

Recombinant Human IL-22 Delivered in Polydopamine Nanoparticle for Inflammatory Bowel Disease and Schizophrenia

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Background:

Emil Kraepelin believed that dementia praecox, the disorder we now call schizophrenia, was the result of brain poisoning with toxins generated in other parts of the body, especially the mouth, intestine, or genitals (1). In this regard, Kraepelin hinted at the microbiome and believed that microbial molecules could drive the pathogenesis of severe psychiatric illness. However, the infectious model of schizophrenia drew limited attention until the launching of Human Microbiome Project and the discovery of innate lymphoid cells (ILCs).

The gut and schizophrenia

Several recent studies have connected schizophrenia with microbial translocation (MT) from the gastrointestinal (GI) tract into the host systemic circulation, eventually reaching the brain (2-5). MT refers to the migration of intestinal microorganisms or toxins into host tissues by passing through the intestinal barrier and lamina propria to reach mesenteric lymph nodes and the systemic circulation. In the central nervous system (CNS), bacteria or their components can trigger psychosis by several mechanisms, including inflammation, impaired autophagy, premature cellular senescence, and aberrant microglial activation (6-9).

The evidence of MT in schizophrenia

1. Patients with schizophrenia have a high prevalence of in-

flammatory bowel diseases (IBD), such as ulcerative colitis and Chron's disease, conditions associated with increased gut barrier permeability and MT (10-12).

2. Patients with schizophrenia present with elevated bacterial translocation markers, including soluble CD14 (sCD14) and lipopolysaccharide binding protein (LBP), emphasizing microbial migration from the immune tolerant GI tract into the bacteria-intolerant systemic circulation (13-15).

3. Patients with schizophrenia exhibit increased blood brain barrier (BBB) permeability, enabling bacteria and/or toxins to ingress the CNS (16-19).

4. The 2011 outbreak of *Escherichia coli* (*E. coli*) in Germany has been associated with the new onset psychosis, connecting this pathogen to neuropsychiatric illnesses (20-21). In addition, *E. coli* has been implicated in urinary tract infection (UTI), conditions often associated with new onset psychosis or schizophrenia exacerbation, linking this bacterium to psychopathology (22-23).

Interleukin-22, the "guardian" of gut barrier

During the human immunodeficiency virus (HIV) epidemic in 1980s, MT drew the attention of researchers and clinicians as this virus depleted interleukin-22 (IL-22), enabling gut bacteria and microbial molecules, such as lipopolysaccharide (LPS) to migrate into host tissues and induce pathology (22-23)(Fig. 1).

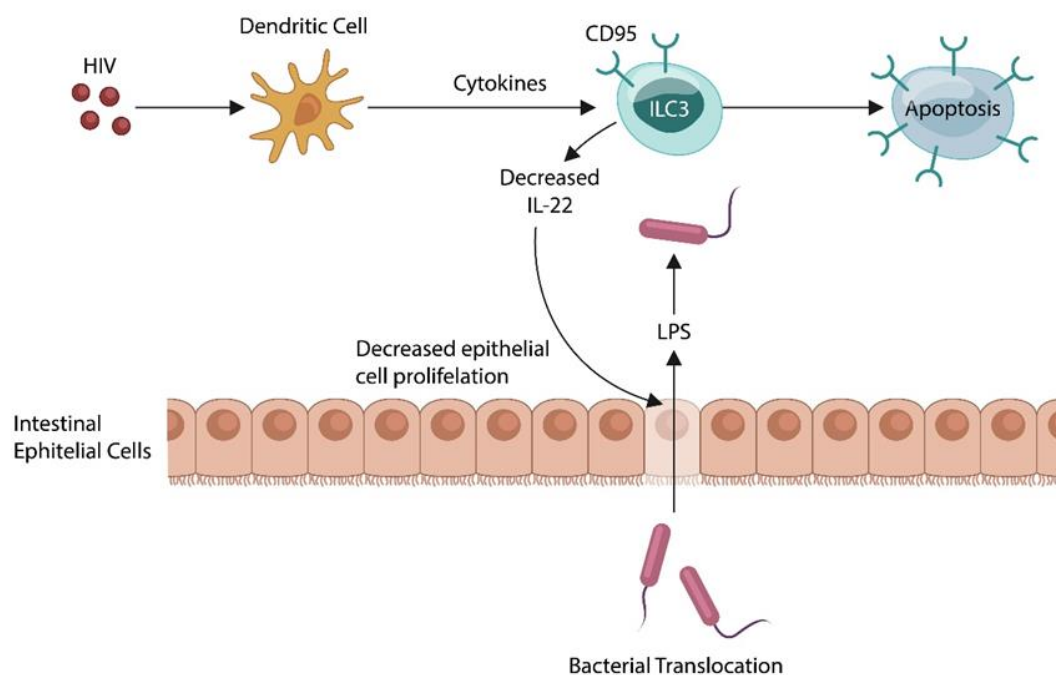


Figure 1: HIV induces apoptotic loss of innate lymphoid cells, type 3 (ILC3), lowering IL-22, the guardian of gut barrier. This, in turn promotes MT into the systemic circulation. Activated host immunity maintains a state of low-grade inflammation, well-documented in IBD and schizophrenia.

Gut microbial community is immunologically tolerated in the GI tract however, upon migration outside the lamina propria, microbiota or its components may trigger inflammation and immunogenicity, reflected in the brain by gray matter volume (GMV) reduction, an established biomarker of schizophrenia (SCZ) or SCZ-like illnesses.

A previous patent application (Publication number: 20240277809), human recombinant IL-22 (HRIL-22) was proposed as a SCZ treatment based on the MT hypothesis, formulated by this author in several papers.

Discovered in 2000, IL-22 is a member of IL-10 family generated by several lymphocyte types, including T helper (Th) 17 cells, $\gamma\delta$ T cells, NKs, and innate lymphoid cells (ILCs)(30). IL-22 controls several intestinal epithelial cells (IEC) func-

tions, including mucus formation, permeability, synthesis of both complement and antimicrobial peptides (AMPs), indicating that this cytokine functions as the master regulator of gut barrier permeability (24).

The crosstalk between IL-22 and its receptor (IL-22R), a dimeric protein comprised of IL-22R1 and IL-10R2, activates the JAK/STAT pathway, a key antibacterial and antiviral system, protecting against pathogens (25-26). As IL-22R contains IL-10R2, it can be cross-activated by IL-10, a cytokine connected to immunological tolerance. Moreover, IL-22 protects against COVID-19, influenza, and inflammatory bowel disease (IBD), indicating that supplementation with this cytokine may ameliorate or totally alleviate these pathologies (27-30).

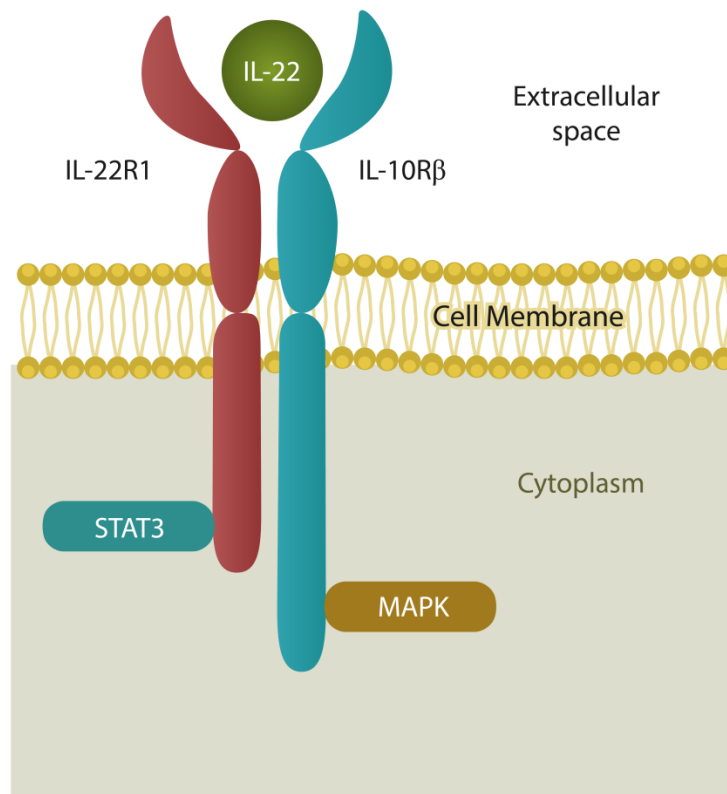


Figure 2: IL-22 attaches to both IL-22R1 and IL-10R β receptors, therefore, its agonist, human recombinant IL-22 (HRIL-22) will exert IL-22 and IL-10 actions. It activates STAT3 and MAPK, effector molecules implicated in IBD and SCZ.

IL-22 and innate lymphoid cells (ILCs)

Novel studies have reported that a subgroup of natural killer cells (NKC) produce IL-22, enhancing the gut barrier and averting MT (31-33). Indeed, research over the past two decades has connected defective NKCs with IBD, SCZ, and cancer (34-37). In the CNS, NKCs participate in adult neurogenesis, cognition, and cellular senescence, suggesting that

under pathological circumstances, these processes may be disrupted (38-40).

NKCs belong to innate lymphoid cells (ILCs), mucosa-anchored non-T, non-B lymphocytes, which also include ILC-1, ILC-2, and ILC-3 (39)(Fig.3).

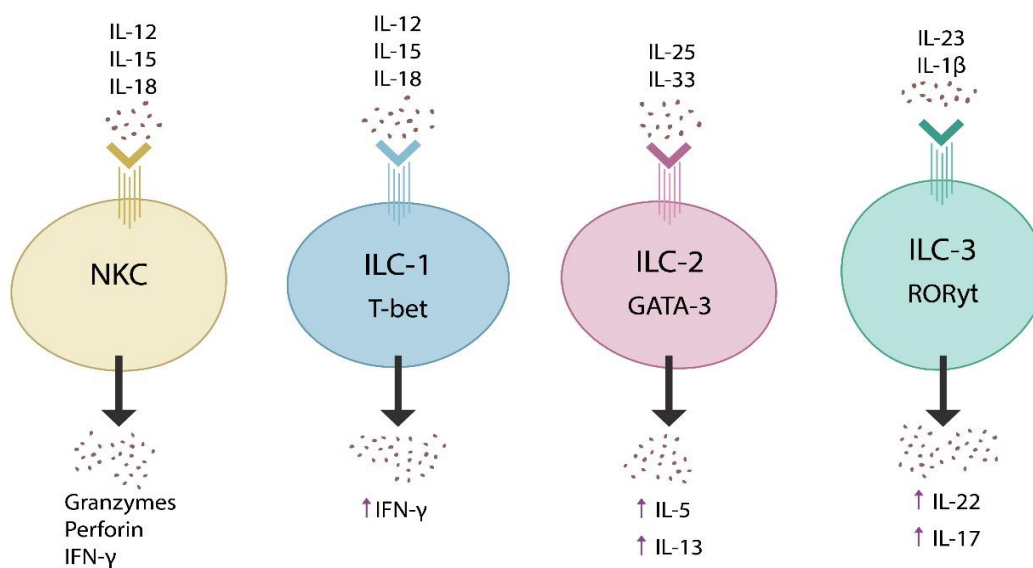


Figure 3: Innate lymphoid cells are comprised of NKCs and innate lymphoid cells type 1, 2, and 3 (ILC-1, ILC-2, and ILC-3). These cells are activated by various cytokines (top), release other cytokines (bottom), and express transcription factors, including T-bet, GATA-3 and ROR γ t. Under pathological circumstances, these lymphoid systems may lead to IBD and MT, contributing to systemic inflammation.

Innate lymphoid cells play a pivotal role in gut barrier homeostasis, nutrient transport, and immune tolerance of both food proteins and gut commensals (39-40). For example, aberrant activation of NKCs by IL-12, IL-15, and IL-18 was reported in IBD linking ILCs to this pathology (41-42). Moreover, IL-22 also promotes protective autophagy, and iron storage in ferritin, lowering the risk of lipid peroxidation, a pathology linked to both IBD and SCZ. Indeed, SCZ was associated with dysfunctional NKCs (43).

Polydopamine (PDA) nanoparticles for IBD

IBD, includes GI tract disorders like Crohn's disease and ulcerative colitis, conditions marked by IECs inflammation and in severe cases, barrier lesions and microbial migration into the systemic circulation.

Due to its adhesive properties and excellent biocompatibility, PDA has garnered attention in biomedical applications, as a drug delivery vehicle, wound healing promoter, and facilitator of tissue engineering (44). PDA is a catecholamine, comprised of polymerized dopamine (DA) oxides that exhibits strong adhesive properties, excellent tolerability, promotes wound healing, cell adhesion, and regeneration. For this reason, it is currently in clinical trials for IBD.

The PDA ability to deliver drugs directly to the inflamed tissues, including IECs, raises the interesting possibility of combining human recombinant IL-22 (HRIL-22) with a PDA nanoparticle, delivering simultaneously two beneficial agents to the injured gut epithelia (45). Indeed, both HRIL-22 and PDA promote wound healing, however, due to its adhesive properties, only PDA can serve as a transport vehicle. For this reason, encapsulating HRIL-22 into PDA has the advantage of delivering two therapeutic agents simultaneously.

IL-22 safety, pharmacokinetic and pharmacodynamic data

HRIL-22 is currently in Phase II clinical trials for the treatment of COVID-19, COVID-19 pneumonia, acute pancreatitis, chronic acute liver failure, alcoholic hepatitis, and graft versus host disease (GVHD)(NCT02406651). Several studies have evaluated the safety, pharmacokinetics, pharmacodynamics, and tolerability of HRIL-22, demonstrating that this is a safe compound with favorable pharmacological parameters (46-47).

Aside from functioning as the guardian of intestinal barrier, IL-22 possesses antibacterial and antiviral properties probably by enhancing autophagy (83-85). Impaired autophagy has been documented in IBD, while IL-22 (or HRIL-22) enhances autophagy, lowers INF- γ and protects intestinal barrier against IBD and MT (48-51).

Amino acid sequence and administration

IL-22 amino acid sequence:

ADPAPISSHC RLDKSNFQQP YITNRTFMLA KEASLADNNT
DVRLLIGEKLFGVSMSERCY LMKQVLNFTL EEVLFPQSDR
FQPYMQEVVP FLARLSNRLS TCHIEGDDLH IQRNVQKLKD

TVKKLGESGE IKAIGELDLL FMSLRNACIH HHHHH.

Natural human IL-22 is comprised of 179 amino acids and possesses an N-terminal containing 33-amino acids, while *Escherichia coli*-generated recombinant human IL-22 forms a dimer structure in solution and contains two disulfide bonds between amino acids 40-132 and amino acids 89-178 (52-53).

HRIL-22, a recombinant fusion protein consisting of two human IL-22 molecules linked to the human IgG2 constant region which extends the IgG2-Fc half-life (99).

In human volunteers, HRIL-22 was administered via intravenous (IV) infusion at 2.0, 10, 30, and 45 $\mu\text{g}/\text{kg}$ and no severe adverse effects were seen. Dose-dependent transient increase in serum amyloid A and C-reactive protein were reported as well as a decrease of serum triglycerides. The compound was safe and well-tolerated (54).

Preclinical studies and clinical trials phases I and II have shown that HRIL-22 is safe in doses up to 45 $\mu\text{g}/\text{kg}$ and has been associated with reduction in inflammatory markers (measured via Lille and MELD score) (55-56).

Preclinical data

IL-22 is a member of the IL-10 cytokine family that facilitates tissue healing, especially the epithelial cells. As it is generated by the leukocytes, cells that are in contact with every tissue and organ, IL-22 showed few adverse effects or hypersensitivity. Preclinical studies found that IL-22 protects epithelia, promotes regenerative processes, and is well-tolerated (57). Preclinical and translational studies in rodents and *Cynomolgus* monkeys, found anti-inflammatory effects and good tolerability (57). Other preclinical studies outlined similar findings, clinically predictable, manageable, and reversible adverse effects (55). In term of epithelial protection, it was established that this compound repairs the barrier function (103).

IL-22 driver of autophagy, including mitophagy and ferritinophagy

Autophagy or self-eating in Greek, is a physiological mechanism in which defective cells, organelles or misfolded proteins are degraded in lysosomes to avert tissue damage by accumulation of molecular debris (58). Autophagy is activated by the aggregation of defective proteins in the endoplasmic reticulum (ER), a calcium (Ca^{2+})-storing intracellular organelle where proteins and lipids are synthesized (59). ER stress, caused by excessive piling up of faulty proteins, activates the unfolded protein response (UPR), a defense mechanism that enables autophagy, restoring homeostasis (60). ER stress sensors, double-stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK), transcription factor 6 (ATF6), and inositol-requiring enzyme 1 (IRE1), detect the misfolded proteins, initiating autophagic degradation (61-62). However, overactivation of UPR can trigger inflammation, leading to aberrant autophagic digestion of healthy mitochondria (mitophagy)

and the iron-storing molecule, ferritin (ferritinophagy), pathologies associated with IBD and SCZ. Indeed, excessive autophagy of mitochondria and ferritin may upregulate intracellular iron, leading to cell loss by ferroptosis, a non-apoptotic form of cell demise. In contrast, IL-22 protects the mitochondrion and promotes protective autophagy as well as iron storage in ferritin, opposing ferroptosis. Since mitochondria are rich in iron, abnormal mitophagy may also trigger iron dysmetabolism, promoting ER stress-mediated pathology (63) (64-67). In contrast, IL-22 as well as the ER stress-lowering drugs may represent the avantgarde of a new generation of IBD and neuropsychiatric treatments (68-69).

In the GI tract, autophagy mediates the crosstalk between gut microbiota and host immunity, while impaired autophagy can disrupt the gut barrier, a characteristic of IBD (70-71). Recent studies found a bidirectional relationship between autophagy and IL-22 as autophagy upregulates this cytokine

and in return, IL-22 activates autophagy, protecting the gut barrier (72-73). Recent studies reported an interaction between autophagy and oxidative stress as antioxidants may suppress autophagy (74). In this regard, IL-22 not only alleviates ER stress but may also exert antioxidant properties as it was shown to lower doxorubicin-induced oxidative stress, linking it further to ER homeostasis (75-76).

The ER is tethered to the mitochondrion through a distinct sub-compartment, the mitochondria-associated membranes (MAMs), an area linked to both autophagy and lipogenesis. In the GI tract, MAM pathology has been implicated in IBD-associated gut barrier dysfunction (77-78).

IL-22 and iron metabolism

IL-22 facilitates hepcidin release from the liver, inhibiting ferroportin, the only known iron-egressing channel, thus, sequestering the iron in the intracellular compartment, in ferritin (79-80)(Fig.4).

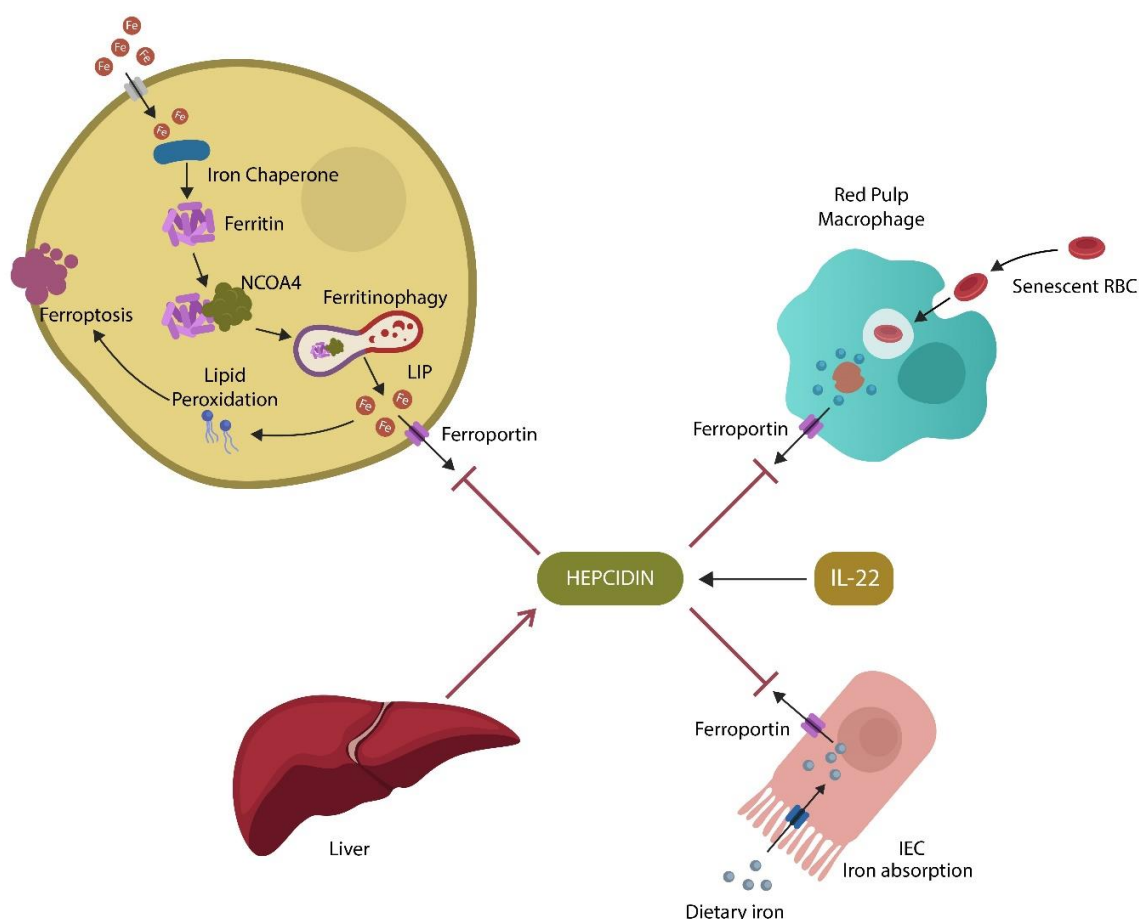


Figure 4: IL-22 induces the release of hepcidin from the liver. Hepcidin degrades ferroportin in many cell types, preventing iron egress from cells. This mechanism lowers the extracellular iron and the toxicity of this biometal. Dysfunctional IL-22-hepcidin-ferroportin axis alters intracellular iron, promoting ferroptosis. Body iron is derived from absorption in the gut and from recycling of old erythrocytes by macrophages in the spleen. Exogenous administration of IL-22 (or HRIL-22) may regulate hepcidin, rescuing cells, from cell death by ferroptosis.

Ferroptosis has been associated with IBD and SCZ. Indeed, iron overload was shown to cause ulcerative colitis and Chron's disease. Therefore, Inhibiting ferroptosis may offer a promising new therapeutic avenue for both disorders (81). It is currently believed that IL-22 may have proinflammatory properties as at times it induces cellular senescence, a proinflammatory phenotype, to limit tissue damage and fibrosis formation. For example, IL-22 has been shown to induce senescence in hepatic stellate cells (HSCs), lowering liver fibrosis (82). Senescent cells secrete a proinflammatory secretome, senescence associated secretory phenotype (SASP), that promotes wound healing, indicating that the proinflammatory properties of IL-22 or (HRIL-22) are adaptive (83-84).

Taken together, IL-22 (or HRIL-22) promotes cellular senescence, a proinflammatory phenotype, to facilitate tissue healing and avert the more serious pathology, such as fibrosis. Cellular senescence and SASP play an adaptive role in tissue healing.

IL-22 for IBD

Aryl hydrocarbon receptor (AhR) is a transcription factor that controls the expression (or silencing) of many genes, probably including the SCZ risk genes. AhR is expressed abundantly at the biological barriers, including gut barrier, and can be activated by exogenous and endogenous molecules. Under physiological circumstances, IL-22 modulates AhR, while aberrant activation of this receptor has been implicated in IBD, and likely SCZ. Currently, IL-22 is in clinical trials for ulcerative colitis (NCT02847052)(85) and was proposed as a SCZ treatment.

In the GI tract, IL-22 is secreted by *Bacteroides ovatus*, a probiotic, found beneficial for IBD (86). Indeed, *Bacteroides ovatus* ELH-B2 may be the avantgarde of the second-generation of probiotics utilized for IBD treatment. In addition, IL-22 is indispensable for the thriving of *Bifidobacterium*, a commensal microbe known for its beneficial effect on IBD (87-88). Indeed, several studies found that *Bifidobacterium*-derived alginic acid, an important protector of intestinal barrier by upregulating T helper (Th) cells, including Th22, IL-22-producing lymphocytes (89-90).

IL-22 and the thymus

IL-22 signals with its receptor on thymic epithelial cells, inducing thymocyte proliferation, opposing cellular senescence (91). For example, in mice, administration of IL-22 after total body irradiation, promoted thymic rejuvenation marked by increased number of thymocytes, lowering cellular senescence (92).

Thymus- activation-regulated chemokine (TARC), now called circulating C-C motif chemokine ligand 17 (CCL17), was found to be upregulated in unmedicated patients with SCZ, suggesting that thymic pathology may trigger premature senescence in patients with this disorder (93). CCL17 was also found upregulated in AD, PD, and aging heart, suggesting that it may be a marker of premature cellular senescence

(94-95). In contrast, preclinical studies found that IL-22 lowers CCL17, indicating beneficial effects against cellular senescence.

Conclusion

HRIL-22 is an antibacterial and antiviral molecule that promotes tissue repair and autophagy in many cell types, including IECs. Combination of HRIL-22 and PDA, another positive regulator of IECs healing may prevent MT more effectively than each agent alone. Here, combination of HRIL-22 with PDA is proposed as an etiopathogenetic treatment for both IBD and SCZ.

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