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Cover Page Footnote

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The Interplay of the Oral-Gut Microbiome with Chronic Inflammation in Rheumatoid Arthritis
and Crohn's Disease

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Abstract

Rheumatoid Arthritis (RA) and Crohn's Disease (CD) are both chronic inflammatory diseases that share developmental and treatment similarities. RA's symptoms include swelling, stiffness, and pain in synovial joints, corresponding with bone and cartilage destruction. CD's symptoms include abdominal pain, bowel obstruction, bloating, diarrhea, and fever. The purpose of this literature review was to investigate the links between these two diseases and propose future treatment and prevention targets. Current treatment for RA and CD aims to suppress inflammation by targeting its mediators. However, this review noted that there should be greater focus on resolving inflammation. Both diseases are characterized by the non-resolution of chronic inflammation due to the interplay of specific cytokines (IL-1, IL-6, TNF), which are proteins that function in cell to cell communication, and due to the dysbiosis of the oral and gut microbiome, which involves a compositional change of residing bacteria. Individuals are predisposed to both diseases via heritability and environmental factors, such as smoking. Finally, development and severity of both diseases depend on mutations in specific regulatory genes, such as STAT4 and PTPN22. Targeting the influx of immune cells, stimulating pro-resolving mediators such as IL-9 and 10, and restoring eubiosis are possible inflammation-resolving mechanisms. There should also be a movement towards prevention rather than disease intervention. Prevention tactics may include the promotion of oral and gut health, quitting smoking, and screening for genetic susceptibility.

Keywords: *Rheumatoid Arthritis, Crohn's Disease, dysbiosis, inflammation*

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Introduction

A malfunctioning immune system is the cornerstone of autoimmune diseases, cancers, and chronic inflammatory diseases. The immune system is composed of leukocytes, cytokines, chemokines, antimicrobial proteins, and barriers, to help to protect the body against foreign invaders. When it malfunctions, local tissue damage and widespread inflammation can result. Rheumatoid Arthritis (RA) and Crohn's Disease (CD) are chronic inflammatory conditions that result from inappropriate immune responses against self-antigens and commensal bacteria, respectively.

RA has become an increasingly prominent extraintestinal manifestation of CD (Yang et al., 2018; Georgiadis, Tzambouras, Ioachim, Tsianos, Agnantis, & Drosos, 2003). For example, a study in South Korea found that RA was found in 10/1000 CD cases (Yang et al., 2018). This association begs the following question: Are RA and CD merely coexisting diseases for some patients or do they share genetic and environmental links that point to similar developments? This literature review aims to investigate the treatments, inflammatory, environmental, and genetic susceptibility factors shared by RA and CD. This analysis will then be used to propose possible treatment and diagnosis options that could target both diseases to prevent or delay disease onset.

Role of Chronic Inflammation in RA and CD Etiology

RA Overview

RA is a T cell mediated autoimmune disorder that affects approximately 1% of the world's population (Cusick, Libbey, & Fujinami, 2012). RA is characterized by inflammation of

the synovial membrane surrounding the joints. RA's synovial inflammation leads to cartilage damage, bone erosion, thickening of the synovial membrane, formation of rheumatoid nodules, fatigue, stiffness and swelling of joints (Klareskog, Catrina & Paget, 2009; Chauhan & Al-Dhahir, 2018). The bone and cartilage damage present in RA patients are due to matrix metalloproteinases (MMPs). MMPs, released by macrophages and fibroblasts, work to gradually destroy the proteins needed to maintain the extracellular matrix structure. Extra-articular damage is also present with RA comorbidities, such as cardiovascular disease, osteoporosis, and lymphomas (Klareskog et al., 2009). A loss of tolerance towards citrullinated proteins is the hallmark of RA autoimmunity. The enzyme, peptidylarginine deiminase (PAD), facilitates the citrullination of proteins. Citrullinated proteins are presented by MHC Class II, where they are eventually recognized by T cells. These T cells proceed to interact with and activate B cells, which then produce and release antibodies against citrullinated protein antigens (ACPAs). ACPAs can recognize, bind, and neutralize the citrullinated protein antigen. ACPA is used as a diagnostic tool and a measure of RA severity, since its serum levels are correlated to the severity of RA symptoms (Du Teil Espina, Gabarrini, Harmsen, Westra, Winkelhoff & Van Dijl, 2018).

CD Overview

CD is a type of Inflammatory Bowel Disease (IBD) that involves inflammation of the gastrointestinal tract, particularly the distal ileum (Ranasinghe & Hsu, 2018). The chronic inflammation associated with CD is responsible for the ulceration of the mucosal layers and granuloma formation in the distal small intestine (Boyapati, Satsangi, & Ho, 2015). Chronic inflammation develops due to the malfunctioning immune system incorrectly identifying normal flora as pathogenic (Margo & Portela, 2010). One of the most widely studied genetic risk factor for CD is the Nucleotide-binding oligomerization domain-containing protein 2 (NOD2),

previously known as CARD15. NOD2 is expressed in immune cells and intestinal epithelial cells, termed Paneth cells. These proteins are essential in turning on the Nuclear Factor-Kappa-B (NF- κ B) pathway. Mutations of the NOD2 gene are found in 40% of Western CD patients and disrupt the protein's ability to recognize foreign microbes (Boyapati et al., 2015). This then negatively affects the cell's ability to process intracellular microbes (Boyapati et al., 2015). This malfunctioning immune response is further amplified by a leaky epithelial barrier, non-regulation of T cells, increased persistence of Toll-like Receptors (TLRs), and impaired autophagy (Margo & Portela, 2010; Baumgart & Sandborn, 2012). The impaired intestinal epithelial barrier is due in part to the action of Paneth cells. Paneth cells participate in the immune response by releasing antimicrobial granules. In CD, Paneth cells tend to have the 300T autophagy gene variant which decreases and disrupts granule release and autophagy (Baumgart & Sandborn, 2012). The epithelial layer is further compromised by the leaky tight junctions which allows for the invasion of more immune cells. These defective immune responses irritate the intestinal lining and mucosal layer and lead to symptoms, such as abdominal pain/tenderness, diarrhea, digestive tract irritation, bloating, gas, fever, weight loss, and anemia (NIH, 2017; Ranasinghe & Hsu, 2018).

Non-resolution of Chronic Inflammation

RA and CD are chronic inflammatory diseases, mediated mainly by neutrophils, macrophages, dendritic cells, and Helper T cells, Th1 and Th17. Inflammation is an immune-system mediated process that is typically activated after tissue injury or invasion of a pathogen. These stimuli then promote leukocytes, such as macrophages and mast cells, to release proinflammatory proteins and chemicals, termed mediators. Chemical messengers, known as cytokines, move from cell to cell and communicate with them to release more inflammatory signals. The most prevalent proinflammatory cytokines in RA and CD are Interleukins (IL-1, IL-

6, IL-12, IL-17), Interferon (IFN), and Tumor Necrosis Factor (TNF). TNF is one of the most essential perpetrators in RA and CD progression. TNF is produced by mononuclear phagocytes and induces angiogenesis and adhesion molecule expression (Ticani, Andreoli, Bazzani, Bosiso, & Sozzani, 2007). Release of proinflammatory cytokines facilitates the dilation of blood vessels, which allows more leukocytes, such as neutrophils and macrophages, to relocate to the infected-area via chemotaxis. The extravasation of leukocytes is mediated by endothelial cells' selectins and integrins. Once these leukocytes reach the target area, they release more cytokines, granules, enzymes, such as proteinase, and ROS/RNS that induce tissue damage (Medzhitov, 2008). The entire inflammatory process causes redness, swelling, and heat release. Resolution of inflammation occurs when the mediators are turned off or broken down by the body, in a cleanup process. This cleanup process involves the cessation of white blood cell recruitment and the removal of white blood cells from the infected area. Macrophages, especially the M2-Like ones, participate in the clean up by removing dead leukocytes and releasing pro-resolving mediators. Pro-resolving mediators include resolvin E1, Lipoxin A4, TGF- β , IL-9, adenosine, and pro-apoptotic factors (TRAIL, FasL) (Schett & Neurath, 2018). Resolution of inflammation protects against further tissue damage. RA and CD are both characterized by the non-resolution of inflammation. When inflammation is not shut off, leukocytes continue to release proinflammatory mediators that lead to chronic tissue damage, granuloma formation, and increasing severity of disease symptoms.

Environmental Factors Linked to RA and CD Susceptibility

Smoking

RA and CD share similar genetic and environmental susceptibility factors. Identifying these susceptibility factors could help to shift how researchers and doctors tackle these immune-

mediated diseases. More importantly, greater insight into the factors that increase one's susceptibility to these diseases could initiate a disease prevention initiative. One of the most well-studied environmental risk factors for RA and CD is smoking. Studies with monozygotic twins, in which one smoked and the other did not, demonstrated that the smokers developed RA in 12/13 cases (Klareskog et al., 2009). Smoking acts as a risk factor for the rheumatoid factor-positive and ACPA-positive RA subsets (Klareskog et al., 2009). The reason for this lies in the role of the PAD enzyme in exacerbating the autoimmune reactions in RA. When cigarette particles enter the lungs, resident macrophages are activated and induce the death of lung cells. This promotes the activity of the PAD enzyme. The resulting citrullinated proteins then bind to MHC on immune cells and promote the synthesis of ACPAs (Klareskog et al., 2009). These antibodies attack the body's own cells, promote inflammation, and increase the severity of RA.

Similarly, smoking increases the risk of developing CD. This association has been linked to a prevalent genetic susceptibility factor in CD. A prominent mutation in Paneth cells (ATG16L1T300A) is triggered by tobacco smoke (Liu et al., 2018). This mutation leads to Paneth cell dysfunction, which is characteristic of CD. This defect impairs autophagy and the antimicrobial granule production (Baumgart & Sandborn, 2012). Furthermore, prenatal and childhood exposure to second-hand smoking increases one's chances of developing CD (Dutta & Chacko, 2016). These findings illustrate that both RA and CD share smoking as an environmental risk that could be controlled or ceased to prevent or delay the onset of these two diseases.

Oral-Gut Dysbiosis

Another environmental risk factor shared by RA and CD is the irregularity of the oral-gut microbiome. The oral-gut microbiome, a community of bacteria that reside in the gastrointestinal

tract, mouth, skin, and urinary tract, has been shown to play an increasingly prominent role in the development of CD and RA. Its association to CD is not as surprising considering that CD's etiology is in the intestinal tract; it is much more interesting to note the recent associations between RA and the gut microbiome. Dysbiotic links shared between the two diseases highlight more inflammatory causes that could be intervened as possible treatments.

The gut microbiome-inflammation link has both environmental and genetic components. The gut microbiome irregularity, termed dysbiosis, is present in CD and RA patients. Dysbiosis can be caused by various factors, such as diet, drug use, antibiotic use, and aging (Du Teil Espina et al., 2018). However, recent research recognizes that dysbiosis may be a symptom and cause of RA and CD. Dysbiosis involves an overall decrease in the diversity of gut bacteria (Hedin, Van der Gast, Stagg, Lindsay, & Whelan, 2017), a decrease in Firmicutes (i.e. *Clostridium*, *Faecalibacterium prausnitzii*), and an increase in the Proteobacteria phylum (i.e. Family: Enterobacteriaceae such as *Escherichia coli*) (Boyapati et al., 2015; NIH, 2017; Hedin et al., 2017). Interestingly, this decrease in bacterial diversity has also been linked to smoking, colorectal cancer, and obesity (Hedin et al., 2017). Bacteria such as *E. coli* have been shown to activate inflammation after interaction with epithelial cells. *E. coli* then induce macrophages to release more proinflammatory chemical messengers, such as TNF (Boyapati et al., 2015). These findings were further solidified after a University of Pennsylvania study concluded that the Proteobacteria phylum also initiated intestinal inflammation in mice (Ni et al., 2017). This means that Proteobacteria, which are already in high levels in the intestine of CD patients, induce intestinal inflammation and continue to promote it. Another study analyzed the gut microbiota of CD-afflicted and non-afflicted siblings. This study found that both siblings had similar gut microbiota compositions and both displayed dysbiotic characteristics (Hedin et al., 2017).

Therefore, dysbiosis is not merely a consequence of inflammatory conditions; it is also an instigator in CD pathogenesis and a risk factor. It's role as a susceptibility factor in CD development could be a possible target for CD onset prevention.

Dr. Gary D. Wu and his team at the University of Pennsylvania investigated the role of nitrogen metabolism in dysbiosis. The researchers found that there was an increase in nitrogen metabolism and an increase in amino acid levels in the stools of CD patients; increased nitrogen metabolism is due to certain bacteria producing the urease enzyme, which makes ammonia to sustain growth (Ni et al., 2017; NIH, 2017). A positive correlation was found between urease presence and dysbiotic activity. If there is more urease, then more amino acid/amino acid derivatives will be produced. The study found that higher amino acid levels in fecal samples correlated to more intestinal inflammation and higher levels of Proteobacteria. Interestingly, when the researchers used a urease-negative *E. coli* strain, no signs of dysbiosis were present (Ni et al., 2017). The negative results observed here indicates that dysbiosis development may depend on the presence of bacterial urease. Such findings need to be observed in humans in order to determine the role urease may play in causing gut dysbiosis, and therefore CD- intestinal inflammation.

The health of the oral-gut microbiome in RA patients provides clues into the development of RA. Oral dysbiosis in RA patients may include increases in bacteria such as *Lactobacillus salivarius*, *Prevotella*, and *Cryptobacterium curtum*. Periodontitis, chronic inflammation of the tissue surrounding teeth, has been linked to RA since 1918 (Du Teil Espina et al., 2018). Patients with periodontitis are twice as likely to develop RA. The reason for this lies in a bacterium that causes periodontitis, *Porphyromonas gingivalis*. *P. gingivalis* can travel from the oral cavity, through the bloodstream, and into the synovial fluid surrounding the joints.

P. gingivalis has an enzyme known as PPAD, that is similar in function to the PAD enzyme that is essential in the development of RA auto-antibodies (ACPAs). This example of molecular mimicry allows for a human's antibodies to recognize the bacterial citrullinated proteins, thereby inducing an immune response like that of RA ((Du Teil Espina et al., 2018). This response aggravated the symptoms of RA (i.e. increased joint damage) by allowing the mobilization of more immune cells, such as Th17, and increasing the production of proinflammatory cytokines (IL-17) and autoantibodies (Du Teil Espina et al., 2018). *P. gingivalis* may further exacerbate the inflammatory symptoms of RA by targeting neutrophils. Neutrophils in RA synovium exhibit amplified Neutrophil Extracellular Traps (NETs) release, which is accompanied by the release of citrullinated proteins, the same proteins that are recognized and targeted for destruction by the ACPA antibodies. This continues the inflammatory and tissue-destructive cycle present in RA. These results demonstrate that oral bacteria exert influence beyond the oral cavity. In the case of RA, oral bacteria may contribute to gut dysbiosis. Oral bacteria's ability to travel to and live in the gut, alter the microbiome, and induce chronic inflammation needs to be curbed for patients with dysbiosis and RA.

Genetic Factors Linked to RA and CD Susceptibility

RA and CD share genetic factors that play a role in the development and pathogenesis of both diseases. RA's heritability is about 60%, whereas CD's heritability ranges from 25-42% (Kurkó, Besenyei, Laki, Glant, Mikecz, & Szekanecz, 2013; Gordon, Trier, Moller, Andersen & Harbord, 2015). Genetic factors contribute to approximately 50% of the overall development of RA (Klareskog et al., 2009). There are approximately 30 loci implicated in RA's development (Kurko et al., 2013). Likewise, CD's etiology is based on genetic mutations in over 71 loci on 17 chromosomes (Baumgart & Sandborn, 2012). CD's genetic risk is further heightened by the fact

that monozygotic twins have an increased risk of developing CD compared to dizygotic twins (Baumgart & Sandborn, 2012). These results demonstrate that environmental and epigenetic factors are not solely responsible for RA and CD development. One of the most well-studied genetic factors for RA is HLA-DRB1, whereas NOD2/CARD15 is the most recognizable genetic factor for CD. However, there are two major genetic mutations shared by both RA and CD that occur in the PTPN2/22 and STAT4 genes. Understanding the underlying genetic causes of these two diseases is essential in taking steps toward early diagnoses.

PTPN2/N22

One well researched correlation between the two is the mutations in certain immune system regulatory genes, known as Protein Tyrosine Phosphatase Non-receptor type 2 and 22 (PTPN2/22) genes. These genes function to regulate immune responses by coding for phosphatases. These phosphatases remove phosphate, from T cell receptors (TCR), Signal Transducers and Activators of Transcription (STAT) dimers, and BH3-only proteins (BIM) (Sharp, Beg, & Naser, 2018). BIM is a pro-apoptotic protein that is involved in the intrinsic programmed cell death pathway (Gogada et al., 2012). The intrinsic apoptosis pathway is in the mitochondria of cells and allows for the release of caspase proteins. The STAT1 gene codes for a STAT protein that plays a role in JAK/STAT cytokine receptor signaling (NCBI, 2019). In this pathway, a cytokine binds to receptors on the surface of a target cell. These receptors dimerize and bring two Janus Kinase (JAK) molecules together for activation. The tails of the receptors act as binding sites for STATs. Once JAK phosphorylates STAT, STAT dimerizes and changes shape in order to enter the nucleus of the cell. Once there, various STATs will promote cell proliferation, differentiation, and growth. The TCR binds to presented antigens and is then activated to stimulate various signal transduction pathways. Activation of T cells have vastly

different effects depending on the type of T cell. The lack of phosphates on the TCR and BIM, inactivate them (Sharp et al., 2018). Dephosphorylation of STAT prevents it from dimerizing and entering the nucleus. As such, this negatively regulates chemokine production (Sharp et al., 2018). Mutations of the PTPN2/22 genes could interfere with the regulation of the immune response. Without proper dephosphorylation, TCRs, BIMs, and STATs will be unrestrictedly active. In RA and CD, this would stimulate T cells to constantly secrete proinflammatory cytokines and hinder the ability of epithelial cells in the joints and intestine to induce leukocyte cell death. This would lead to a toxic cycle of activated leukocytes promoting inflammation.

A study performed by Dr. Saleh Naser and his team at the University of Central Florida sought to determine which mutations on the PTPN2/22 genes were responsible for the hyperproliferation of T cells in RA. The study found that the single nucleotide polymorphism (SNP) rs478582 in PTPN2 and rs2476601 in PTN22 were significant in the development of RA. Dr. Naser and his team concluded that patients with both mutations had 6.5-fold more risk of getting RA than the control subjects. The PTPN22 rs2476601 SNP (location: 1p12) was also identified as a susceptibility locus for CD. Different SNPs in PTPN2 such as rs1893217, rs740495, and rs1736020, were identified in CD (Baumgart & Sandborn, 2012). The rs2476601 and rs478582 SNPs increased T cell proliferation and the expression of Interferon- γ (IFN- γ). Greater T cell proliferation as mentioned earlier means that there was a lack of regulation by PTPN2/N22. This would further promote the inflammatory cycle seen in RA. Interestingly, not only were the mutations that inhibited PTPN2/22 prevalent in RA subjects, but overall there was less PTPN2/22 mRNA expression (Sharp et al., 2018). This indicates that mutations and overall reduced expression of these two regulatory genes exacerbate the disease process. It does so by allowing the TCR to be responsive to antigen presentation by an antigen-presenting cell that was

stimulated by proinflammatory cytokines, such as TNF α and IL-1. Activation of the TCR then initiates the NF- κ B signaling pathway. This pathway ends when the NF- κ B transcription factor goes to the nucleus and stimulates the expression of cytokines and chemokines. These cytokines bind to epithelial cells, stimulate the JAK/STAT pathway to produce more chemokines, and inhibit apoptosis. Both RA and CD feature an imbalance between T effector cells and regulatory T cells (T_{reg}). As such, Th cells, particularly Th17, are overactive, whereas T_{reg} cells are not. When Th17 cells are continually activated and present in large amount, they induce greater tissue damage by producing more IL-17 and IL-22. Since both RA and CD are heavily T cell mediated, the consequences of PTPN22 dysfunction and its role in the T effector and T_{reg} cell imbalance need to be further investigated.

STAT4

Another genetic susceptibility factor shared by RA and CD is STAT4. As mentioned above, STAT encompasses a group of transcription factor proteins that play a role in signal transduction pathways. STAT4 is located within dendritic cells and macrophages (Gu et al., 2015). STAT4 is responsible for promoting the differentiation of T cells into helper T cells, particularly Th1 and Th17, the activation of monocytes, and the production of IFN- γ , IL-12, and IL-23 (Glas et al., 2010). This transcription factor plays a role in the pathogenesis of both RA and CD. In CD, STAT4 has been shown to be constitutively activated. One genotypic study performed by Dr. Stephan Brand and his team from the University of Munich, found that the patients homozygous for STAT4 SNP rs7574865 presented with earlier onset of CD symptoms and more frequent disease compared to the wildtype and heterozygous genotypes (Glas et al., 2010). The association between RA and STAT4 has been studied for well over a decade. However, there are some discrepancies in the overall conclusions of these case-control studies;

the main discrepancy lies between ethnic groups. Some studies have found no significant correlation between STAT4 mutations and RA, whereas others have when using a different ethnic group as the test and control subjects. For example, one case study found that the minor T allele of the STAT4 SNP rs7574865 was not significantly associated with Syrian RA patients (Tarakji, Habbal, & Monem, 2018). On the other hand, a meta-analysis conducted by a team of researchers in China, demonstrated that ethnicity and genotype play a role in the degree of susceptibility conferred by the STAT4 SNP rs7574865 gene. According to this analysis, the TT, GT +TT, and T allele genotypes were significantly associated with RA within the European, Asian, African, and Latin American ethnic groups (Gu et al., 2015). These associations were independent of whether the subject had Rheumatoid Factor-positive or negative RA. While there is still not a conclusive theory of the association between RA and the STAT4 SNP, the status of STAT4 in RA-affected joints is conclusive; STAT4 over-expression in the synovium of RA patients is linked to the rs7574865 mutation (Gu et al., 2015). Nonetheless, this degree of uncertainty concerning STAT4 and RA's association highlights a major issue when testing for susceptibility genes: patients diagnosed with the same disease may have varying genetic causes. Ethnicity may be an important environmental factor that could hint at varying degrees of susceptibility to diseases. Therefore, it is imperative that the healthcare paradigm move towards individual screenings, and treatments for people who present similar symptoms of a disease.

Current Treatments for RA and CD

RA and CD share more than the same susceptibility factors; they share much of the same treatments. There are no cures for RA and CD; as such, treatment is geared towards reducing or resolving symptoms. The current treatments for RA and CD range from synthetic drugs to biologic agents; nonetheless the focus of treatment is mainly on suppressing inflammation,

reducing disease activity and potentially entering a remission state. This stems from the treat-to-target approach utilized in autoimmune disease intervention.

The main classes of drugs prescribed are disease-modifying antirheumatic/anti-inflammatory drugs (DMARDs/DMAIDs), glucocorticoids, and nonsteroidal anti-inflammatory drugs (NSAIDs). The main issues with common RA and CD drugs are the risk of aggravating comorbidities, high costs, and side effects. NSAIDs such as aspirin and acetaminophen, reduce swelling but are not as commonly prescribed when treating CD because of their tendency to irritate the intestinal lining (Crohn's and Colitis Foundation, 2005). NSAID side effects also include osteoporosis, hypertension, and ulceration in RA patients (Sharp et al., 2018). Glucocorticoids, such as Prednisone, mimic the effects of cortisol and suppress the immune system. However, they are not for long-term use because of the higher risk of infections and cardiovascular complications compared to other treatment types (Burmester & Pope, 2017). DMARDs and DMAIDs are used to intervene the damage to the joints and intestinal mucosa. The common DMARDs are listed in **Table 1** below. The most commonly prescribed synthetic DMARD is Methotrexate. Methotrexate is often used as the initial monotherapeutic drug when starting RA treatment. Conventional DMARDS, such as Methotrexate, can lead to fatigue, liver damage, nausea, cytopenia, intolerance by the gastrointestinal tract, and increased risk of infections (Burmester & Pope, 2017). Furthermore, Methotrexate is not advised for women who intend to bear children and for those with liver conditions (Baumgart & Sandborn, 2012). However, combination therapy of Methotrexate with a biologic agent can be more effective than monotherapy (Burmester & Pope, 2017).

Biologic agents are more targeted; however, they do increase the risk of acquiring infections, higher cholesterol, psoriasis and congestive heart failure (Burmester & Pope, 2017).

Biologics are typically delivered via injections. Specific biologic drugs target different chemicals and proteins in the body, and thereby lead to unique adverse events. For example, drugs that inhibit JAK, such as Tofacitinib, could promote gastrointestinal side effects and lymphopenia. The most commonly used biologic in RA and CD treatment is anti-TNF (Sharp et al., 2018). The side effects of anti-TNF drugs include increased risk of tuberculosis, herpes zoster infection, psoriasis, hepatotoxicity, and lymphomas (Burmester & Pope, 2017; Park & Jeon, 2018). Another complication with the use of biologic therapies is the threat of anti-drug antibody formation. The body may recognize a drug-based monoclonal antibody as a foreign threat and seek to eliminate it. The drug would be treated as a foreign antigen and be presented to T and B cells. This would then lead to the differentiation of plasma cells which will secrete antibodies against the drug. These antibodies neutralize or lower the half-life of the drug (Fiehn, 2016). This was seen in popular anti-TNF biologics, such as Infliximab and Adalimumab (Fiehn, 2016). Methotrexate used in conjunction with a biologic agent, has been shown to decrease the production of anti-drug antibodies and thereby increase the survival of the drug in the body. This demonstrated that combination therapy with methotrexate and a biologic is more effective. This treatment approach helps to lower inflammation, while also reducing tissue damage (Klareskog et al., 2009). Another significant benefit of anti-TNF and methotrexate combination therapy is the decreased threat to the cardiovascular system (Fiehn, 2016). Combination therapy, while the most efficient, is still only effective in half of CD treatment cases (Boyapati et al., 2015). The complications associated with synthetic drugs and biologic agents often lead to patients constantly changing drugs or changing doses. Ten years after diagnosis with CD, approximately 47% of patients need surgery, but still relapse afterwards (Bressler et al., 2015). With RA drug therapy, 40% of patients still become disabled in ten years (Chauhan & Al-Dhajir, 2018). More

effective treatment options need to be developed in order to resolve chronic inflammation and achieve long-lasting remission.

Table 1. Common DMARDs Used to Treat RA and CD

Drug	Formula	Purpose
Methotrexate	Folate antagonist	Inhibits adenosine metabolism
Infliximab	IgG monoclonal antibody	Anti-TNF
Etanercept	TNF receptor with IgG1's FC domain	Anti-TNF
Adalimumab	Human IgG monoclonal antibody	Anti-TNF
Anakinra	IL-1 receptor antagonist	Binds to IL-1 receptor to prevent IL-1 from binding to its receptor
Tofacitinib (Xeljanz)& Baricitinib	Janus Kinase Inhibitor	Binds to JAK and stops activation of the JAK/STAT pathway
Tocilizumab	Monoclonal antibody	Anti-IL6 receptor
Rituximab	Monoclonal antibody	Anti-CD20-deactivates B cells
Abatacept	CTLA4 and Fc region of IgG	Blocks the CD28-B7 interaction by binding to B7 ligand on APCs

RA and CD Disease Prevention and Intervention Proposals

The previous discussion about the most common treatments for RA and CD has made it clear that new treatment avenues need to be taken. Treating just the symptoms of RA and CD is not enough. Remission for both diseases could be achieved if the diseases are treated early in

order to stop major tissue damage (Hanauer, 2017). Therefore, better preventive steps should be implemented. Since RA and CD have relatively high heritability and genetic causal factors, pre-disease genetic screening is essential in identifying one's degree of susceptibility to these diseases. Since RA typically affects older adults, with typical disease onset during the range of 30 to 60 years old, genetic screenings should be conducted at the age of 30 and every ten years afterwards. CD's onset targets a younger population ranging from 15 to 35 years old. As such, genetic screenings should take place after puberty onset and every ten years afterwards.

Identification of the PTPN22 and STAT4 mutations early could allow for proper steps to be taken to delay onset of the two diseases. Additionally, the oral and gut microbiota of patients with moderate to severe RA and CD should be analyzed. Proper analysis could identify dysbiosis as a factor in disease progression. Therefore, appropriate steps, such as the use of probiotics, can be taken to correct this measure. Furthermore, a disease prevention initiative could be undertaken in primary care clinics to address the importance of oral health and cessation of smoking.

Patients need to be informed of the effects of *P. gingivalis* on oral health and inflammation, so that they may take steps in their daily routines to help lower the severity of RA symptoms.

Furthermore, all individuals whom are genetically susceptible to RA and/or CD should be informed of the risks smoking carries, in order to eventually develop a plan to limit or quit the habit to lessen the risk of developing these diseases.

Treatments to Limit Leukocyte Extravasation

Currently, the most common biologic treatment for both RA and CD is anti-TNF drugs. These drugs neutralize TNF cytokines, which does play an essential role in perpetuating chronic inflammation. However, TNF is just a mediator of inflammation. As mentioned above, anti-drug antibody formation and increased risks of infections are major risks associated with Anti-TNF

treatment. Anti-TNF treatment can lead to primary non-response in 10-30% of patients, and loss of response in 23-46% of patients (Park & Jeen, 2018). Nonetheless, immunotherapy can be a highly selective and potent treatment when used properly. Cytokines do not remain in one location; chemotaxis allows distant leukocytes to respond to the cytokine signals and translocate. Leukocytes respond to these chemical signals and release more proinflammatory factors. As such, greater emphasis needs to be on targeting leukocytes themselves. Limiting the extravasation of neutrophils via use of anti-integrins may be the key. Integrins are heterodimeric receptors on the surface of leukocytes, which interact with adhesion molecules on endothelial cells. Targeting integrin would limit the influx of leukocytes into inflamed tissues. A possible target for both diseases would be $\alpha 4\beta 1$, an integrin molecule expressed on many leukocytes. One anti-integrin drug, Natalizumab (anti- $\alpha 4$ subunit), became a premier treatment for CD. However, the drug unintentionally reached the central nervous system and lead to increased risk of brain infections. This dilemma mimics a common trend with current biologic agents: these agents tend to have systemic effects, rather than local effects. Systemic immunosuppression leads to adverse side effects and increased risks of infections. Therefore, more precisely targeted immunotherapy options must be pursued. For CD, specifically, $\alpha 4\beta 7$ would be apt target because it is found on GI lymphocytes (Park & Jeen, 2018). As such, Vedolizumab, an IgG antibody against $\alpha 4\beta 7$ integrin that is specific to the intestine, is a better option for CD patients. Clinical trials have shown that Vedolizumab initiated mucosal healing, did not affect brain immunity, and only had a 4% chance of developing anti-drug antibodies (Park & Jeen, 2018). Its side effects include headache, nausea and nasopharyngitis, which are must less severe than Anti-TNF inhibitor side effects. A similar RA treatment targeting integrins specific to the synovial membrane, such as $\alpha 5\beta 1$ integrin which recognizes fibronectin, $\alpha 1\beta 1$, $\alpha 10\beta 1$, and $\alpha 11\beta 1$ which recognize collagen,

could be successful in limiting lymphocyte extravasation (Lowin & Straub, 2011). Intercepting extravasation could be extremely beneficial to patients suffering from numerous inflammatory conditions as it stops the cycle of cytokine-lead inflammation. Further research on the effects of tissue-specific anti-integrin therapies need to be conducted to gauge the efficacy and safety of such treatments.

Another treatment aimed at limiting extravasation is E6011. E6011 is currently undergoing clinical trials for CD. E6011 is a monoclonal IgG antibody that targets fractalkine (FKN), which is a CX3C chemokine that enables integrin-independent and dependent leukocyte extravasation (Tanaka et al., 2017). E6011 has already shown promising results for RA patients; E6011 reduces inflammation and leads to decreased swelling and tenderness around joints (Tanaka et al., 2017). The adverse effects of E6011 are much less severe than other biologic agents, thereby making it a promising immunotherapy.

The Use of IL-9 and ILC2 in Resolving Inflammation

RA and CD are characterized by the non- resolution of inflammation. Current biologic treatments tend to target proinflammatory cytokines. However, there are pro-resolving cytokines that could be the future of cytokine-targeted therapy. One promising avenue is the use of Type 2 Innate Lymphoid Cells (ILC2s). ILC2s produce IL-9, IL-4, and IL-13, activate T_{reg}'s, and trigger the expression of the M2 macrophage phenotype (Schett & Neurath, 2018). IL-9 and ILC2 levels are lowered in patients with RA (Rauber et al., 2017). IL9 overexpression has been shown to accelerate the resolution of RA, resolve joint swelling, reduce synovitis, and lower tissue damage and bone erosions by activating ILC2s in mice models (Rauber et al., 2017). IL-9's anti-inflammatory effects could also be useful in reducing granuloma and mucosal damage in CD.

Promoting ILC2 and IL-9 expression could possibly be the key to resolving inflammation and inducing tissue repair in chronic inflammatory conditions.

Restoring Eubiosis via Probiotics

This literature review delved into the association between dysbiosis and RA and CD. Dysbiosis seems to be both a causal factor and an effect of the two diseases. As such, proper preventative and interventionist measures could be taken to reduce the risk of getting these diseases in genetically predisposed individuals or to decrease the chronic inflammation in already affected patients. One possible treatment avenue is the use of probiotics to restore eubiosis. *Prevotella histicola*, *Lactobacillus casei*, and *Lactobacillus paracasei* have been shown to be possible routes to eubiosis. *P. histicola* ameliorates arthritis in mice; *L. casei* uses lactocepsin, a protease, to reduce the amount of proinflammatory cytokines in RA patients (Du Teil Espina et al., 2018). *L. casei* is already a marketable probiotic; it is found in certain probiotic supplements, cheeses and yogurts. One study found that *Lactobacillus rhamnosus* stopped the formation and release of NETs (Du Teil Espina et al., 2018). Limiting NETosis would decrease the amount of ACPAs, as mentioned earlier in this paper. Another promising probiotic is commensal bacteria, *Faecalibacterium prausnitzii*, which are decreased in dysbiotic individuals. *F. prausnitzii* has been shown to be anti-inflammatory by decreasing the IL-8 levels, increase pro-resolving IL-10 levels (Martin et al., 2017). The brand, OMNI-Biotic created a supplement which contains fructo-oligosaccharides and galacto-oligosaccharides to promote the proliferation of *F. prausnitzii*. Therefore, the bacterial growth is being promoted indirectly. In the future, more direct administration of the probiotic could be a more potent therapy. The use of probiotic therapy may be the key to restoring eubiosis, which might then limit the symptoms of chronic inflammation. Further testing needs to be conducted with human subjects in order to

measure the effects of probiotic treatment on dysbiosis and inflammation. Dysbiosis may also be countered by more invasive measures, such as a fecal microbial transplantation (FMT). Targeting *P. gingivitis* is another probable method. *P. gingivitis* exacerbates inflammation due to molecular mimicry. One study showed that an antibody against the fibrillin protein made by *P. gingivitis* helps to alleviate periodontitis and RA. For patients with extreme dysbiosis, the use of antibiotics may be helpful. The study conducted by Dr. Wu and his team at the University of Pennsylvania demonstrated that a combination therapy of vancomycin, neomycin, and PEG altered the microbiota of subjects favorably (Ni et al., 2018). However, the use of antibiotics must be cautioned due to their ability to further decrease the diversity of the gut microbiota. Therefore, probiotics could be the least aggressive option in restoring eubiosis.

Concluding Remarks

RA and CD share genetic and environmental factors that lead to disease onset and progression. The current treatments for RA and CD are aimed towards inflammation suppression and have adverse side effects that limit long term use of the same medication and dosage. Therefore, the use of anti-integrins and pro-resolving cytokines could help to resolve inflammation, while the use of probiotics could naturally restore gut eubiosis. Overall, health promotion and disease prevention initiatives targeted towards smoking and oral/gut health could be of great value in delaying the onset of these diseases in genetically predisposed individuals.

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Appendix A

Table 2. Abbreviations

Abbreviation	Definition
ACPA	Antibodies against citrullinated protein antigens
BIM	BH3-only protein
CD	Crohn's Disease
DMAID	Disease modifying anti-inflammatory drug
DMARD	Disease modifying anti-rheumatic drug
FasL	Fas Ligand
HLA-DRB1	Human leukocyte antigen DRB1 gene
IFN	Interferon
Ig	Immunoglobulin (antibody)
IL	Interleukin
ILC2	Type 2 innate lymphoid cell
JAK	Janus kinase
MHC	Major histocompatibility complex
MMP	Matrix metalloproteinase
NET	Neutrophil extracellular trap
NF- κ B	Nuclear factor kappa light chain enhancer of activated B cells
NOD	Nucleotide binding oligomerization domain containing protein
NSAID	Non-steroidal anti-inflammatory drug

PAD	Peptidylarginine deiminase
PTPN2/22	Protein tyrosine phosphatase non-receptor type 2 and 22
RA	Rheumatoid Arthritis
ROS/RNS	Reactive oxygen/nitrogen species
SNP	Single nucleotide polymorphism
STAT	Signal transducer and activator of transcription
TCR	T cell receptor
Th	Helper T cell
TLR	Toll like receptors
TNF	Tumor necrosis factor
TRAIL	TNF-Related Apoptosis Inducing Ligand
T _{reg}	Regulatory T cell