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Abstract

Autoimmune disease refers to a systemic immune response by the body against its own healthy tissue and cells. This results in various non-specific and systemic inflammatory processes that evolve into more than 100 individual diseases. Numerous biological similarities exist between the different pathophysiological pathways, including biochemical cascades and inflammasome mediators. This paper aims to investigate whether contracting one form of autoimmune disease can lead to the development of polyautoimmunity and multiple autoimmune syndrome. Scientists have identified chronic levels of high stress as a contributor to higher levels of C-reactive protein and several immune modulating interleukins, which can lead to both autoimmune and polyautoimmune processes (Steptoe et al., 2007). Immunologists and virologists have established how viruses can lead to autoreactive immune activity through molecular mimicry and epitope spreading. These same processes are found in all forms of inflammation and may explain the connection between undiagnosed adult-onset celiac disease and multiple autoimmune syndrome. Many genetic pathways have been identified as drivers of both individual autoimmune conditions and specific inflammasome mediators that could be responsible for familial based autoimmunity and specific subtypes of multiple autoimmune syndrome. Collectively, these studies underlie and illustrate a direct connection between several contributors that definitively link autoimmunity with polyautoimmunity.

Introduction

Autoimmunity is defined as the misdirected immune response by an organism against its own healthy tissue and cells. Encompassing as many as one hundred individual diseases, autoimmune disease affects nearly 23 million Americans of all ages and has been referred to by many as the next frontier in the battle for longevity (NIH 2012). Some of the more common manifestations of autoimmunity include Crohn's disease, colitis, systemic lupus erythematosus, Sjogren's syndrome, celiac disease and type 1 diabetes. The specific mechanisms and causes of these diseases are still the subject of investigation, some of which will be explored in the following discussion. It is widely recognized that autoimmune disease is on the rise across nearly all age groups and social categories (Dinse et al., 2020). The reason for this increase is unclear, though many believe that environmental conditions as well as behavioral factors may be to blame.

As the general rate increases, an important question arises. Does contracting one form of autoimmune disease raise the risk of developing another? Since many symptoms of autoimmune disease overlap with one another, perhaps a connection between them exists. For instance, Sjogren's, Behcet's and celiac disease all present with aphthous ulcers in the mucosal lining of the oral cavity. Even though overlapping symptoms clutter the differentials and make a definitive diagnosis more elusive, these commonalities may demonstrate a connection between the various diseases. In addition to overlapping symptoms, many autoimmune diseases share specific pro-inflammatory cytokines such as IL-1, IL- 6, and TNF-alpha, which trigger the release of inflammation markers like CRP, Fibrinogen, and Haptoglobin (Castro, Gourley, 2010). Another study found that specific CD4+ T lymphocytes responsible for misidentifying healthy tissue as foreign were found in 3 separate autoimmune diseases (Christophersen et al., 2019). Using mass cytometry and RNA sequencing, the CD4+ T lymphocytes were first identified in celiac patients but were later linked to Systemic lupus and multiple sclerosis. While only a correlation, the findings may explain why some immune modalities are more susceptible to make mistakes and whether contracting one disease such as celiac raises the risk of more activity.

Since there are multiple drivers of disease, the investigation into polyautoimmunity and how its diseases are linked will need to focus on several factors, including the environment, hormones, and genetic predispositions. Perhaps the environment and exposure to chemicals and pollution are interfering with a healthy immune system? Maybe bacterial diseases and viruses are propelling the immune system to turn on itself in multiple ways? Lastly, can specific genes be contributing to patterns that have been established between specific conditions such as celiac and type 1 diabetes?

Methods

The research reviewed in this article was obtained using several online databases and search tools, including Pubmed, JSTOR, and Google Scholar. Information was also accessed through the Touro College Libraries database using EBSCO and ProQuest.

Discussion

Mechanisms of Autoimmunity

Before exploring the polyautoimmunity connection, it is important to first analyze and define the autoimmune response itself. Over the last several decades, scientists have formulated several explanations to illustrate the specific pathways and mediators responsible for a typical immune reaction in the body's tissues. Researchers isolated and identified one such pathway using cytometry and RNA sequencing on tissue derived from inbred C57BL mice. Upon initial activation, CD4+ T cells produce cytokine tumor necrosis factor (TNF), which engages its

TNF receptor on mononuclear phagocytes (MP). This leads to the synthesis of pro-cytokine interleukin (IL)-1B. Concurrently, CD4+ cells also express membrane-bound Fas-Ligand (FasL), a subgroup of the tumor necrosis receptor family, which activate death receptor Fas signaling in nearby macrophages, leading to the induction of the inflammation process. This eventually results in Caspase-8-dependent-pro-IL-1B cleavage. Caspase-8 is believed to regulate inflammation through the modulation of mRNA expression in inflammasomes (Gurung, Kanneganti, 2015). The researchers concluded that the inflammasome-independent cytokine interleukin 1B was believed to be responsible for the systemic inflammation found in general autoimmune responses. Consequentially, when tumor necrosis factor receptors or Fas signaling was inhibited in the population, the mice were protected from cell-driven immunity (Jain et al., 2019).

These cytokine interleukins (IL-1B, IL-18, IL-6) have been identified in further studies to be a central player in innate immune responses due to their interaction with inflammasomes. Broadly speaking, cytokine interleukins have been found to be present in almost every immune reaction. However, what makes each reaction unique and specific to individual tissues and organ systems is the type of inflammasome involved in the response (Rathinam et al., 2012). Inflammasomes were first discovered in 2002 as a prominent component of type 2 diabetes and systemic gout. As a type of macrophage, these inflammasomes are a key player in cytosolic surveillance, constantly scanning the interstitial space for signs of tissue injury or infection. The human genome has been found to contain twenty-three Nod-like-receptor (NLR) nucleotide-binding and oligomerization domains (Nods), many of which codify and assemble into inflammasome complexes. Each of these different complexes interacts with and control for the release of cytokine interleukins in response to various bacterial pathogens, viruses, and even cancer (Rathniham et al., 2012). In a healthy individual, these specific pathways of inflammatory signaling are kept in check in order to respond only to the invading microorganism. When this process breaks down, autoimmunity develops. It is important to keep these unique pathways and cellular components in mind when investigating polyimmunity and the link between individual diseases.

Stress and Poly-Autoimmunity

During the last several decades, significant research has been directed on the role that stress plays in the development of autoimmune disease. Various forms of both short-and-long-term stress exacerbate already existent conditions such as rheumatoid arthritis (RA). One twelve-week study involving forty-one women suffering from RA found a significant relationship between even minor stress and joint pain (Zautra et al., 1997). However, these studies were unable to provide an association between chronic stress and the initial manifestation of diseases. Researchers focused on four common pro-inflammatory cytokines in patients with increased levels of acute stress, IL-1B, IL-6, TNF-alpha, and C reactive protein (CRP), and cortisol. One meta-analysis examined 30 studies in order to determine the effects that stress had on these robust effects for higher levels of IL-1B, IL-6 and TNF-alpha while the results for CRP were mixed (Steptoe et al., 2007). It is possible that these higher levels of interleukin exasperated by stress leads to multiple autoimmune conditions being contracted. One 2018 study aimed to investigate the link between stress and developing autoimmunity. The retrospective cohort study followed 1,171,104 people, 106,464 of whom were diagnosed with a stress-related disorder. The results showed that the stressed patients were almost three times more likely (95% CI, 9.2 per 1000) to develop some form of autoimmunity versus the non-stressed cohort (95% CI, 2.99-3.25 per 1000). In addition, patients were also more likely to develop multiple autoimmune conditions, especially when they did not seek any treatment for anxiety (Song et al., 20 Though this study did not investigate why stress causes autoimmune disease, the correlation clearly indicates that stress plays a prominent role in the development of multiple autoimmune conditions and more research will be needed to establish why this occurs.

Viruses and Polyautoimmunity

There are two main hypotheses proposed to explain the connection between viral pathologies and autoimmunity. One coined "molecular mimicry" by Robert Fujinami in 2006 refers to the misrecognition of an antigen by a memory B-cell. The belief is that immunological memory is achieved after initial microbial and viral infection by a host-pathogen. Antigens from the initial infection stimulate humoral immunity and the production of plasma cells and memory B-cells. If these antigens reappear during the secondary response, they will reactivate the plasma B-cells to proliferate and then destroy the invading pathogen. If an organism's self-antigen mimics the viral antigen in some way, then a secondary response is likely to occur against the body's own tissues (Kim et al., 2007). There are three identified ways that this might occur. The first is when the original antigen and the self-antigen share identical amino acid sequences in their primary protein structure. A second possibility is when secondary and tertiary structures mimic each other, such

as with similarities regarding polarity, hydrogen, and disulfide bonding. A third type of molecular mimicry exists when one antibody becomes capable of recognizing two or more antigens with completely different structures (Cunningham 2009). Researchers now believe that this third mechanism is the result of individual T-cells exhibiting receptors for both foreign and self-antigens. When a foreign insult triggers the T cell, it then moves to attack healthy body tissue as well. This third mechanism has consistently been linked to multiple autoimmune diseases or polyimmunity (Cusick et al., 2012). For instance, studies have linked Herpes simplex virus to stromal keratitis and type 1 diabetes, streptococcus to rheumatoid myocarditis and poststreptococcal autoimmune disorder, as well as many others (Munz et al., 2009).

Another hypothesis that explains how viruses generate autoimmune disease is that a virus induces a systemic and non-specific activation of the immune system that eventually leads to an overexcitability state and autoreactive immunopathology (Munz et al., 2009). Known as the "bystander activation," this line of reasoning stems from the fact that, similar to stress, those already suffering from autoimmune conditions tend to fare worse with their symptoms whenever they are infected with a virus. Scientists believe that the pro-inflammatory environment in the body initiates a release of self-antigens from infected tissue. The antigens are then mistakenly taken up by major histocompatibility complexes (MHC) or antigen-presenting cells (APC), which then present these self-antigens to autoreactive T cells that have already migrated to the damaged tissue (Fujinami 2006). This can sometimes lead to a concatenation of events known as "epitope spreading," where these T cells begin attacking other self-antigens that mimic the previous one, further inflaming the tissue and releasing even more self-epitopes. This phenomenon has been observed in multiple sclerosis, autoimmune encephalomyelitis and myasthenia gravis and has been linked to viruses such as EBV, rotavirus and cytomegalovirus (Smatti et al., 2019). It is important to note growing evidence that viruses may also play a protective role in preventing autoimmunity by activating regulatory immune responses that work to suppress inflammation and inhibit cytokine interleukins. In addition, scientists still do not know whether higher viral loads or compromised immune systems during the infection period, raise the risk of autoimmunity.

This second idea regarding how bystander activation and molecular mimicry leads to multiple autoimmune syndrome (MAS) illustrates how inflammation leads to more inflammation. This concept may explain the essence of another important phenomenon. For many years, doctors have emphasized the importance of treating previously diagnosed autoimmune conditions and disorders in order to improve a patient's prognosis and quality of life. These treatments have included the use of biologics, corticosteroids, dietary modifications and lifestyle changes. Scientists have long believed that inflammatory processes that are left unchecked can lead to the development of coronary artery disease and even cancer. Now, researchers have discovered another important reason to aggressively treat these immunological processes: untreated autoimmunity increases the risk of developing further autoimmune conditions. In 1999, researcher Andrea Ventura postulated that for individuals with celiac disease, the later the age of diagnosis, the greater the risk of developing a second autoimmune condition as well as cancer (Ventura et al., 1999). For example, those who were diagnosed between the ages of four and twelve had a 14% risk of developing another condition, while those over twenty years of age had a 34% risk. For each one-year increase in age at diagnosis, the chances for developing another disease increased by 1.1% regardless of gender or weight. In his study, Ventura explained that the longer the duration of exposure to gluten, the higher the prevalence of other autoimmune conditions developing. Further studies by other researchers revealed that 15% of untreated celiac patients eventually developed type 1 diabetes and that 26% percent developed autoimmune thyroid disease such as Hashimoto's thyroiditis and Graves' disease (Lauret, Rodrigo, 2013). These studies were significant because most of these patients were asymptomatic and prior to that, many questioned the importance of adhering to a strict gluten-free diet. In a later paper published in the Journal of Pediatrics, Ventura advocated for the strict use of a gluten-free diet to reduce and even prevent the manifestation of secondary autoimmune activity, after he demonstrated that celiac patients who followed a strict gluten-free diet for two years were more than 50% less likely to develop other autoimmune conditions. (Ventura et al., 2000). Additionally, other studies also reported similar findings regarding Crohn's disease and colitis. In one study, patients were found to be 2.5 times more likely to develop a co-morbid inflammatory disease within five years after an initial diagnosis (Bernstien et al., 2005).

While the absolute reason for this phenomenon hasn't yet been identified, many hypothesize that the prolonged state of inflammation, caused by high concentrations of glutamine and proline found in the protein fraction of rye, wheat, spelt and barley contribute to other diseases. Specifically, these residual peptides and amino acids initiate a cascade of interleukins (IL-1B, IL-6 and IL-18) that trigger the proliferation of other inflammatory markers, including inflammasomes and C-reactive protein (CRP). Higher levels of CRP have been implicated in coronary

artery disease as well as rheumatoid processes. In addition, specific phenotypes of CD4+ helper T-cells that are activated in celiac disease are of the same subtype involved in some of the other conditions such as systemic lupus and multiple sclerosis (Christophersen et al., 2019). (Though these specific T-cells comprise less than 2% of all the Helper T-cells in the body, they are disproportionately responsible for the identification of most self-antigen responses that take place within these inflammatory pathways.) This phenomenon seems to be related to the mechanism of molecular mimicry and dual T cell activation discussed earlier, which takes place in response to viral infections. However, in this scenario, an initial autoimmune condition takes the place of the virus and contributes to a set of circumstances where the body continuously mistakes healthy tissues as foreign and as a threat. It is clear from these studies that untreated or resistive autoimmune processes have a direct effect on the risk of further developing other forms of chronic inflammation which may lead to the manifestation of other autoimmune conditions.

Genetics and Polyautoimmunity

Upon examination, autoimmune diseases appear to manifest in clusters. Though Ventura investigated all forms of autoimmunity, he reported that individuals with celiac were much more predisposed to developing type 1 diabetes and thyroid disease versus ulcerative colitis or Addison's disease. Rheumatoid arthritis has been linked to Sjogren's syndrome, while systemic lupus erythematosus has been linked to multiple sclerosis. Indeed, so specific are these clusters that investigators have now classified these groups into three clinical subtypes (Cojocaru et al., 2010). Of note, each of these subtypes contain at least one skin condition and one connective tissue disease.

I. Type 1 is comprised of polymyositis, thymoma, giant cell myocarditis and myasthenia gravis.

II. Type 2 consists of rheumatoid arthritis, Hashimoto's, scleroderma, and Sjogren's syndrome.

III. Type 3 is the largest subgroup and includes Addison's disease, type 1 diabetes, vitiligo, psoriasis, autoimmune hemolytic anemia, dermatitis herpetiformis, idiopathic thrombocytopenic purpura (ITP), Sjogren's syndrome, myasthenia gravis and systemic lupus erythematosus.

Patients diagnosed with having more than one autoimmune condition are said to have polyimmunity, while patients diagnosed with more than two are classified as having multiple autoimmune syndrome (MAS) type i, ii, or iii. These classifications are not absolute; however, they provide clinicians and scientists with an understanding of what to look out for and how to treat each patient based on their specific classification. Researchers have discovered that families also seem to develop these illnesses as a group. For example, a mother may develop Addison's disease while a daughter is diagnosed with lupus and a grandson has vitiligo (Cardenas-Roldan et al., 2013). This occurrence seems to confirm that in addition to the environment, genetics play a broad and important role in the development of multiple autoimmune syndrome which will be discussed.

Scientists employed genome-wide association study (GWAS), genome scans and RNA sequencing to investigate common genetic etiologies that contribute to autoimmune diseases and polyautoimmunity. They identified loci responsible for the human leukocyte antigen (HLA) region on DNA that contribute to autoimmunity. The researchers also identified loci shared between the most common autoimmune conditions which included IL23R, OLIG3/TNFAIP3 and IL2RA. The study revealed that type 1 diabetes was genetically associated with rheumatoid arthritis and that Crohn's disease was linked with ulcerative colitis. It also underlined how some diseases seem capable of developing without any genetic links, particularly systemic lupus erythematosus (SLE) and systemic sclerosis. This would suggest that not all forms of autoimmune disease are caused by genetic heritability and phenotype. Rather, genes play a sizable role in the broader picture of how autoimmunity manifests (Ramos et al., 2011).

The Major Histocompatibility Complex (MHC) gene has been investigated as an important factor in autoimmunity. Located on chromosome 6, the locus codes for cell surface proteins found on numerous lymphocytes as well as receptors found on almost every living cell in humans. Scientists performed a genome-wide association study (GWAS) on the MHC gene which compares the allele/genotype frequency between individuals that have been affected by disease and those who have not. The study visually confirmed that the MHC locus is a major predicator in most autoimmune conditions (Kochi, 2016). The most common MHC genes include HLA-A, HLA-B and HLA- DP/DQ/DR. Since these genes play a crucial role in the adaptive immune response, perhaps it is possible to surmise that MHC genes are involved in the formation of autoimmunity in general. However, this does not explain why one patient develops Crohn's disease and one Hashimoto's disease. The development of a specific disease or condition can be caused by a single allele, yet this does not prove that a single allele can cause polyautoimmunity. For example, rheumatoid arthritis has been linked to multiple HLA-DRB1 alleles such as *01:01,

*04:01, *04:05 and *09:01 while Ankylosing spondylitis is known to be caused by the allele, HLA-B27 (Newton et al., 2004).

Researchers have identified a mutation in the genetic factor PTPN22 as an important driver of multiple autoimmune syndromes. PTPN22 is responsible for encoding lymphoid-specific tyrosine phosphatase, a critical regulator of T-cell receptor signaling pathways. A single nucleotide missense mutation involving PTPN22 has been linked to rheumatoid arthritis, type-1 diabetes and systemic lupus erythematosus. FC receptors (FcRs) on the surface of immune cells recognize immune complexes comprised of autoantigens and autoantibodies. After the immune complex binds to the receptor, FcRs release Src and Syk family kinase which leads to antigen uptake, presentation and secretion of interleukins and proteins that initiate an immune response. Tyrosine phosphatase encoded by PTPN22 inhibits the release of Src and Syk kinase, thereby regulating the FcR immune response in dendritic cells. In one study, patients who had a C1858T missense polymorphism in PTPN22, were found to have higher levels of Scr and Syk kinase as well as higher instances of type 1 diabetes. In another study, bone marrow derived dendritic cells of wild type mice (PTPN22-/) were compared with dendritic cells from knockout mice with PTPN22-/-. The PTPN22-/- dendritic cells had higher levels of T cell proliferation and activity (Clarke et al., 2018).

Studies examined innate immunity to determine if genes responsible for the initial immune response play a role in autoimmune development. In innate immunity, macrophages and dendritic cells express toll-like receptors which recognize patterns on virus antigens and then activate type 1 interferons responsible for immunomodulatory and antiviral responses. These interferons or cytokines bind to receptors on white blood cells which activate a cascade of secondary messengers which interfere with the further proliferation of the invading virus. A subgroup of the interferon proteins, the type 1 interferon, has been implicated in myositis and systemic lupus erythematosus. Research demonstrated that patients with lupus displayed higher levels of type 1 interferons at diagnosis when compared with individuals without symptoms of disease (Padilla, Niewold, 2016). Additionally, genome wide association studies for systemic lupus erythematosus discovered multiple gene and loci sites that were directly linked with type 1 interferons and its associated signaling pathways. These included IFIH1, IRF5, IRF7, TLR7, IRAK1 and TYK2. Other studies using GWAS identified these loci sites in other autoimmune conditions. For example, type 1 diabetes, psoriasis and Addison's disease have been linked to IFIH1. Interestingly, these three diseases are all included in the type 3 subgroup of multiple autoimmune syndrome (MAS) described earlier. Similarly, the IRF5 loci was correlated with primary biliary cirrhosis, Crohn's disease, colitis and rheumatoid arthritis.

Patients with lupus who presented with the IRF5 risk haplotype also had higher levels of signal transducer and activator of transcription 4 (STAT4). STAT4 is a transcription factor involved in the differentiation of T-helper 1 (Th1) cells. Researchers believe that increased levels of STAT4 may increase the activity and proliferation of these T cells leading to autoimmunity (Kochi Yuta, 2016). STAT4 is activated by type 1 interferons and is responsible for the synthesis of IFN-y, another interferon type. This discovery highlights how one gene factor can drive multiple different components that lead to disease. IRF5 produces excess interferons that may exacerbate an autoimmune response in the innate immune system, while simultaneously activating STAT4 which is involved in adaptive immunity. Also noted in the literature, was that lupus patients who presented with the PTPN22 mutation discussed had reduced levels of TLR7 induced type 1 interferons, possibly indicating heterogeneity of disease expression (Wang et al., 2015). These studies clearly indicate that genetics play a role in both innate as well as adaptive immunity and that there are several overlapping genetic variances that contribute to the manifestation of multiple autoimmune conditions.

Studies performed using genome-wide association studies (GWAS) identified and linked individual genes with specific autoimmune conditions. Researchers investigated whether one gene can be responsible for general autoimmunity encompassing a broad number of non-specific autoimmune conditions. One study focused on the ITGAM gene, a genetic region responsible for the alpha-chain subunits found in a cell surface receptor of neutrophils and monocytes named Integrin-aMB2. A variant at exon 3 (rs1143679) within the ITGAM gene was thought to up-regulate the binding capacity of Integrin-amB2 which would increase the susceptibility to multiple autoimmune syndromes. However, SNP genotyping, statistical and meta-analysis of the gene region confirmed that there was no significant association between systemic sclerosis, scleroderma, rheumatoid arthritis and the ITGAM gene. Only systemic lupus erythematosus was found to be directly correlated with the re1143679 mutation found in the population (Anaya et al., 2011). Still, researchers have identified a general autoimmune contributor using GWAS. As previously discussed, pro-inflammatory cytokines play a major role in the development of autoimmune conditions. Researchers studying the origins of celiac disease discovered an association between celiac

disease and the receptor for Interleukin-23 (IL-23). Two subunits (p40 and p19) within IL-23 are found within the IL-12 and IL-1B receptors as well. (IL-12 receptors are composed of p40 and p35 heterodimers while IL-1B contains p19 dimers.) Additionally, the p19 (IL23R) subunit on IL-23 is located just 3'downstream to the p40 subunit (12RB1) on IL-12. This highlights just one of the many connections between cytokinetic interleukins and autoimmune disease. Indeed, the IL-23 receptor has also been linked to psoriasis, rheumatoid arthritis, Crohn's disease and multiple sclerosis (Tang et al., 2012). Other diseases have been linked to specific interleukins as well. IL-2 and IL-2R were found to have a direct connection with psoriasis, Gaucher disease, rheumatoid arthritis and type 1 diabetes while IL-21 was linked with multiple sclerosis as well as inflammatory bowel disease. The studies did not investigate or confirm whether contracting one of the autoimmune conditions raised the risk of developing another. However, it seems plausible that if genetic and environmental conditions caused one disease, they could lead to a second one.

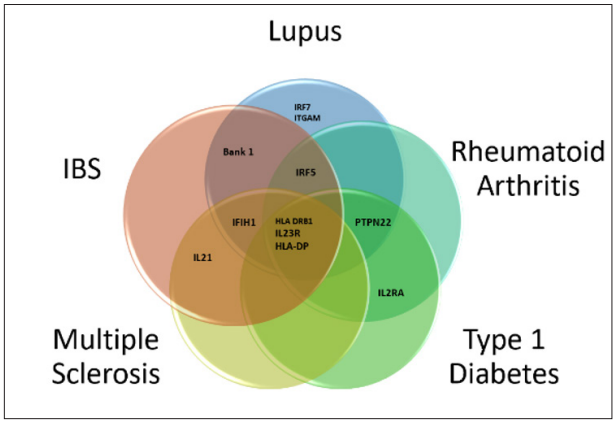

Figure 1 illustrates the various linkages between differentially expressed genes and five common autoimmune conditions.

Researchers at the Benaroya Research institute attempted to map the many genetic connections between each autoimmune disease in order to determine how one may lead to the other. They began by investigating why patients with Down syndrome are 15-100 times more likely to develop some form of autoimmunity, many of whom develop polyautoimmunity as well. Additionally, these disorders are varied, affecting both endocrine and non-endocrine systems. Diseases commonly seen include thyroid disease, type 1 diabetes, scleroderma, Sjogren's syndrome, systemic lupus erythematosus, autoimmune hemolytic anemia and celiac disease. A biorepository of blood and tissue samples was established using tissue extracted from the Down syndrome population as well as from their healthy siblings. Since Down syndrome is caused by trisomy 21 (HSA21) and is genetic in nature, researchers focused on the genetic drivers in these patient's immune responses and composition. They also investigated whether one gene could be the driving force behind all these illnesses. The data identified a gene called dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 1A (DYRK1A) as a possible driver of autoimmunity. Previously, this gene was linked to the cognitive decline and neuro-developmental conditions found in most patients with Down syndrome (Feki, Hibaoui, 2018). Patients with Down syndrome express an excessive amount of DYRK1A as a result of the extra chromosome HSA21, leading to a buildup of proteins that lead to memory deficit and motor abnormalities. Scientists hypothesized that DYRK1A produces excess proteins that prevent the body from shutting off unnecessary inflammatory immune responses leading to autoimmune disease.

In a separate study, researchers worked to identify substances that could increase the number of Treg cells, white blood cells that suppress other immune cells, in order to prevent autoimmunity. The scientists believed that by increasing Treg cells while maintaining or even inhibiting T helper cells, a novel therapeutic approach to autoimmunity could be found. Using Similarity Ensemble Approach (SEA) and chemoinformatic methods involving 3,100 substances, the team isolated a chemical called B-carboline alkaloid harmine and discovered its ability to reduce autoimmune activity in induced inflammatory reactions in vitro. Further studies demonstrated that harmine acts in part by inhibiting DRYK1A which led to differentiation of Treg cells. More importantly, when DRYK1 was inhibited, T1 helper cell and T17 helper cell differentiation remained constant or was reduced. The team then tested harmine's impact on Treg and T helper cells in vivo, using three separate subtypes of inflammation; type 1 diabetes, colitis and asthma. The three inflammatory diseases were chosen for their T cell properties, diverse genetic backgrounds and distinct tissue types. When Foxp3 mice were induced with type 1 diabetes, the mice developed diabetes approximately 10 days after injection. When the mice were induced under TregHarmine conditions, onset was delayed by a minimum of seven days. Next, when mice with ulcerative colitis were injected with TregHarmine, mucosal inflammation in the intestines was significantly reduced. Finally, researchers induced Foxp3 mice with airway inflammation using intratracheally administered ovalbumin. When these mice were treated with Harmine, a significant suppression of inflammation was noted (Kohr et al. 2015). These findings benefit the hypothesis that the overexpression of DYRK1A in patients with Down

syndrome may contribute directly to the development of autoimmune disease by increasing differentiation of T1 helper cells, while simultaneously preventing the expression of anti-inflammatory Treg cells. This might explain the broad spectrum of disorders seen in Down syndrome since helper T cells and Treg cells are involved in almost all autoimmune disorders. Additionally, as a DYRK1A inhibitor, B-carboline alkaloid harmine should be further investigated as a therapeutic for Down syndrome patients with autoimmune conditions. Another potentially important question is whether inhibiting DYRK1A can also decrease some of the neurological symptoms seen with Down syndrome cases, since DYRK1A has also been associated with the mental retardation and cognitive delay that is prevalent in these cases.

GWAS was able to identify and establish a substantial link between genetics and autoimmune disease. In addition, many of these genes have also been linked to multiple autoimmune syndromes and illnesses. However, just because an individual is genetically predisposed does not guarantee the development of one or several autoimmune conditions. Epigenetically, these genes can be regulated due to several mechanisms and several epigenetic processes have been linked to autoimmune disease. These include DNA methylation, post-translational histone protein modifications, chromatin remodeling and RNA regulation of gene expression. DNA methylation involves the addition of a methyl group to carbon 5 on the cytosine molecule of cytosine phosphate-guanosine resulting in 5-methylcytosine. The methyl groups occupy the major groove of DNA, thereby silencing the gene by blocking proteins and transcription factors from forming transcription complexes on the DNA helix. DNA demethylation can also occur through the enzyme-catalyzed removal of cytosine methyl groups. Researchers studying systemic lupus erythematosus were able to identify specific epigenetic processes by focusing on the development of peripheral blood mononuclear immune cells of patients affected with lupus and then comparing them to their identical monozygotic twin siblings. The results identified approximately 50 instances of DNA hypomethylation in the gene regions of the lupus patients. Absolute cause for the hypomethylation was not identified, although possibilities that were mentioned include UV exposure, age, viruses and environmental stress (Surace and Hedrich, 2019). More research is needed to investigate DNA methylation in other autoimmune conditions as well as other immune cell types.

Histone modifications occur via covalent posttranslational alterations of amino acids at the N-terminal end of histone proteins. These changes include adding or removing a phosphate, acetyl and methyl group that transforms the chromatin structure, making the DNA unavailable for transcription. A similar concept called chromatin remodeling occurs when ATP-powered protein complexes attached to chromatin, alter, remove or transfer the nucleosome to another part of a chromosome. Scientists explored the genetic links of Cryopyrin-associated periodic syndrome (CAPS), a rare autoimmune disease that consists of three phenotypic processes: Muckle-Wells syndrome, neonatal-onset multisystem inflammatory disease and familial cold autoinflammatory syndrome. The results of one study revealed a down-regulation of numerous genes which included the histone proteins SUMO1 and HIST2H2AC as well as histone deacetylase enzymes HDAC1/2 (Surace and Hedrich, 2019). However, a second study involving CAPS demonstrated excessive levels of DNA demethylation which results in an epigenetic up-regulation of genes as the driver of the inflammatory process (Tormo et al., 2017). These studies illustrate the immense complexity of histone modifications and epigenetics in general. Though the two studies appear to contradict each other, it is highly plausible that epigenetic events not only vary considerably between diseases but even between individuals as well. Still, these studies were limited in scope and design and more research is needed to fully understand the epigenetic connection to CAPS and how different events drive the genetic expression of inflammatory processes.

RNA regulation involves the repression of gene expression through long and short noncoding RNAs (ncRNA). Long ncRNA's are silent and lack an extended open reading frame required for translation. Short ncRNA's include micro-RNAs (miRNAs), short interfering RNAs (siRNAs) and piwi-interacting RNAs (piRNAs). MicroRNAs are transcribed as precursor molecules 80-100 bases long and after hydrolytic cleavage are processed to contain 20-23 bases. The shortened span allows them to interfere with DNA methyltransferase thereby inhibiting DNA methylation. During the CAPS studies mentioned earlier, researchers were able to identify a direct association between miRNA and upregulation of the STAT4 gene responsible for CD4+ T helper 1 cell proliferation. In addition, STAT3 and STAT1 were also upregulated, resulting in increased cytokinetic activity, specifically IL-6 and IL-17A (Surace and Hedrich, 2019). Since epigenetics contain many factors, it is difficult to determine the exact role it plays in polyautoimmune disease. However, epigenetic processes have been identified in some of the universal genes described earlier. For example, the ITGAM gene that contributes to multiple autoimmune diseases contains approximately 40 sites of DNA methylation and

histone modifications. Though scientists are unsure of the specific effects and links for these sites, many roles and possibilities exist. As science continues to explore the complex concept of gene expression and epigenetic factors, researchers will surely uncover many other associations between multiple autoimmune diseases and epigenetics.

Conclusion

Research has identified several risk factors for developing polyautoimmunity. It is clear from the data that the presence of one autoimmune disease raises the risk for developing further illnesses. Chronic and acute forms of stress facilitate autoimmune processes by raising inflammatory markers in the bloodstream. Though viruses and bacteria typically prime the adaptive immune system for future responses, molecular mimicry, bystander activation and epitope spreading can direct a vulnerable immune system to turn on itself. Furthermore, untreated and protracted forms of inflammation might lead to autoimmune disease through bystander activation or similar forms of immune dysfunction. Genetic processes involving interleukins and inflammasome signaling, regulate the many components responsible for managing a healthy immune system. Mutations and hereditary factors involving these genes can directly contribute to multiple autoimmune diseases. Lastly, epigenetic elements driven by DNA methylation and hypomethylation of cytosine bases as well histone modification and RNA regulation can lead to the development of multiple autoimmune diseases, though the exact connection is not yet fully understood. The data does not establish absolute causation of any one contributing factor for developing polyautoimmunity; however, each additional variable enhances the risk over time. Patients who are genetically predisposed to autoimmune disease and are chronically stressed or have contracted multiple viruses in their lifetime, have a significant risk of developing an autoimmune disease. If inflammation levels of the initial disease are not managed, patients face an increased risk of developing another condition. It is important for physicians and healthcare professionals to be aware of their patient's genetic profile, susceptibility and history to determine the probability of further autoimmune development. Communication among the healthcare team is essential since patients may have multiple doctors treating several conditions, each without knowledge of the patient's complete history. Finally, through more research into the causes and associations of polyautoimmunity and multiple autoimmune syndrome, doctors will be able to better diagnose, treat and eventually prevent this abstruse and perplexing condition.

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