting to speculate that the salivary microbiome would be less diversified during springtime, likely accounting for the absence of *Alloprevotella rava* [32].

Conclusion

The oral cavity is an essential gateway to the human GI tract that affects the composition of the gut microbiome and by extension that of other organs. Several earlier studies have associated both the salivary and intestinal microbial communities with suicidal behavior, linking this pathology to the gene-microbiota interface [33,34].The translocation of microorganisms outside of the GI tract and the generation of antibodies to antigens mimicking neuronal proteins have been linked to suicidal behavior, connecting this pathology to immunity and autoimmunity. Moreover, as MHC genetics was associated with the risk of suicide as well as autoimmune diseases, in the near future, suicidal behavior may be reconceptualized as an infectious or immune, rather than psychiatric illness [35]. Indeed, prior to the discovery of Helicobacter Pylori (H. Pylori), peptic ulcer disease was included among psychiatric disorders, setting a precedent for this type of pathogenetic shifts [36].

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