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Review

Rogue T Cells and LncRNAs: Two Strong Contenders for Autoimmune Disorders

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Abstract: The importance of a properly regulated immune response has been explored through various research-oriented methods. It has proved that having an effective and well-regulated immune response helps prevent many minors and serious diseases. Any kind of dysregulation in the working of the immune system may lead to severe consequences. An autoimmune disorder is one such consequence in which the component of the immune system starts targeting self-cells of the body, treating them as self-antigen producing autoantibodies and immune complexes resulting from the failure of immune responses both at a central and peripheral level. Currently, many autoimmune disorders are prevailing across the world, and new diseases need attention.

In this review, we have written about the functions of T cell, LncRNAs and also some interactions between the LncRNAs and miRNAs in the pathogenesis of Multiple sclerosis (MS), Systemic lupus erythematosus (SLE), Type 1 diabetes (T1D), Rheumatoid arthritis (RA). To find the functions of these autoimmune disorders we have done intensive literature search during this we also found that GAS5 and MALAT are common in MS, SLE, T1D, RA. And finally, we have also mentioned the therapeutic drugs which neutralizes the different cluster of differentiation (CDs) and also suppresses the T cell differentiation in MS, SLE and RA. For T1D therapeutic strategies and various types of insulin are mentioned.

Keywords: autoimmunity; T-Cell; LncRNAs; miRNAs; RA; T1D; MS; SLE

1. Introduction

An autoimmune disorder is when our immune system fails to recognize or differentiate between self and non-self-entity of the body. This misdirected immune response may be the result of several factors. These factors can be environmental triggers, genetic susceptibility (both coding and non-coding), failure of immune tolerance, dysregulated immune cell differentiation. These disorders are considered significant clinical problems because of their complex nature, and understanding via limited factors is not possible as many factors are responsible for the pathogenesis of the diseases. The study on autoimmune diseases is critical because of its chronic nature, treatment cost, and increasing prevalence rate. More than 80 autoimmune disorders are prevailing globally, and each varies significantly in terms of its progression in different parts of the body [1].

Some autoimmune diseases are restricted to particular tissues or organs, such as type I diabetes (T1D), multiple sclerosis (MS), and myasthenia gravis, also termed organ-specific. At the same time, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome are considered systemic or disseminated autoimmune diseases. Autoantibodies and cytotoxic T-cells mediate the pathogenesis of these diseases. Helper T-cells (T_H) have a significant role in all autoimmune disease progression [2]. This review is mainly based on the most prevalent diseases globally: systemic lupus erythematosus, Multiple sclerosis, Type 1 diabetes, and Rheumatoid arthritis. These diseases are described individually in various sections such as epidemiology, T-cell role, non-coding RNAs, and therapeutic methods. Systemic lupus erythematosus is a systemic

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autoimmune disease that may affect every organ and tissue of the body. Systemic lupus erythematosus is an example of a complex disorder whose mechanism of pathogenesis comprises type I interferon, complement system, dysregulation of various cytokines, immune complexes, and autoantibodies by multifocal lesions within the CNS (in both the white matter and Gray matter)[3, 4]. Multiple sclerosis is also a complex autoimmune disorder of the central nervous system, with multifocal lesions in white matter and grey matter. Multiple sclerosis is caused by chronic inflammatory demyelination and axonal loss in the brain and spinal cord. Type 1 Diabetes Mellitus is an organ-specific disease caused by autoimmune destruction of beta cells in the pancreas leading to insufficient insulin production inside the body. This autoimmune destruction occurs because of the failure of central immune tolerance and peripheral tolerance [5]. Rheumatoid arthritis is one of the common systemic inflammatory autoimmune diseases, which cause painful, swollen joints that can severely affect physical function and quality of life. It generally affects people belonging to the age group of 50-60 years [6].

Several studies revealed the role of LncRNAs in the pathogenesis of Systemic lupus erythematosus, Multiple sclerosis, Type 1 diabetes, and Rheumatoid arthritis. The upregulation and downregulation of several LncRNAs are associated with autoimmune diseases. LncRNAs such as *MALAT1* and *GAS5* are common in SLE, MS, T1D, and RA; thus, pointing to their significant role in the causation of these diseases. Furthermore, studies found that different T cell types in different diseases are typical; however, they differ in mechanisms and target organs. Nevertheless, this has given an idea of how differentiated T-cells can be approached to understand the pathogenesis of diseases.

2. Epidemiology

2.1. Systemic lupus erythematosus (SLE):

The SLE is a chronic autoimmune disease. It has a significant health impact globally within the top 20 leading conditions that cause death in females aged 5-64 [7]. Studies revealed the variable prevalence of SLE within the same country and geographical regions. Childhood SLE (cSLE) has a higher prevalence for lupus nephritis (LN) in India, and there are variations in response to treatment of LN. SLE data is limited for a long-term outcome of LN in Childhood SLE from the Indian subcontinent [9]. In India, the most common SLE disease is LN, and the mean age of the diagnosis of LN is 13.7 ± 3.5 years. Lupus nephritis (LN) is a highly affected disease in SLE; almost 70% of SLE patients have Lupus nephritis [10]. According to Indian Health Service (HIS), the prevalence with ethnic distribution in American Indian/Alaska Native is 178 in 100000 [11]. SLE is commonly found in Females as compared to Males with a ratio of 9:1 [12].

2.2. Multiple sclerosis (MS):

According to Atlas of MS 2020, there are 2.8 million cases around the world [13]. This suggests that 1 in 3,000 people is suffering from MS. The estimated number of people with MS has increased from 2.3 million in 2013 to 2.8 million in 2020. There is a 14.69% increase in global prevalence from 2013 to 2020. The global prevalence per 100,000 population in 2013 was 29.26 that increased to 43.75 in 2020. In India, 145,800 people are suffering from MS, which means every 1 in 9,500. Around 6,500 new cases are reported each year [13].

MS is an autoimmune disorder that causes nerve demyelination and inflammation, disrupting signals transmitting across the CNS. The exact cause of MS is still unknown. However, several genetic and environmental factors are considered as risk factors for MS. Genetic factors involved are HLA-DRB1, IL7R [14][15]. Vitamin D, EBV (Epstein-Barr virus infection), and smoking are some environmental factors that are engaged with MS [16] [17]. Low serum levels of Vitamin D have been observed in MS patients as compared to the ordinary person. This indicates that a low vitamin D level could elevate the risk and EBV-positive persons are more prone to developing MS [17].

Hemminki et al. 2009 proposed an increased frequency of disease in relatives of the person affected by MS [18]. Monozygotic twins are more prone to MS than dizygotic

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twins. There may be a linkage between the genes that influence dizygotic twinning and other genes that protect against it [19]. Total cases in females are more prevalent than males around the globe. In India, out of total cases (1, 45,800), 63% of people are females [13]. The reason behind more cases in females is still not exactly clear. El-Etr M, Vukusic S, Gignoux L, et al. (2005) suggest that differences in hormones also influence MS susceptibility and severity [20].

2.3. Type 1 diabetes (T1D)

The autoimmune destruction of the beta cells in the pancreas results in a chronic illness known as Type 1 diabetes, which is further characterized by the body's inability to produce insulin. The disease onset is typical in children but may also affect adults.

For all the patients who have diabetes, T1D accounts for nearly 5-10%. The most affected age group belongs to under 20 years as ≥85% of all diabetes cases lie in this age group across the world, and that is why it is considered to be the diabetes of youth [21]. It is estimated that each year 132,600 cases are newly diagnosed, and 1,106,500 people aged 0-19 years have type 1 diabetes [22]. The annual rate for new patients in the US from 2011-2012 for ages under 20 years was about 21 in 100,000[23]. In 2016 and 2017, a study was conducted for adults diagnosed with diabetes in the US, and it was found that type 1 diabetes accounted for nearly 5.6% of cases[24].In the prevalence of type 1 diabetes, geographical variation also plays a significant role as it is less common in people from the Asian region than in the European area. According to a report, there has been a more rapid disease increment in ethnic groups and non-white racial. Type 1 diabetes affects males and females in an equal ratio [25].

2.4. Rheumatoid arthritis (RA)

The epidemiological studies state that the global prevalence of RA is around 0.5 – 1% of the world population [26–28]. In India the prevalence is 0.51-0.75% of population [27]. In Europe, it is 9-36 per 100000 people annually; North America is 31-45 per 100000 person-annual, Asia and the Middle East it is 8-42 per 100000 person-annual [28]. The frequency in women is higher than in men; it is likely to be two-three folds. This higher frequency in women is due to the stimulatory effects of estrogen on the immune system; however, the hormonal factor role is yet controversial in the development of RA [29]. Genetics plays a strong role in RA. A study was conducted by Okada Y et al. to estimate the heritability of RA in twins; seropositive twins for anti-citrullinated protein antibodies (ACPAs) showed higher heritability compared to seronegative as for ACPAs. Genome-wide association study (GWAS) technologies have identified more than 100 genetic loci associated with RA [30]. However, twin study showed the disease concordance in monozygotic twins is 15 to 30%, and in dizygotic twins, it is 5% [31]. The patients who are positive for ACPAs and rheumatoid factor have been strongly associated with class II human leukocyte antigen (HLA)-DRB1 alleles in MHC (Major Histocompatibility Factor), which contains shared epitopes, especially HLA-DRB1*01 and HLA-DRB1*04 are associated for the developing the risk of RA. Additionally, there are susceptible HLA's alleles like HLA-DRB1*13 and HLA-DRB1*15. The T-cell senescence is triggered not only by HLA molecules ((shared epitopes)) but also by potential pro-inflammatory signalling function, distinct from its role in antigen recognition. These uncover a link between RA and HLA alleles (DRB1 alleles is 11%)

Some susceptible non-HLA alleles are PADI4, PTPN22, BLK, ANKRD55, IL6ST, AFF3, CD28, TNFAIP3, PRL, and NFIA. The PADI4 gene is involved in the protein citrullination by encoding a peptidyl enzyme arginine-debase (PADI4), and it is an essential function for the development of disease [32]. PTPN22 (Phosphatase protein tyrosine phosphatase non-receptor type 22) gene shows the second strongest association with RA after HLA-DRB1. PTPN22 R620W (C1858T), this polymorphism leads to change in amino acids from Arg (R) to Trp (W) at 620 base pairs position; it confers the risk to disease. This PTPN22 allele is expressed in hematopoietic cells and acts as a negative regulator of

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antigen receptor signalling in B and T cells. Decreased T-cell receptor signalling lead to impaired regulatory function and has also been observed in Treg cells [30].

There are modifications to DNA histones of acetyl and methyl groups that bind to it. These are known to be epigenetic marks. These epigenetic marks of active chromatin are enriched in $CD4^+$ T helper cells of RA patients. Methylation levels are higher in smokers with ACPA-positive and who carry the HLA-DRB1 allele [29].

3. The role of t-cells in autoimmune disorders

3.1. Systemic lupus erythematosus (SLE):

T-cells play a prominent role in the breakdown of immune tolerance and lead to the development of Autoimmune Diseases. T-cell activation depends upon various inflammatory mediators, cytokines, chemokines, transcription factors, and epigenetic modifications. Genetics, environmental and hormonal factors are involved in the pathogenesis of SLE, and till now, the pathogenesis is unclear because of its complex mechanism [33] [34].

T-cells immune tolerance is interrupted due to defective apoptosis and multiple altered signalling pathways [34][33]. Defective apoptosis due to the formation of excessive NETs (neutrophil extracellular traps) formation and imbalance of NETs degradation leads to accumulation of apoptotic debris (Nucleic material, proteins), which act as autoantigens [34]. These autoantigens can trigger TLRs (Toll-like receptors) expressed on the surface of APC (Antigen-presenting cells). Interaction between autoantigens and TLRs leads to inappropriate antigen presentation to T-cells, leading to differentiation of T-cells into different subsets (Th1, Th2, and Th17). Under normal conditions (immune balance), Th1 and Th2 cells regulate and inhibit each other through cytokines. Increased function of Th2 and decreased function of Th1 is observed in SLE patients, leading to disruption of immune balance. Th2 cells are also involved in activating B-cells by releasing IL-4, IL-6, and IL-10, which further induce the production of autoantibodies (Fig-1) [33, 34].

Tregs are involved in the maintenance of immune tolerance by regulating the function of effector T-cells. A reduced number of Tregs leads to a breakdown of immune tolerance. Th-17 cells secrete IL-17 and IL-21 [35]. Increased levels of IL-17 have been confirmed in the kidney of patients, and this IL-17 confirms the participation of Th-17 in SLE. IL-17 also upregulates the production of autoantibodies by upregulating the survival and differentiation of B-cells [35–37].

T-Cell Receptor (TCR) signalling pathway, CD44-Rock-ERM (ezrin/radixin/moesin protein) signalling pathway, and PI3K-Akt-mTOR signalling pathway are examples of altered signalling pathways. In the TCR signalling pathway, expression of CD3ζ (marker expressed on the mature T-cell surface) chain was significantly decreased, which initiates a cascade of different processes (Higher Calcium influx in T-cells, alteration of expression of genes including *CD40L*) [33, 38]. Altered expression of *CD40L* promotes B-cells differentiation, proliferation, and antibody production [33]. In the CD44-Rock-ERM signalling pathway, enhanced expression of CD44 (cell surface molecule involved in T-cell activation and adhesion), Rock (Rho-associated protein Kinase), ERM was observed, which affects the differentiation of Th17 (a subset of effector CD4+ T-cell), controls the production of IL17 and IL21. IL17 promotes Th17 to participate in SLE and work together with B-cell stimulating factor to upregulate B-cell differentiation, leading to autoantibodies' production [33, 39, 40]. In the PI3K-Akt-mTOR signalling pathway, enhanced activity of PI3K and Akt upregulates mTOR activation in blood (T and B-cells) samples of SLE patients. mTOR promotes the synthesis of proteins involved in the division, proliferation, and survival of T, B-cells, which is positively correlated with SLE severity [33, 41].

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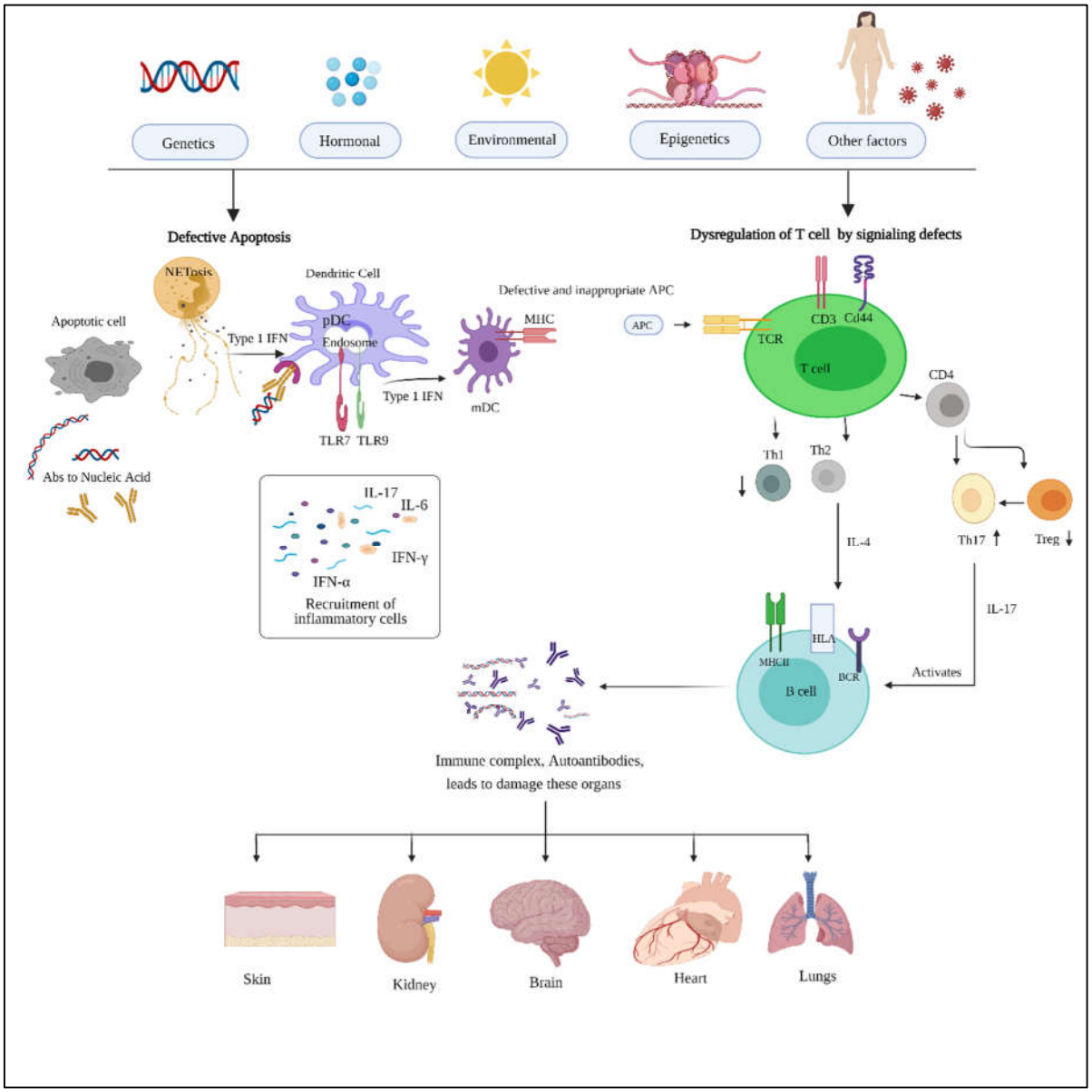

Figure 1. T cells Dysregulation in systemic lupus erythematosus.

Apoptotic cells and Neutrophils play a role in the pathogenesis of SLE by the formation of NETs which leads to accumulating apoptotic debris that acts as autoantigens. High levels of type 1 IFNs are released by pDC (plasmacytoid dendritic cell), mDC (Myeloid Dendritic cell). Furthermore, the inappropriate antigen presentation by DC (dendritic cell) to T-cell leads to the differentiation of a different subset of T-cell (Th1, Th2, Th17, Tregs) secrete IL-6, IL-10, IL-17, IL-4 that leads to Th2 maturation, thereby promoting the humoral response, and stimulates B-cell activation and proliferation that release antibodies towards own antigens (nucleoproteins of the cell) form immune complex deposited into tissues that cause inflammation and organ damage. IL-4, IL-6, IL-10, IL-17, which promotes B-cell activation, production of autoantibodies, immune complex.

3.2. Multiple sclerosis (MS):

Multiple factors are involved in MS development, due to which the exact pathology is still unclear. It can arise due to the genetic susceptibility of a person or due to environmental factors. The initial trigger point of MS is still a question, whether it begins in the periphery or CNS.

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Lesions are the hallmark of MS that consists of immune cells, which are actively involved in inflammation and demyelination of axonal cells that crossed the blood - brain barrier to reach the CNS. There are two primary opposing hypotheses regarding activation of the immune response. First, activation begins in the periphery, and autoreactive T-cells are activated due to molecular mimicry mechanism at periphery site (outside of CNS), bystander activation, and dual expression of TCR (T-cell receptors) with different specificities [43]. Now, these cells migrate to lymph nodes, and from lymph nodes, a minimal number of antigen-specific T-cells and B cells will invade CNS to form lesions during MS development [44]. $CD4^+$ T-cells release cytokines, and plasma cells release antibodies that target myelin sheath and glial cells resulting in tissue inflammation and damage. Further, the blood-brain barrier gets open to other immune cells, resulting in lesions' formation due to the influx of monocytes and other lymphocytes [45].

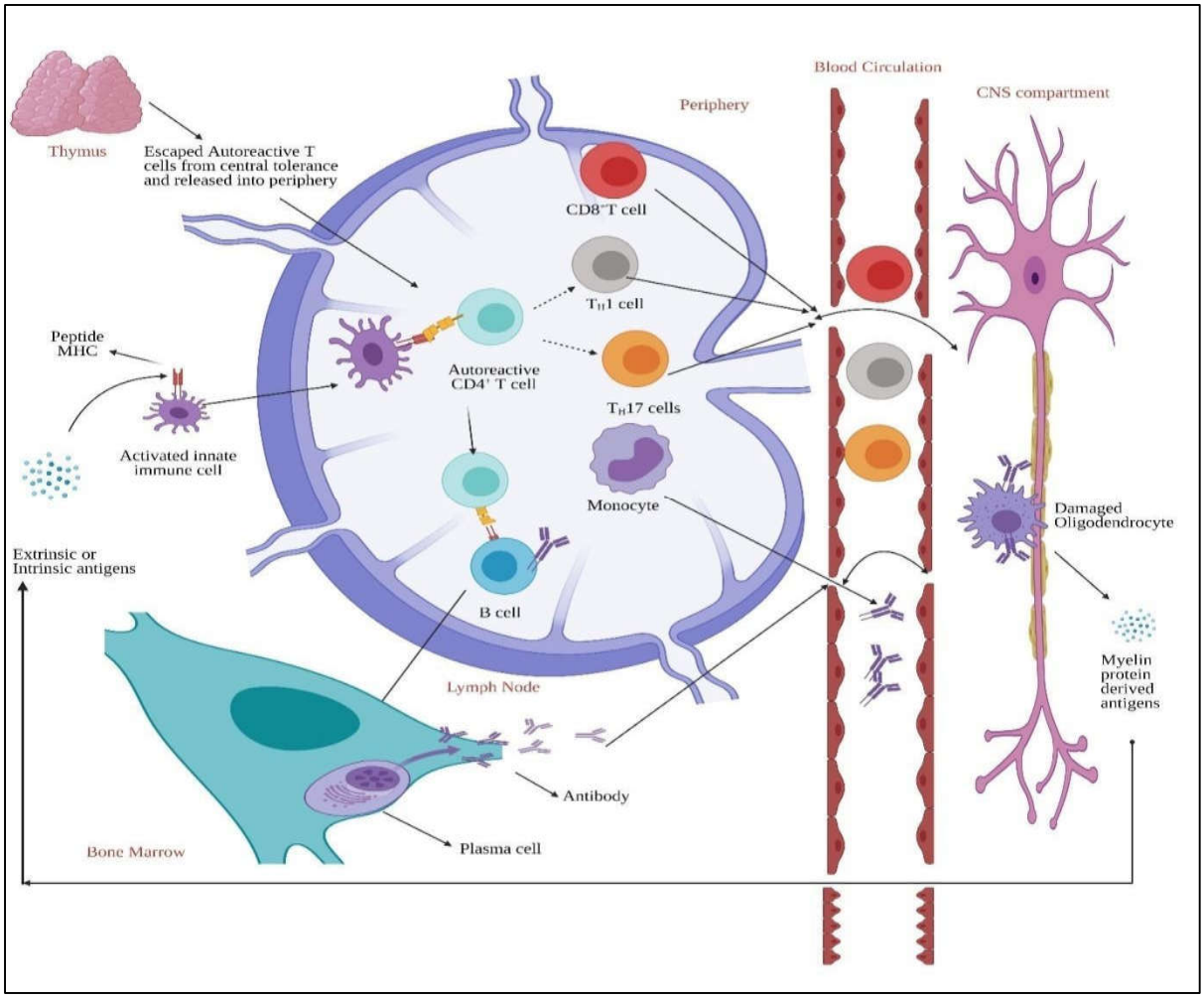

Figure 2. Immune cell dysregulation during Multiple sclerosis.

Some autoreactive T cells escaped from the central tolerance process (in the thymus) into Lymph drains. These autoreactive cells can be activated by extrinsic antigen not derived from CNS; (e.g., Bacteria, Smoke constituents) by various processes like molecular mimicry, bystander activation, or intrinsic antigen derived from CNS; (e.g., Myelin protein-derived antigens). Activation is done by priming autoreactive T-cells with processed antigen presented by dendritic cells. Once activated, these cells are transformed into aggressive effector cells and infiltrate CNS by crossing the blood-brain barrier and B cells and other innate immune cells. This leads to inflammation and tissue damage. B cells proliferate into antibody-secreting plasma cells that migrate to bone marrow or inflamed tissue.

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The second hypothesis states that activation of an immune response begins in CNS, then the infiltration of autoreactive lymphocytes is happening as a secondary response [44]. For example, genetic mutation defects in oligodendrocytes lead to the death of these cells, which results in activation of microglial cells without considerable infiltration of lymphocytes. This indicates that adaptive immune response is not the primary cause of lesion formation in MS development. Due to oligodendrocyte loss in lesions, myelin-protein-derived antigens are believed to be the main targets. Antigens are carried in the CSF (Cerebrospinal fluid) across the cribriform plate to the nasal mucosa and then drained into cervical lymph nodes. A secondary adaptive immune response is induced due to the priming of T-cells and processed antigen by dendritic cells in lymph nodes [46]. Interaction with antigen leads to activation of autoreactive T-cells (CD8+ T cells, differentiated CD4+ T helper 1 (Th1), and T17 cells). These activated T-cells and B-cells, and other innate immune cells infiltrate the CNS, leading to inflammation and tissue damage. This inflammatory response leads to monocyte recruitment into the CNS and naive CD4+ T cell activation through epitope spreading, enhancing inflammation [47].

3.3. Type 1 Diabetes (T1D):

Coppieters et al. reviewed the importance of CD4+ and CD8+ T-cells role in beta cell destruction. It has been noticed about the infiltration of immune cells in the pancreatic section of Type 1 diabetes patients and in extreme cases immune infiltration within the islets of individuals are found very severe [48, 49].

Human leukocyte antigens (HLAs) class II alleles have a vital role in the pathogenesis of type 1 diabetes. In human patients, HLAs class II alleles such as *DR4*, *DQ8*, and *DQ2* possess the highest genetic risk for T1D. This also gives evidence about the crucial role of HLA II-restricted $CD4^+$ T-cells in disease pathogenesis. Antibody production and islet-resident macrophages are enhanced by B cells in coordination with $CD4^+$ T-cells and effector $CD8^+$ T-cells [50, 51]. The various components of innate and adaptive immune systems are involved in destroying the islet β-cell in T1D. Autopsy studies of patients suffering from T1D showed mononuclear cell infiltrate in Islets, a condition termed Insulitis [52]. These mononuclear cells infiltrate in islets mainly comprise of macrophages, B cells, and T cells. For the progression of the disease, both $CD4^+$ and $CD8^+$ T cells are required. The Th1 cells and cytotoxic T lymphocytes (CTLs) are responsible for destroying the insulin-producing β cells through effector functions and direct killing, respectively. Inflammatory cytokines such as TNF-α and IFN-γ are produced by cytotoxic T lymphocytes. This is one mechanism by which β-cells are destroyed, affecting insulin secretion. In targeting the β-cells, TNF-α and IFN-γ work in a combined way with IL-1β produced by macrophages. Perforin secretion and activation of the Fas-Fas-L pathway (apoptosis) are other mechanisms used by CTLs to direct the killing of β-cells [52].

Due to the breakdown of various key checkpoints, the chance of Type 1 diabetes increases. Naïve $CD4^+$ and $CD8^+$ T-cells, reactive to islets, escape from the thymus and are included in the pancreatic lymph node due to the defective central tolerance. Islet antigen is represented by the dendritic cells interacting with autoreactive $CD4^+$ T-cells inside the pancreatic lymph node. After the interaction, it can differentiate into pTreg, T helper 1 (Th1), anergic cells, or T_{FH}. Antibodies, which have high affinity and specificity to islets, are produced by B cells with the help of T_{FH} cells. To the $CD8^+$ T-cells, which are also specific to islets, antigen presentation is enhanced by Th1 cells by activating dendritic cells and leading to misleading effector $CD8^+$ T-cell. The secretion of pro-inflammatory cytokines interferon-gamma (IFNγ) and TNFα induce beta-cell death by accumulatingTh1 cells to the pancreas. ROS, TNFα amplify the beta-cell death cycle, and IL-1β produced by M1 macrophages in the islets stimulated by Th1-derived IFNγ and TNFα. $CD8^+$ T-cell infiltration inside pancreatic beta cells is increased by resulting inflammation, and through perforin and granzyme B, beta-cell is killed directly. During this process, nT_{regs} and pT_{regs} try to reduce this response via TGF- beta and IL-10[53]. The factors influencing dysregulation of T1Dis illustrated in Figure 3.

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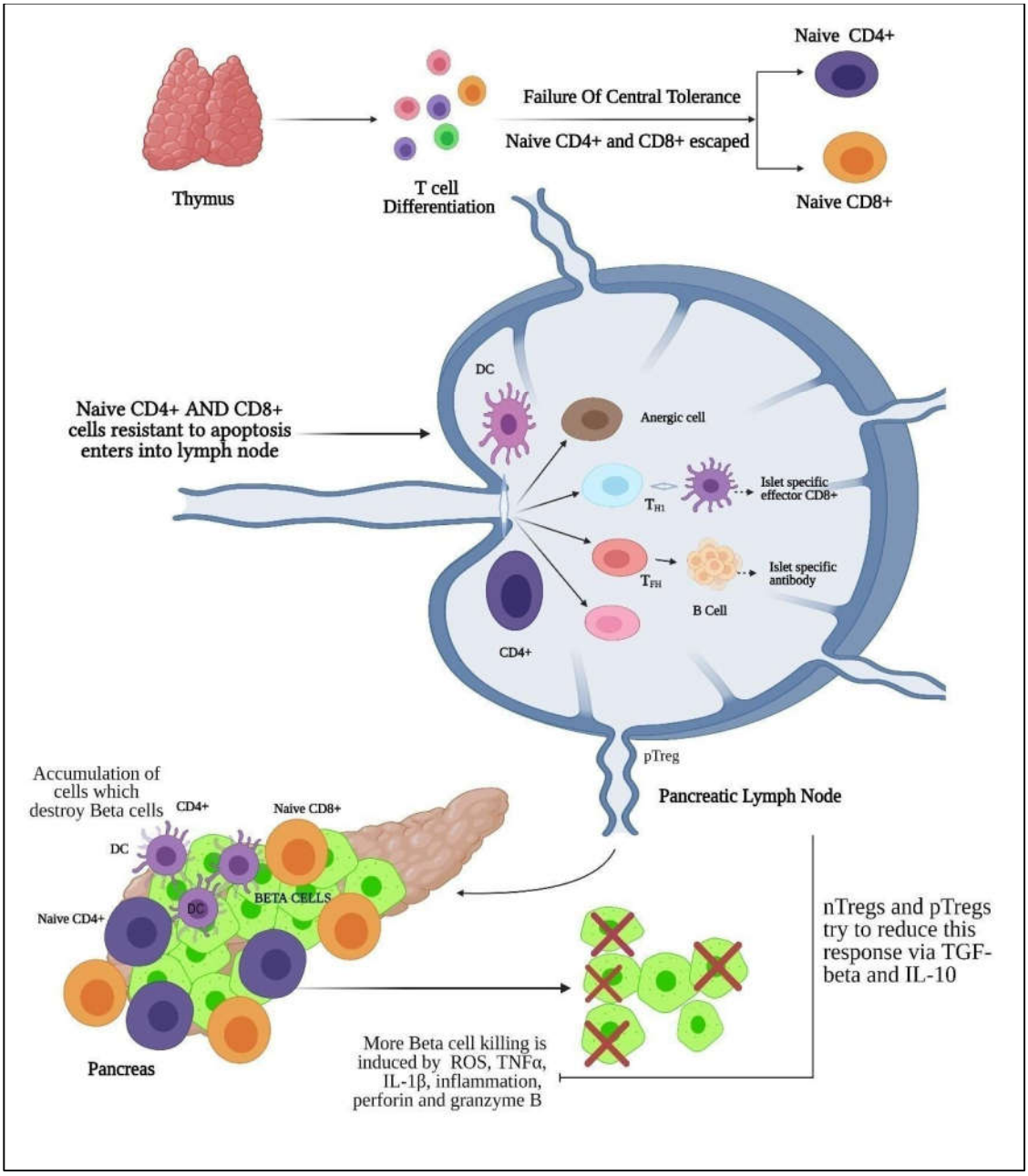

Figure 3. Factors influencing dysregulation of Type 1 diabetes. (A) T-cell differentiation and breakdown of central tolerance **(B)**Naïve CD4+ and CD8+ entry into pancreatic lymph node (**C**) Accumulation of islets specific cells that destroy the pancreas' Beta cells.

Furthermore, in the pathogenesis of T1D, the role of T helper 17 (Th17) cells is investigated. Th17 cells are involved in several inflammatory autoimmune diseases and protect mucosal barriers from opportunistic infections. As discussed earlier, the imbalance between Th17 cells and T regulatory (Treg) also leads to T1D [54, 55]. The differentiation of Th17 is controlled by RORγt (ligand-regulated nuclear receptor), having a binding partner, DEAD-box protein 5 (DDX5), as shown by Huang et al. [56]. The transcription of particular Th17 genes and Th17 cell-mediated inflammatory diseases further coordinated by the interaction between DDX5 and *RORγt*. The *Rmrp* (an evolutionarily conserved nuclear lncRNA) acts as the bridge between DDX5 and ROR *γt interaction*. This indicates that LncRNA *Rmrp* is associated with T-cells in the pathogenesis of type 1 diabetes. In addition to these, patients with cartilage-hair hypoplasia have mutated *Rmrp*. Additionally, in mice, decreased expression of particular Th-17 genes, altered chromatin interaction, and

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reduced interaction between the DDX5 and *RORγt* were obtained due to the mutation in *Rmrp*[56].

3.4. Rheumatoid arthritis (RA):

The metabolic abnormalities that have been derived in naïve $CD4^+$ T-cells in RA patients, when compares with the regular patients, due to the repression of regulatory glycolytic enzyme PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3), leads to reduced pyruvate and lactate production. This repression shunts glucose to the pentose phosphate pathway. As a result, levels of both ATP and Pyruvate are low, and NADPH is high. Due to this PPP shunting, T-cells ignore cell cycle checkpoints, and it leads to hyper proliferation. Due to this hyper proliferation, premature T-cell aging occurs and eventually leads to tissue invasion [57]. Due to increased levels of NADPH, ROS neutralization is observed. The activation of *ATM* (Ataxia telangiectasia mutated) is altered. As the *ATM* is essential in the cell cycle to detect DNA damage, it stops the cell in the G2/M phase and initiates the DNA damage repair. This altered activation leads to the bypass of T-cells (G2/M checkpoint). These $CD4^+$ T-cells hyper proliferate and change from naïve T-cells to memory state early. The altered activation of cell cycle kinase *ATM* leads to hyperproliferative and differentiation biased towards the Th1 and Th17 lineage that accelerates tissue invasion [58].

In RA patients, $CD4^+$ naïve T-cells show various defects, out of which is mitochondrial dysfunction. The damage of mtDNA in the mitochondrial activity of T-cells by losing MRE11A causes suppression of ATP production by impairing the electron transport chain. This mitochondrial failure leads to reduced ROS and fails the redox signalling. This *MRE11A* deficiency causes the shortening of telomere, accelerates the T-cell aging by CD57 induction, and promotes synovitis by invading synovial tissue. MtDNA is recognized by the inflammasome and triggers lytic cell death by activating caspase-1. Due to N-myristoyl transferase one deficiency, AMPK (AMP-activated protein kinase) is misrouted. It fails to prevent activation of mTORC1 (mammalian target of rapamycin complex 1), and it is a hallmark for the generation of short-lived effector T-cell [59].

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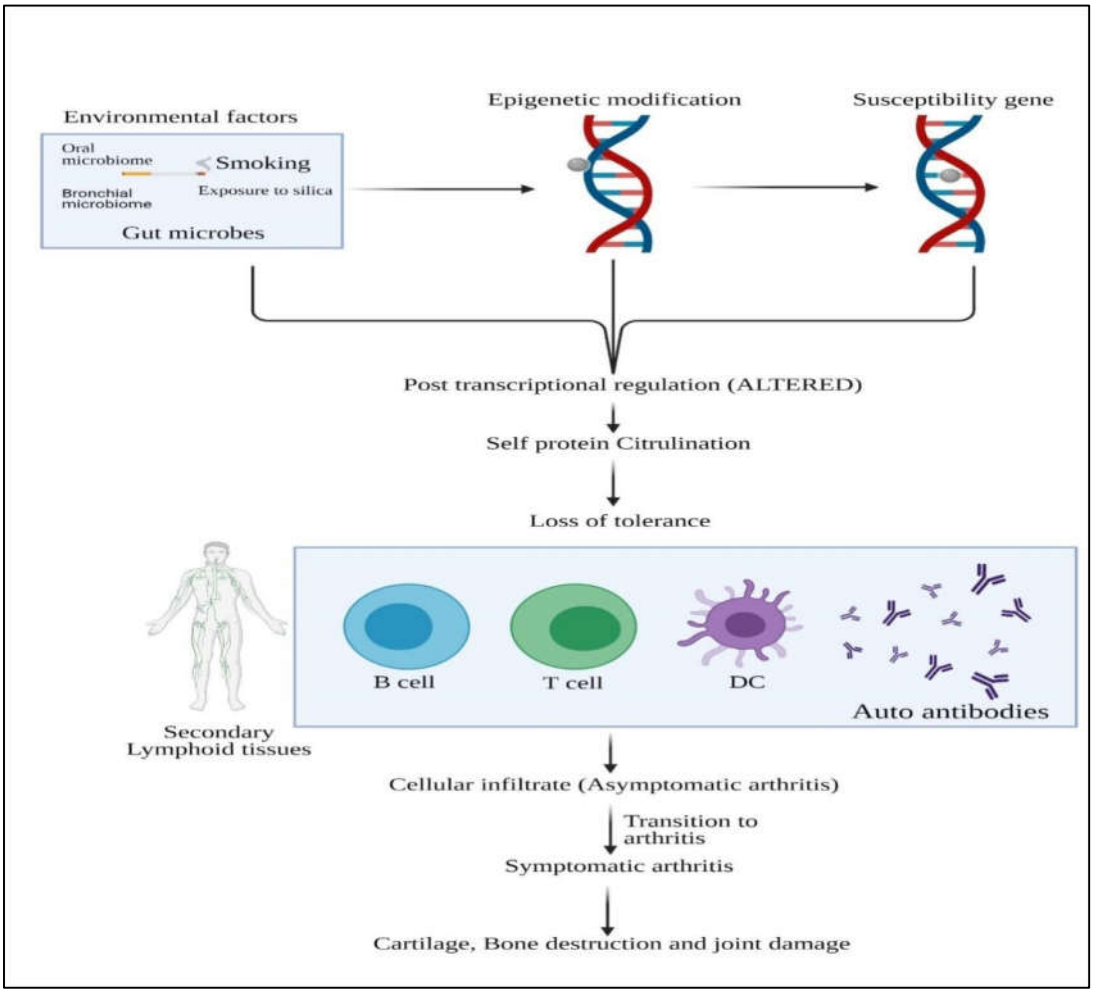

Figure 4. Events that lead to a progression of Rheumatoid arthritis.

In pre-rheumatoid arthritis, epigenetic modification alters the posttranscriptional change, which causes the loss of tolerance in the cellular environment in the synovium. In post-rheumatoid arthritis, transition to arthritis causes cartilage and bone destruction.

In RA, the infiltration of T-cells in the synovial membrane causes the activation of fibroblasts and macrophages. Later, these are transformed into tissue destructive effector cells. The role and activation of T-cells in RA are yet unclear to understand. There is some evidence that is convincing that the role of $CD4^+$ T-cells in the contribution of RA. During preclinical RA development in a cell, post-translational conversion occurs in a matrix protein (such as fibronectin), intracellular proteins of amino acid sequence from arginine to citrulline, and known to be as citrullination. The enzyme, which induces it, peptidyl arginine deiminases. It also presents in oral microbiota *P. gingivalis*, so citrullination may also be influenced by microbiota. Thereby it promotes a generation of ACPAs and RF [29]. Because of citrullination, the altered peptides bind to the MHCs, especially to the shared epitopes. Therefore, this leads to the modifications of own antigens. In joints due to hyperplasia, it triggers cytokine and causes inflammation; this may also lead to autoantigens' transformation [60, 61]. These modifications can be recognized by antigen-presenting cells (APC), and it triggers the immune response. APCs now migrate to lymph nodes and activate $CD4^+$ T-cells. These T-cells activate B cells through Co-stimulation in the germinal centre (GC). B cell stimulation takes place for the synthesis of antibodies that recognizes the self-proteins [29]. Refer to figure 4 for understanding the progression of RA.

In synovium, there is an activation of macrophages by stimulating cytokines such as TNF-α, IL-1, IL-6. This leads to the stimulation of Fibroblast synoviocytes (FLS) which further activates and proliferates. Upon activation, these FLS can migrate from joint to

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joint, termed symmetrical arthritis. FLS assists in stimulating RANKL, and these cytokines lead to the generation of osteoclasts, which lead to bone erosion [62]. FLS also enables proteases (MMPs), which lead to the degradation of cartilage. In the synovium, we can observe the T-cell, which can be ~50% of immune cells. These CD4+ T-cells secrete IL-17, which helps to promote macrophage activity, expression of RANKL and helps in the stimulation of FLS. In the synovial fluid, neutrophils are observed, which allows producing ROS and proteases [29]. In this fluid, immune complexes are observed, which leads to inflammation. Angiogenesis helps increase vascular permeability and increases adhesion molecules. This angiogenesis helps to infiltrate immune cells. This infiltrate of autoantigens causes inflammation [63]. Refer to figure 5 for the pathogenesis of RA.

Interaction between T cell receptor and antigenic peptide associated with HLA class II molecule and between costimulatory molecules: CD28:CD80/CD86 is essential for proper activation of T-cell. In RA, CD4+ T-cells with the HLA-DRB allele are strongly associated and found more aggressive. The majority of RA patients reported that $CD4^+$ T-cells lose the CD28 ($CD4^+CD28^{null}$) expression and gain perforin and granzyme expression thus have tissue-injurious capabilities [64, 65]. T cell-mediated therapy uses abatacept (soluble CTLA4 immunoglobulin) to inhibit the co-stimulation between the CD28 and its ligands CD80/CD86-stimulation. Affinity studies revealed that CTLA4 has more affinity to CD28 than CD80/CD86; thus, competitive cell co-stimulation inhibition [66]. Upon activation of $CD4^+$ T-cell through TCR, PD-1 expression has to be expressed, but it is reduced and leads to a defect in peripheral tolerance and favours autoimmunity in RA patients [67].

The role of Th17 and Tregs in RA, Th17 cells produces IL-17; this IL-17 induces cytokines such as IL-6 and TNF-α. IL-17 also induces macrophage activation and differentiation of osteoclasts. Thus, it promotes bone and cartilage degradation. The balance between Th17/Treg plays an essential role in RA because Foxp3+ Treg cells help in inhibiting autoimmunity and immune tolerance [57, 68]. In RA FLS, the hexokinase 2 (HK2) overexpression induces the level of MMP, IL-6. Using 3-bromopyruvate (BrPA), which inhibits HK2, suppresses dendritic cell activation and cytokine expression, and balancing Th17/Treg may be possible [57].

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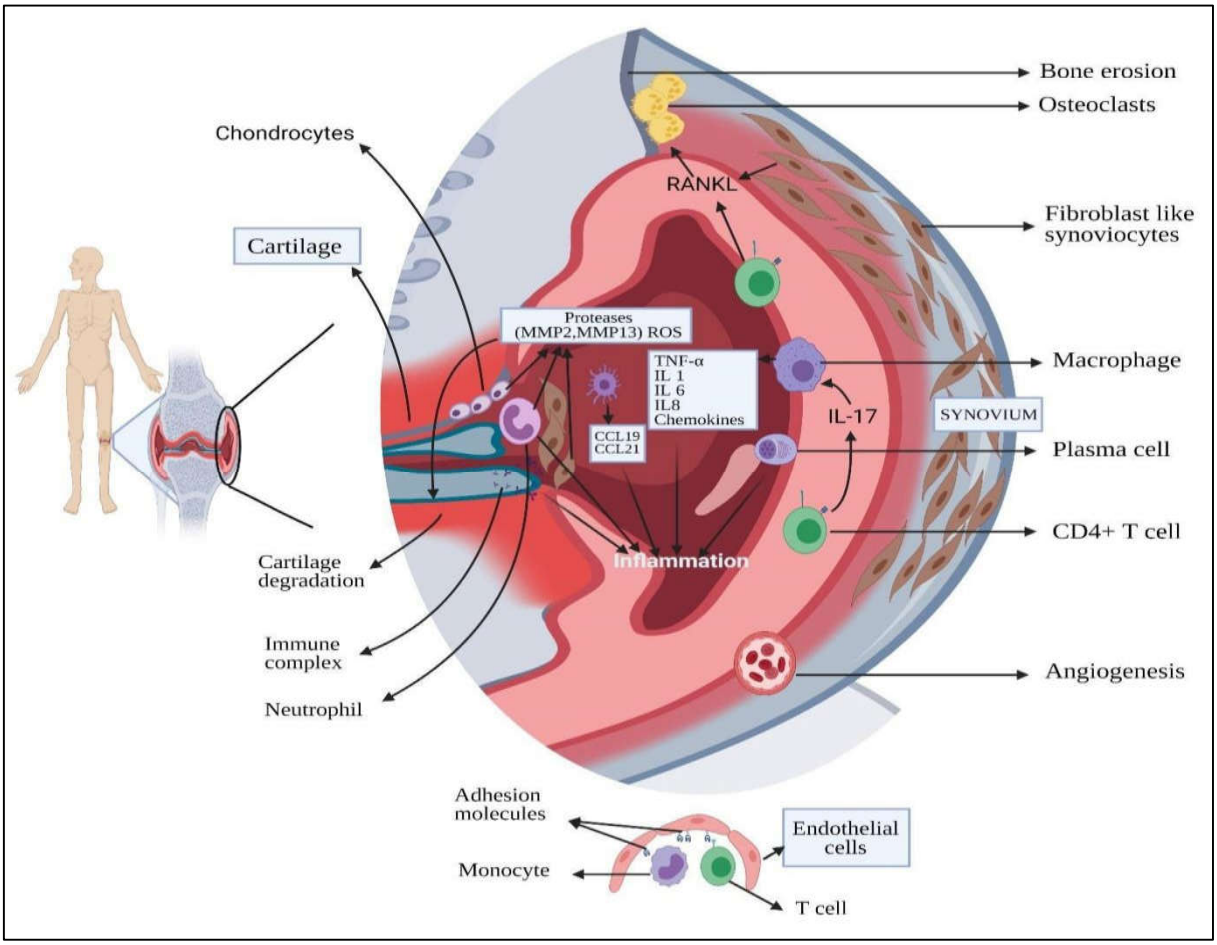

Figure 5. Pathogenesis of Rheumatoid arthritis in bone.

The autoantigens (which enter into the synovium by angiogenesis), FLS, Chondrocytes, Neutrophil, and complex immune interactions lead to cytokine production and tissue damage. Altering ROS and causing bone erosion and cartilage degradation.

4. Role of long non-coding rnas in the pathogenesis of immune disorders

Long non-coding RNAs (LncRNAs) are RNAs having a size of more than 200 nucleotides. LncRNAs lack protein-coding function. In recent years it has been established that LncRNAs have a significant role in the pathogenesis of various diseases because of their ability to influence gene expression directly (by acting on DNA) and indirectly (working on transcriptional factors) [69].

4.1. Systemic lupus erythematosus:

Autoantibody production and accumulation of immune complexes in different parts of body organs and tissues damage of its own body cells and dysregulated cellular homeostasis body function [70]. Nuclear enriched abundant transcript 1 (*NEAT1*) is highly expressed LncRNA in (PBMCs) peripheral blood mononuclear cells in monocytes of the SLE patients compared with healthy controls. *Invitro* study of this LncRNA shows that *NEAT1* regulates LPS-induced expression of IL-6, CCL2, and CXCL10 that plays a role in the pathogenesis of SLE and *NEAT1* acting inflammatory regulator by MAPK signalling pathway [71].

LncRNA growth arrest-specific transcript 5 (GAS5) and its expression was found decreased in B cell and CD4+ T cells of SLE patients compared to healthy individuals. GAS5 affects metabolic state of cell and induces the apoptosis in SLE patients. [74]. The expression of *Linc0949* in SLE patients is lower compared to healthy individuals and it plays a

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role in the regulation of proinflammatory cytokines IL-6 and tumor necrosis factor (TNF-α). The expression of Linc0597 is higher in Lupus Nephritis of sle patients compared to healthy individuals and involves in the innate immunity and proinflammatory cytokine secretion, and production of IL-6, TNF-a and have a role in sle pathogenesis [72][70].

MALAT 1 LncRNA is upregulated in SLE patients and regulate SIRT1 pathway, that induces the expression of IL-21, In sle patients' production of IL-21 had found higher compared with healthy individuals that indicates MALAT1 have a role in the pathogenesis of sle [70][10]. LncRNA taurine upregulated *gene1* (*TUG1)* in human sample of PBMCs is low in SLE patient's correlates with ESR, SLEDAI disease duration, and Lupus Nephritis (LN) approximately 50%- 80% of sle patients have affected by LN. In mice, the expression of TUG1 is upregulated and participate in the protection of NF-kB inhibition on kidney injury. Lnc-DC activates the STAT3 pathway and regulates the expression of T- cell activation, differentiation of Th17, and production of IL-12 in sle patients. Level of Lnc-DC is high in LN patients compared to sle patients. [70] [74]. Refer to Table 1 for the function of LncRNAs.

Table 1. Function and Expression of LncRNAs in SLE.

FUNCTION AND EXPRESSION OF LNCRNA IN SYSTEMIC LUPUS ERYTHEMATOSUS			
LncRNA	**Function**	**Expression**	**References**
GAS5	Induces the apoptosis in sle,	Downregulation in plasma, PBMC. Upregulated in CD4+ T- cell	[70]
MALAT 1	Regulate SIRT1 pathway and increased IL21 expression.	Up regulation	[70][10]
NEAT1	Correlates with SLEDAI. It regulates the expression of IL-6, CCL2, and CXCL10. Activation of IFN and late MAPK pathway.	Upregulation	[70][71]
Linc0949	Regulation of proinflammatory cytokines IL-6 and tumor necrosis factor (TNF-α)	Downregulation	[70][72]
RP11-2B6.2	It regulates the IFN-I pathway through epigenetic inhibition of SOCS1.	Upregulation	[70][74]
TUG1	It was Involved in the protection of NF-kappa B inhibition on kidney injury. correlates with ESR, SLEDAI disease.	Upregulation in kidney	[70][74]
Linc0597	Regulation of proinflammatory cytokines IL-6 and tumor necrosis factor (TNF-α). Higher in LN.	Downregulation in PBMC	[70][74]
Inc-DC	Higher expression in LN patients compared with SLE patients without nephritis. T- cell activation, Th17 proliferation, IL-12 production.	Downregulation	[70]

Aberrant expression of miRNAs (hsa-miR145, hsa-miR-17, and miR-143) is observed [75]. MiR21 regulates the signalling of lymphocytes, and its expression level in CD4+ T cells is associated with SLE disease activity index (SLEDAI) scores. A high expression level of LncRNA *GAS5* and MiR-21 is observed. Qiang et al. (2018) observed the association of long non-coding RNA GAS5 and miR-21 levels in CD4+ T cells [76]. Aberrant expression of miRNAs (hsa-miR145, hsa-miR-17, and has-miR-143) is observed [75]

4.2. Multiple sclerosis:

Like other autoimmune disorders, many LncRNAs, including *BDNF-AS, GAS5, NEAT1, MALAT1, DDIT4, PANDA, TUG1, Linc-MAF, Inc-DC, UCA1, CCAT2, Linc-MAF, IFNG-AS1-OO1, IFNG-AS1-OO3,* and *HOTAIR,* are involved in MS development (Table 2). *BDNF-AS* (brain-derived neurotrophic factor antisense RNA) is a lncRNA that acts as a negative regulator of BDNF by suppressing the transcription of BDNF in nerve cells [77]. *GAS5* lncRNA binds with glucocorticoid receptors' DNA domains, leading to suppression of glucocorticoid receptors [78]. *NEAT1* lncRNA regulates the expression of cytokine

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genes involved in antiviral responses such as interleukin (IL)-8 [79]. *MALAT1* lncRNA regulates the splicing-factor expression and MS-related alternative splicing events in MS [80]. *DDIT4* lncRNA regulates the differentiation of Th17 by affecting the *DDIT4*/mTOR signalling pathway [81]. *Inc-DC* is involved with the differentiation of dendritic cells from human monocytes, regulating the DC activation of cells [82]. *PANDA* and *TUG1* lncRNA play a role in apoptosis of oligodendrocytes by p53 [79]. *UCA1* and *CCAT2* work together to cause cell inflammation and cell cycle arrest [83]. *Linc-MAF* regulates the Th1/Th2 differentiation [84]. *RN7SK RNA* is involved in the regulation of $CD4^{+}$T cells [85]. *FAS-AS1* (Fas cell surface death receptor- antisense 1) is involved in the regulation of Fas receptor [86]. *NRON* lncRNA is involved in the regulation of expression of NFAT [87]. *IFNG-AS1-OO1* and IFNG-AS1-OO3 lncRNA regulate the expression of IFN-y in Th1 cells [88]. *HOTAIR* role associated with Inflammation regulation and Vitamin D [89].

Table 2. Function and Expression of LncRNAs in MS.

FUNCTION AND EXPRESSION OF LNCRNA IN MULTIPLE SCLEROSIS			
LncRNA	**Function**	**Expression**	**References**
SBDNF-AS	Suppress the transcription of BDNF in several cells, so it acts as a negative BDNF regulator	Upregulated	[77]
GAS5	It was involved in suppressing glucocorticoid receptors (GRs) in patients with MS.	Upregulated	[78]
NEAT1	Regulates the expression of cytokine genes involved in antiviral responses such as interleukin (IL)-8	Upregulated	[112]
MALAT1	Regulates the splicing-factor expression and MS-related alternative splicing events in MS	Upregulated	[80]
DNA-damage-inducible transcript 4 (*DDIT4*)	Regulates differentiation of Th17 by affecting *DDIT4*/mTOR signalling pathway	Upregulated	[81]
Inc-DC	Role in DC (dendritic cells) differentiation from human monocytes regulates the DC activation of T cells.	Upregulated	[82]
PANDA (P21 associated ncRNA DNA damage activated)	It stabilizes p53 protein in response to DNA damage and induction of apoptosis in oligodendrocytes.	Upregulated	[79]
TUG1	Involved in induction of apoptosis by p53	Upregulated	[79]
UCA1	Involved in this disorder through mechanisms such as inhibition of cell cycle arrest and promotion of inflammation along with *CCAT2*	Upregulated	[83]
CCAT2	Cytokine induction is involved in inflammatory and cell cycle arrest mechanisms along with *UCA1*.	Upregulated	[83]
Linc-MAF	Regulates the Th1/Th2 differentiation.	Upregulated	[84]
RN7SK RNA	Involved in regulation of CD4+T cells	Upregulated	[85]
FAS-AS1	Involved in Regulation of Fas receptor	Downregulated	[86]
THRIL	Involved in regulation of innate immunity	Upregulated	[86]
NRON	Involved in regulation of expression of NFAT	Downregulated	[113]
IFNG-AS1-OO1	Regulates the expression of IFN-y in Th1 cells	Upregulated	[114]
IFNG-AS1-003	Regulates the expression of IFN-y in Th1 cells	Upregulated	[114]
HOTAIR	The role associated with Inflammation regulation and Vitamin D	Upregulated	[89]

Many miRNAs like miR-155, miR-142-3p, miR326, miR-145, miR-155, miR-22, and miR584 are associated in MS patients [90]. MiR-155 has been associated with other inflammatory disorders and functions like immune cell activation and dysregulation of blood-brain barriers. Glatiramer acetate significantly reduced the expression of MiR-155 and miR142-3p in T cells, therefore, indicating its role in MS pathogenesis [91]. MiR27a, which inhibits the negative regulators of Th17 cell differentiation, is upregulated in MS patients [92]. MiR-128, miR-27b, and miR-340 are up-regulated, promote Th1 differentiation and inhibit Th2 differentiation [93]. MiR-15b (involved in inhibition of Th17 differentiation) is

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found to be down-regulated [94]. MiR-132, which suppress T cell proliferation, downregulation is observed [95]. Up-regulation of miR-9-5p and down-regulation of miR-106a-5p in relapsing phase of MS patients is observed [96]. Association between LncRNA and miRNAs has also been discovered. Down-regulation of *TUG1* attenuates MS through inhibition of inflammation by sponging miR-9-5p via targeting NF-κB1/p50, is an example of association between LncRNA and miRNA [97].

4.3. Type 1 diabetes:

The dysregulation of several LncRNAs is significant in the pathogenesis of Type 1 diabetes (Table 3). The expression of these LncRNAs in patients with respect to healthy individuals could be over-expressed or under-expressed.

Table 3. Function and Expression of LncRNAs in T1D.

FUNCTION AND EXPRESSION OF LNCRNA IN TYPE 1 DIABETES			
LncRNA	**Function**	**Expression**	**References**
MALAT1	Insulin secretion is reduced as a result of over-expression of *MALAT1*. *MALAT1* expression is associated with decreased level of expression of Pancreatic duodenal homeobox-1.	Upregulated	[5]
TUG1	The insulin secretion and programmed cell death is dysregulated which promotes disease progression.	Downregulated	[5]
HI-LNC25	The protein coding gene *GLIS3* is associated with this lncRNA. This gene encodes an islet transcription factor (TF) and responsible for turning on/off other genes associated with insulin secretion.	Downregulated	[104]
βlinc1	This lncRNA regulates the proliferation of islets by encoding certain transcriptional factors. These transcriptional factors play significant role in managing the nearby genes for proper insulin secretion as it is found in the mouse model that glucose homeostasis is lost when *βlinc1* lncRNA found to be dysregulated.	Downregulated	[115]
MEG3	lncRNA play role in insulin secretion and programmed cell death in mouse MIN6 cells and isolated mice. Mutation in this lncRNA results in disturbed glucose homeostasis.	Downregulated	[115]
TUNAR (*HI-LNC78*)	In human islets, glucose-induced insulin secretion was a knockdown of *TUNAR*.	Downregulated	[103]
PLUT (*HI-LNC71*)	In EndoC-βH1 cells, primary islet cells, mouse β cell line MIN6->*PDX1* is a key pancreatic β cell transcriptional regulator. *PLUT* regulates *PDX1*.	Downregulated	[103]
GAS5	By downregulating D-cell cycle protein pathways, proliferation in Min6 β-cell lines and cell cycle G1 can be suppressed and arrested respectively by inhibition of *GAS5*.	Downregulated	[69]
LncRNA uc.322	Insulin secretion and insulin transcription factors (*PDX1* and Foxo1) was elevated	Upregulated	[69]
Lnc13	The activity of the pro-inflammatory STAT1 pathway and secretion of the related chemokines was elevated.	Upregulated	[5]

The over- expression of MALAT*1*in T1D patients could lead to decreased expression of transcriptional factor Pancreatic duodenal homeobox-1 (*PDX1*). The expression is reduced because of the failure of H3 histone acetylation of *PDX1.* [98]. *LncRNA uc.322* have a great role in the increased secretion of insulin and insulin transcription factors (*PDX1 and FOXO1*). The upregulation of this lncRNA provides a great opportunity to the cells of the pancreatic islets for undergoing growth and differentiation. This process is associated with the *SOX6* expression level which lies in the exon region of the *SOX6 gene*. [69]. The over-expression of *Lnc13* in pancreatic β-cells is associated with STAT1 gene activity which is one of the crucial gene in monitoring the functioning of multiple immune system. This lncRNA is also responsible for increased secretion of certain chemokine. Therefore, as a result of increased inflammatory responses in the pancreatic β cells, *Lnc13* is considered to be involved in the pathogenesis of T1D [5].

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TUG1 LncRNA is specific to the pancreas as compared to other tissues LncRNA *TUG1* was significantly expressed in the mouse pancreas, thus playing an essential role in the functioning of β-cell. Both in vivo and in vitro downregulation of *TUG1* causes programmed cell death of β-cells, affecting insulin secretion. The amount of glucose causes the inhibition of TUG1 expression, leading to dysregulation of glucose-stimulated insulin secretion (GSIS) in Min6 cells. Also, insulin secretion is reduced by *TUG1*inhibition in normal mice [69]. Downregulation of *TUG1* in mouse β cells is associated with reduced insulin synthesis and secretion and increased programmed cell death, which leads to hypoglycaemia [99]. In LncRNA *MEG3*, Glucose plays a vital role similar to *TUG1* as it continuously regulates the expression. In normal mice, impaired β-cell apoptosis, insulin synthesis, and secretion are caused by inhibition of *MEG3*. In Min6 cells, downregulation of *MEG3*reduces insulin synthesis by reduced expression of PDX*1* and *MafA* [100]. The development of pancreas and adult β-cell function, *PDX1* plays a critical role.

Similarly, in mature β-cells, *MafA* is mainly expressed. Both *PDX1* and *MafA* are transcription factors specific to islets. They work in a way that enhances the synthesis of insulin by inducing the insulin gene promoter in response to increased blood glucose [101].

In mouse MIN6 cells, the knockdown of *βlinc1* caused the downregulation of various tissue factors (TFs) such as *Pax6, Nkx2.2*, and *Mafb*, specific to islets [102]. It has also been observed that when *βlinc1* is striking out in the adult mice, it results in impaired islet development along with disrupted glucose homeostasis [102]. Interestingly, three significant islet TFs (*Pax6, Nkx2.2,* and *MafB*) and β cell genes on chromosome 2 are mainly regulated by *βlinc1,* all of which are linked with the development of endocrine along with maintaining the morphology of islet [102]. In T antigen-excised EndoC-βH3 cells, decreased insulin content and dysregulated glucose-stimulated insulin secretion are observed by the striking out of lncRNA *TUNAR* (*HI-LNC78*) [103].

In mature β cells, the *GLIS3* gene is downregulated because of the knockdown of trans-acting lncRNA *HILNC25 (LINC01370),* which is also islet-specific [104]. *GLIS3* is a possible gene for type 1 and type 2 diabetes responsible for encoding an islet transcription factor (TF). The role of another LncRNA *PLUTO* in human pancreatic β-cells is found to be downregulated. *PLUTO* is essential as it regulates *PDX1* by affecting local 3D chromatin structure and *PDX1* transcription. In islets derived from donors with T2DM, both *PLUTO* and *PDX1 are* found to be downregulated, and impaired glucose tolerance is observed. This indicates that *PLUTO* plays a vital role in the pathophysiology of insulin secretion [103]. The knockdown of *GAS5* in primary islets and cell lines results in the reduction of *PDX1, MafA*, and *GLUT2*. GLUT2, which acts as a glucose transporter, is essential as GLUT2 inactivation to activate the glucose-sensitive genes, which may cause impaired Glucose-stimulated insulin secretion [105]. In addition to this, proliferation in Min6 β-cell lines could be suppressed, and GAS5 inhibition may arrest cell cycle G1 by impaired regulation of D-cell cycle protein pathways [106].

In β-cells, the disruption of the *Lnc13* gene prevents expression of polyinosinic-polycytidylic acid (PIC)-induced *STAT1* and pro-inflammatory chemokine to some extent. Furthermore, PIC, a viral mimetic, promotes translocation of Lnc13 from the nucleus to the cytoplasm, thereby catalysing the interaction between STAT1 mRNA and poly [rC] binding protein 2(PCBP2). The exchange of Lnc13-PCBP2 regulates the stability of the STAT1 mRNA. Thus, in an allele-specific manner, this interaction assists inflammation in β-cells [107]. Refer to Table 3 for the function of LncRNAs.

The downregulation Peroxisome Proliferator-activated Receptor Gamma (PPARγ) caused a reduction in the Plasminogen Activator Inhibitor-1 (PAI-1), Transforming growth factor-beta 1 (TGF-β1), collagen IV (Col IV), and fibronectin (FN). PPARγ is the target of *miR-377* and is associated with the expression of *TUG1*. The expression level of *miR-377*is downregulated by lncRNA *TUG1* by acting as an endogenous sponge of *miR-377*. Thus, inhibition of PPARγ, the target gene of miR-377, is reduced and eases the extracellular matrix accumulation of mesangial cells. Therefore, helping in understanding the pathogenesis of diabetic nephropathy [108].

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4.4. Rheumatoid Arthritis

In the pathogenesis of RA, miRNAs are dysregulated and responsible for the negative regulation of genes, which are encoding for chemokines, cytokines, and signalling molecules. LncRNAs have been observed in the dysregulation of T cells, synovial cells, PMBCs in RA [72, 109]. *H19* is the first identified LncRNA in RA in the synovial tissues and highly expressed in patients. This expression is due to the upregulation of the pro-inflammation factor Tie-1 in endothelial cells. Tie-1 also induces the downregulation of TLR2 simultaneously. This simultaneous expression suggests a link between the *H19* and Toll-like receptor two signalling pathways [110]. Growth arrest-specific 5 (*GAS5*) is another LncRNA, in which the expression level is reduced in CD4+ cells in patients [72]. LncRNAs *LOC100652951* and *LOC100506036* expressions are upregulated in T cells, and the target of *LOC100506036* is decreasing the expression level of SMPD1/NFAT1 [72, 109]. Another LncRNA *HOTAIR* expression increases in PBMCs, and exosomes. That leads to the migration of the activated macrophages and the activation of MMPs (MMP2, MMP13) [109]. These MMPs may cause the degradation of the cartilage matrix in RA patients [72]. *MALAT 1*, *ZFAS1*, *C5T1*, *lincRNA-p21*, *GAPLINC* are some important LncRNAs in RA [72, 109, 111]. Refer to Table 4 for the function of LncRNAs.

Table 4. Function and Expression of LncRNAs in RA.

FUNCTION AND EXPRESSION OF LNCRNA IN RHEUMATOID ARTHRITIS			
LncRNA	**Function**	**Expression**	**Reference**
H19	Cytokine regulation	Upregulated	[116]
GAS5	Involved in the suppression of the glucocorticoid receptor (GR) through its RNA	Downregulated	[72]
LOC100652951	Production of cytokines	Upregulated	[72]
LOC100506036	expression level of NFAT and SMPD1 and contribute to inflammatory response	UP	[72]
HOTAIR	Involves in the inflammation, migration of macrophages, and activation of MMP2 and MMP13	UP	[72, 109]
MALAT 1	Maintains expression of caspase-3 and caspase-9 for FLS apoptosis	UP	[72]
ZFAS1	Involves in migration and invasion of RA FLS	UP	[117]
C5T1	Regulation of complement system	UP	[72]
lincRNA-p21	DNA damage and T cell apoptosis	Down	[118]
GAPLINC	Cell migration, proliferation, cytokine generation	UP	[119]

MiRNAs expressed in RA, such as miR-6089, are downregulated and target TLR4, inhibiting the inflammatory response. MiR-338-5p is upregulated and leads to apoptosis, migration of FLS, and proliferation by targeting NFAT5 [109]. MiR-548a-3p, miRNA-150-5p, miR-708-5p, miR-143-3p, miR146a/b, miR155, miR16, miR223 are some miRNAs which are dysregulated and expressed in RA patients [109, 111].

Some interactions between LncRNA and miRNA in RA, LncRNA *GAPLINC* interacts with miRNA-382-5p and miRNA-575 and involves regulating FLS by enhancing cell migration and cell proliferation, and cytokine production. *HOTAIR* interacts with miR-138 and causes the inhibition of activation of the NF-κB pathway. LncRNA *ZFAS1* by downregulating miR-27a and modulates the FLS migration and invasion [109, 111]

4.5. Common LncRNAs observed in SLE, MS, T1D, and RA

Many LncRNAs in the development of autoimmunity and inflammation identified using different microarray techniques. The expression of LncRNA is different for various autoimmune diseases, but few are common in some autoimmune disorders (Table 5).

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Table 5. Common LncRNAs in Systemic lupus erythematosus (SLE), Multiple sclerosis (MS), Type 1 diabetes (T1D), Rheumatoid arthritis (RA).

LncRNA	SLE	MS	T1D	RA	Reference
GAS5	↓	↑	↓	↓	[69, 70, 72, 78]
MALAT1	↑	↑	↑	↑	[5, 10, 70, 72, 80]
NEAT 1	↑	↑			[70, 71, 112]
TUG1	↑(Kidney) ↓(PBMC)	↑	↓		[5, 70, 74, 79]

4.6. THERAPEUTIC TARGETS AND APPROACH:

The therapeutic targets have been highlighted by understanding the molecular and cellular mechanisms. To neutralize the inflammatory markers and reduce T cells, several drugs in clinical trials may be tested. Signalling pathways such as NF-kB, MAPKs, and JAK-STAT are associated with autoimmune diseases' progression and are needed to activate the T cell that further helps B cells produce auto-antibodies. Some of the potential therapeutic targets in SLE, MS, and RA are CD28, CD40, cytotoxic T-lymphocyte antigen 4 (CTLA-4), COSL/ICOS, inhibition of TNF-α, inhibition of cytokine upregulation of inflammatory mediators, and by inhibiting the signalling events [33, 120]. There are many drug treatments where these drugs are targeting T-cells; those drugs are discussed in Table 6.

Table 6. Antibodies Targeting Drugs and its properties.

SYSTEMIC LUPUS ERYTHEMATOSUS		
Drug	**Properties**	**Reference**
Abatacept	Competing with CD28 and Blocking co-stimulatory factors	[33] [121][122]
BG9588	Anti-CD40 antibody to treat LN. Acts as CD40 ligand inhibitors.	[33]
Dapirolizumab	Anti-CD40L	[33]
MEDI-570	Anti-ICOS. Antagonistic antibody directed against (ICOS) inducible T-cell costimulatory.	[33]
AMG557	Anti-ICOSL. Its mechanism of action is B7-related protein one inhibitors; Immunomodulators	[33][123]
Theralizumab	Anti-CD28. Its mechanism of action is Antibody-dependent cell cytotoxicity; T lymphocyte stimulants	[33]

MULTIPLE SCLEROSIS		
Drug	**Properties**	**Reference**
Glatiramer	Bind with MHC molecules (HLA DRB1* variants) Competition with various myelin antigens for their presentation to T cells	[124]
Human interferon beta	decreases antigen presentation as well as the proliferation of inflammatory T-cells	[125]
GZ402668	antibody against the human CD52 (huCD52) protein and to assess its effect on cytokine release and lymphocyte depletion	[125]
Mitoxantrone	Inhibit T-cell and macrophage proliferation and impair antigen presentation, as well as the secretion of interferon-gamma, TNFα, and IL-2.	[124]

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Antigen-coupled cell tolerization	co-administration of encapsulated or free Ag with tolerogenic nanoparticles (tNPs) comprised of biodegradable polymers that encapsulate rapamycin are capable of inhibiting Ag-specific transgenic T cell proliferation and inducing Ag-specific regulatory T cells (Tregs)	[126]

RHEUMATOID ARTHRITIS		
Drug	**Properties**	**Reference**
Abatacept	Compete with CD28 and disrupts co-stimulation	[66]
Cyclosporin A	Blocks cytoplasmic signalling to suppress T cell responses	[66]
Tacrolimus (FK506)	Blocks cytoplasmic signalling to suppress T cell responses	[66]
Alemtuzumab	Anti-CD52	[120]
Keliximab	Anti-CD4 monoclonal antibody	[120]
clenoliximab	IgG4 of CD4 antibody	[120]
ABT-122	IL-17 inhibitor	[127]
Bimekizumab	IL-17 inhibitor	[127]

For Type 1 diabetes, currently, not much option is available to treat type 1 diabetes; there is no cure for diabetes. Recently lots of research is taking place in the field of stem cells. According to the Diabetes Research and Wellness Foundation, a scientist from the US is working on human stem cells to be converted into potential beta cells. Some beneficial therapeutic strategies include-

1. Ex vivo Tregs infusion is specific to the pancreas and reacts broadly [53].
2. Peptide-linked apoptotic splenocytes approach to re-educate T_{H1} cells [53].
3. Beta cells that were engineered and resistant to T cell-mediated attack can be employed [53].
4. Beta cell-intrinsic expression enhancement of defence molecules in [53].

Some other therapeutics methods for type 1 diabetes include GLP analogs such as Exenatide and Liraglutide, which stimulate insulin secretion. To satisfy the defects of β cells, insulin injections are also incorporated. With the help of islet neogenesis associated protein (INGAP) peptide therapy, increased islet survival and islet cell regeneration are promoted [128].

Many therapeutic methods are under clinical trials; some include an insulin pump, artificial pancreas, immune modulation, stem cells, and beta-cell encapsulation. Out of all this, some methods are showing promising results along with minor side effects. Immunotherapy/modulation is one of the desired approaches that should be explored more and simple techniques like insulin pumps, showing promising results [129].

Currently, the treatment that is widely adopted for type 1 diabetes is insulin. Various types of insulin are used with different brands. Refer table 7[129].

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Table 6. Types of Insulin and its examples.

INSULIN TYPES	EXAMPLES
Short-acting (regular) insulin	Actrapid (Novo Nordisk), Humulin S (Lilly), InsumanRapid (Aventis), Humulin R and Novolin R
Rapid-acting insulin	Insulin glulisine (Apidra), insulin lispro (Humalog), and Insulin Aspart (Novolog).
Long-acting insulins	Insulin glargine (Lantus, Toujeo Solostar), insulin detemir (Levemir) and insulin degludec (Tresiba)
Intermediate-acting insulins	Insulatard (Novo Nordisk), Insuman Basal (Aventis)

Several other medications like aspirin, high blood pressure, and cholesterol-lowering drugs are also prescribed for some people. Along with this, particular healthy practices like a good diet, exercise, and good sleeping patterns are also recommended.

5. Concluding remarks

With significant advancements in autoimmune-related research, our understanding of autoimmune disorders is consistently increasing. Therefore, questions related to mechanisms, trigger points, and involvement of LncRNAs and the interactions between the LncRNAs-miRNAs can be to the molecular mechanisms involved in autoimmune disorders. However, still, there are many research questions gaps. Here in this review, we summarize the most current knowledge related to epidemiology, the pathogenesis of some of the most common autoimmune disorders associated with T cell dysfunction, LncRNAs, miRNAs, CircRNAs. LncRNAs research in autoimmune disorders is still in the early phase. In autoimmune disorders, many LncRNAs are differentially expressed and also interacts with miRNAs involves in cell signalling pathways which causes dysregulation of T cell differentiation. To find the exact functions of these LncRNAs further experiments and research need to be done Rapid integration of data related to autoimmune disorders and emerging technologies is the essential requirement. In addition, proper annotations of LncRNAs, functional structures, and their interaction is a problem that has to be solved in the future. With data, integration with new emerging technologies, unknown mechanisms of autoimmune disorders and LncRNA involvement, and the interactions between the LncRNAs-miRNAs can be a goal for future treatment of autoimmune disorders.

References

1. Rosenblum MD, Remedios KA, Abbas AK (2015) Mechanisms of human autoimmunity. J Clin Invest 125:2228–2233. https://doi.org/10.1172/JCI78088
2. Theofilopoulos AN, Kono DH, Baccala R (2017) The multiple pathways to autoimmunity. Nat Immunol 18:716–724. https://doi.org/10.1038/ni.3731
3. Huang WJ, Chen WW, Zhang X (2017) Multiple sclerosis: Pathology, diagnosis and treatments (review). Exp Ther Med 13:3163–3166. https://doi.org/10.3892/etm.2017.4410
4. Hauser SL, Cree BAC (2020) Treatment of Multiple Sclerosis: A Review. Am J Med 133:1380-1390.e2. https://doi.org/10.1016/j.amjmed.2020.05.049
5. Taheri M, Eghtedarian R, Dinger ME, Ghafouri-Fard S (2020) Emerging roles of non-coding RNAs in the pathogenesis of type 1 diabetes mellitus. Biomed Pharmacother 129:110509. https://doi.org/10.1016/j.biopha.2020.110509
6. Sparks JA (2019) In the Clinic® rheumatoid arthritis. Ann Intern Med 170:ITC1–ITC15. https://doi.org/10.7326/AITC201901010
7. Yen EY, Singh RR (2018) Brief Report: Lupus—An Unrecognized Leading Cause of Death in Young Females: A Population-Based Study Using Nationwide Death Certificates, 2000–2015. Arthritis Rheumatol 70:1251–1255. https://doi.org/10.1002/art.40512
8. Carter EE, Barr SG, Clarke AE (2016) The global burden of SLE: Prevalence, health disparities, and socioeconomic impact. Nat Rev Rheumatol 12:605–620. https://doi.org/10.1038/nrrheum.2016.137
9. Srivastava P, Abujam B, Misra R, et al. (2016) Outcome of lupus nephritis in childhood-onset SLE in North and Central India: Single-centre experience over 25 years. Lupus 25:547–557. https://doi.org/10.1177/0961203315619031
10. Ye DQ, Wu GC, Hu Y, et al. (2019) Differential plasma expression profiles of long non-coding RNAs reveal potential biomarkers for systemic lupus erythematosus. Biomolecules 9: https://doi.org/10.3390/biom9060206

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 1 July 2022 doi:10.20944/preprints202207.0001.v1

11. Stojan G, Petri M (2018) Epidemiology of systemic lupus erythematosus: An update. Curr Opin Rheumatol 30:144–150. https://doi.org/10.1097/BOR.0000000000000480
12. Goulielmos GN, Zervou MI, Vazgiourakis VM, et al. (2018) The genetics and molecular pathogenesis of systemic lupus erythematosus (SLE) in populations of different ancestry. Gene 668:59–72. https://doi.org/10.1016/j.gene.2018.05.041
13. (2020) Atlas of MS 3 rd edition. 1–37
14. Alcina A, de Abad-Grau MM, Fedetz M, et al. (2012) Multiple sclerosis risk variant HLA-DRB1*1501 associates with high expression of DRB1 gene in different human populations. PLoS One 7:1–9. https://doi.org/10.1371/journal.pone.0029819
15. Gregory SG, Schmidt S, Seth P, et al. (2007) Interleukin 7 receptor alpha chain (IL7R) shows allelic and functional association with multiple sclerosis. Nat Genet 39:1083—1091. https://doi.org/10.1038/ng2103
16. Munger KL, Levin LI, Hollis BW, et al. (2006) Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 296:2832–2838. https://doi.org/10.1001/jama.296.23.2832
17. Houen G, Trier NH, Frederiksen JL (2020) Epstein-Barr Virus and Multiple Sclerosis. Front Immunol 11:3315. https://doi.org/10.3389/fimmu.2020.587078
18. Hemminki K, Li X, Sundquist J, et al. (2009) Risk for multiple sclerosis in relatives and spouses of patients diagnosed with autoimmune and related conditions. Neurogenetics 10:5–11. https://doi.org/10.1007/s10048-008-0156-y
19. Hansen T, Skytthe A, Stenager E, et al. (2005) Risk for multiple sclerosis in dizygotic and monozygotic twins. Mult Scler 11:500–503. https://doi.org/10.1191/1352458505ms1202oa
20. El-Etr M, Vukusic S, Gignoux L, et al. (2005) Steroid hormones in multiple sclerosis. J Neurol Sci 233:49–54. https://doi.org/10.1016/j.jns.2005.03.004
21. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ (2010) Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am 39:481–497. https://doi.org/10.1016/j.ecl.2010.05.011
22. Nam Han Cho (chair) et al. (2017) Eighth edition 2017
23. Centers for Disease Control and Prevention (2014) National Diabetes Statistics Report: Estimates of Diabetes and its Burden in the United States. US Dep Heal Hum Serv
24. Xu G, Liu B, Sun Y, et al (2018) Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: Population based study. BMJ 362:. https://doi.org/10.1136/bmj.k1497
25. Mayer-Davis EJ, Lawrence JM, Dabelea DSA, et al (2017) Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002–2012 and for the SEARCH for Diabetes in Youth Study. 376:1419–1429. https://doi.org/10.1056/NEJMoa1610187.Incidence
26. Smolen JS, Aletaha D, McInnes IB (2016) Rheumatoid arthritis. Lancet 388:2023–2038. https://doi.org/10.1016/S0140-6736(16)30173-8
27. Handa R, Rao URK, Lewis JFM, et al (2016) Literature review of rheumatoid arthritis in India. Int J Rheum Dis 19:440–451. https://doi.org/https://doi.org/10.1111/1756-185X.12621
28. Wang L, Wang FS, Gershwin ME (2015) Human autoimmune diseases: A comprehensive update. J Intern Med 278:369–395. https://doi.org/10.1111/joim.12395
29. Smolen JS, Aletaha D, Barton A, et al (2018) Rheumatoid arthritis. Nat Rev Dis Prim 4:1–23. https://doi.org/10.1038/nrdp.2018.1
30. Okada Y, Eyre S, Suzuki A, et al (2019) Genetics of rheumatoid arthritis: 2018 status. Ann Rheum Dis 78:446–453. https://doi.org/10.1136/annrheumdis-2018-213678
31. McInnes IB, Schett G (2011) Mechanism of Disease The Pathogenesis of Rheumatoid Arthritis. N Engl J Med 365:2205–2219
32. Kurkó J, Besenyei T, Laki J, et al (2013) Genetics of rheumatoid arthritis - A comprehensive review. Clin Rev Allergy Immunol 45:170–179. https://doi.org/10.1007/s12016-012-8346-7
33. Pan L, Lu MP, Wang JH, et al (2020) Immunological pathogenesis and treatment of systemic lupus erythematosus. World J Pediatr 16:19–30. https://doi.org/10.1007/s12519-019-00229-3
34. Tsokos GC, Lo MS, Reis PC, Sullivan KE (2016) New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol 12:716–730. https://doi.org/10.1038/nrrheum.2016.186
35. Horwitz DA (2008) Regulatory T cells in systemic lupus erythematosus: Past, present and future. Arthritis Res Ther 10:1–9. https://doi.org/10.1186/ar2511
36. Yang J, Chu Y, Yang X, et al (2009) Th17 and natural treg cell population dynamics in systemic lupus erythematosus. Arthritis Rheum 60:1472–1483. https://doi.org/10.1002/art.24499
37. Ma J, Yu J, Tao X, et al (2010) The imbalance between regulatory and IL-17-secreting CD4+ T cells in lupus patients. Clin Rheumatol 29:1251–1258. https://doi.org/10.1007/s10067-010-1510-7
38. Mak A, Kow NY (2014) The pathology of t cells in systemic lupus erythematosus. J Immunol Res 2014:. https://doi.org/10.1155/2014/419029
39. Li LJ, Zhao W, Tao SS, et al (2017) Comprehensive long non-coding RNA expression profiling reveals their potential roles in systemic lupus erythematosus. Cell Immunol 319:17–27. https://doi.org/10.1016/j.cellimm.2017.06.004
40. Li Y, Harada T, Juang Y-T, et al (2007) Phosphorylated ERM Is Responsible for Increased T Cell Polarization, Adhesion, and Migration in Patients with Systemic Lupus Erythematosus. J Immunol 178:1938–1947. https://doi.org/10.4049/jimmunol.178.3.1938
41. Tang H, Tan G, Guo Q, et al (2009) Abnormal activation of the Akt-GSK3$β$ signalling pathway in peripheral blood T cells from patients with systemic lupus erythematosus. Cell Cycle 8:2789–2793. https://doi.org/10.4161/cc.8.17.9446
42. Kearney H, Altmann DR, Samson RS, et al (2015) Cervical cord lesion load is associated with disability independently from atrophy in MS. Neurology 84:367–373. https://doi.org/10.1212/WNL.0000000000001186

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 1 July 2022 doi:10.20944/preprints202207.0001.v1

43. Ji Q, Perchellet A, Goverman JM (2010) Viral infection triggers central nervous system autoimmunity via activation of CD8 + T cells expressing dual TCRs. Nat Immunol 11:628–634. https://doi.org/10.1038/ni.1888
44. Henderson APD, Barnett MH, Parratt JDE, Prineas JW (2009) Multiple sclerosis: Distribution of inflammatory cells in newly forming lesions. Ann Neurol 66:739–753. https://doi.org/10.1002/ana.21800
45. Hemmer B, Kerschensteiner M, Korn T (2015) Role of the innate and adaptive immune responses in the course of multiple sclerosis. Lancet Neurol 14:406–419. https://doi.org/10.1016/S1474-4422(14)70305-9
46. Ransohoff RM, Engelhardt B (2012) The anatomical and cellular basis of immune surveillance in the central nervous system. Nat. Rev. Immunol. 12:623–635
47. McMahon EJ, Bailey SL, Castenada CV, et al (2005) Epitope spreading initiates in the CNS in two mouse models of multiple sclerosis. Nat Med 11:335–339. https://doi.org/10.1038/nm1202
48. Coppieters KT, Dotta F, Amirian N, et al (2012) Demonstration of islet-autoreactive CD8 T cells in insulitic lesions from recent onset and long-term type 1 diabetes patients. J Exp Med 209:51–60. https://doi.org/10.1084/jem.20111187
49. Rodriguez-Calvo T, Suwandi JS, Amirian N, et al (2015) Heterogeneity and Lobularity of Pancreatic Pathology in Type 1 Diabetes during the Prediabetic Phase. J Histochem Cytochem 63:626–636. https://doi.org/10.1369/0022155415576543
50. Pociot F, Lernmark Å (2016) Genetic risk factors for type 1 diabetes. Lancet 387:2331–2339. https://doi.org/10.1016/S0140-6736(16)30582-7
51. Thayer TC, Delano M, Liu C, et al (2011) Superoxide production by macrophages and T cells is critical for the induction of autoreactivity and type 1 diabetes. Diabetes 60:2144–2151. https://doi.org/10.2337/db10-1222
52. Unders K, Unders L Diabetes Type 1 Diabetes. 2–6
53. Burrack AL, Martinov T, Fife BT (2017) T cell-mediated beta cell destruction: Autoimmunity and alloimmunity in the context of type 1 diabetes. Front Endocrinol (Lausanne) 8:1–15. https://doi.org/10.3389/fendo.2017.00343
54. Ryba-Stanisławowska M, Skrzypkowska M, MyŚliwiec M, MyŚliwska J (2013) Loss of the balance between CD4+Foxp3+ regulatory T cells and CD4+IL17A+ Th17 cells in patients with type 1 diabetes. Hum Immunol 74:701–707. https://doi.org/10.1016/j.humimm.2013.01.024
55. Ferraro A, Socci C, Stabilini A, et al (2011) Expansion of Th17 cells and functional defects in T regulatory cells are key features of the pancreatic lymph nodes in patients with type 1 diabetes. Diabetes 60:2903–2913. https://doi.org/10.2337/db11-0090
56. Huang W, Thomas B, Flynn RA, et al (2015) DDX5 and its associated lncRNA Rmrp modulate TH17 cell effector functions. Nature 528:517–522. https://doi.org/10.1038/nature16193
57. Pucino V, Certo M, Varricchi G, et al (2020) Metabolic Checkpoints in Rheumatoid Arthritis. Front Physiol 11:1–12. https://doi.org/10.3389/fphys.2020.00347
58. Weyand CM, Zeisbrich M, Goronzy JJ (2017) Metabolic signatures of T-cells and macrophages in rheumatoid arthritis. Curr Opin Immunol 46:112–120. https://doi.org/10.1016/j.coi.2017.04.010
59. Weyand CM, Goronzy JJ (2021) The immunology of rheumatoid arthritis. Nat Immunol 22:10–18. https://doi.org/10.1038/s41590-020-00816-x
60. Scott DL, Wolfe F, Huizinga TWJ (2010) Rheumatoid arthritis. Lancet 376:1094–1108. https://doi.org/10.1016/S0140-6736(10)60826-4
61. Hill JA, Southwood S, Sette A, et al (2003) Cutting Edge: The Conversion of Arginine to Citrulline Allows for a High-Affinity Peptide Interaction with the Rheumatoid Arthritis-Associated HLA-DRB1*0401 MHC Class II Molecule. J Immunol 171:538–541. https://doi.org/10.4049/jimmunol.171.2.538
62. Firestein GS, McInnes IB (2017) Immunopathogenesis of Rheumatoid Arthritis. Immunity 46:183–196. https://doi.org/10.1016/j.immuni.2017.02.006
63. Birch JT, Bhattacharya S (2010) Emerging trends in diagnosis and treatment of rheumatoid arthritis. Prim Care - Clin Off Pract 37:779–792. https://doi.org/10.1016/j.pop.2010.07.001
64. Cope AP, Schulze-Koops H, Aringer M (2007) The central role of T cells in rheumatoid arthritis. Clin Exp Rheumatol 25:S4-11
65. Scheinecker C (2009) The Role of T Cells in Rheumatoid Arthritis. Rheum Arthritis 91–96. https://doi.org/10.1016/B978-032305475-1.50018-5
66. Weyand CM, Goronzy JJ (2006) T-cell-targeted therapies in rheumatoid arthritis. Nat Clin Pract Rheumatol 2:201–210. https://doi.org/10.1038/ncprheum0142
67. Li S, Liao W, Chen M, et al (2014) Expression of programmed death-1 (PD-1) on CD4+ and CD8+ T cells in rheumatoid arthritis. Inflammation 37:116–121. https://doi.org/10.1007/s10753-013-9718-8
68. Okano T, Saegusa J, Takahashi S, et al (2018) Immunometabolism in rheumatoid arthritis. Immunol Med 41:89–97. https://doi.org/10.1080/25785826.2018.1531186
69. Shen S, Chen J, Deng X, Shen L (2018) Long non-coding RNAs in diabetes and diabetic cardiomyopathy. Non-coding RNA Investig 2:54–54. https://doi.org/10.21037/ncri.2018.09.02
70. Zou Y, Xu H (2020) Involvement of long non-coding RNAs in the pathogenesis of autoimmune diseases. J Transl Autoimmun 3:100044. https://doi.org/10.1016/j.jtauto.2020.100044
71. Zhang F, Wu L, Qian J, et al (2016) Identification of the long non-coding RNA NEAT1 as a novel inflammatory regulator acting through MAPK pathway in human lupus. J Autoimmun 75:96–104. https://doi.org/10.1016/j.jaut.2016.07.012
72. Gao Y, Li S, Zhang Z, et al (2018) The role of long non-coding RNAs in the pathogenesis of RA, SLE, and SS. Front Med 5:1–14. https://doi.org/10.3389/fmed.2018.00193

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 1 July 2022 doi:10.20944/preprints202207.0001.v1

73. Luo Q, Li X, Xu C, et al (2018) Integrative analysis of long non-coding RNAs and messenger RNA expression profiles in systemic lupus erythematosus. Mol Med Rep 17:3489–3496. https://doi.org/10.3892/mmr.2017.8344
74. Liao Z, Ye Z, Xue Z, et al (2019) Identification of Renal Long Non-coding RNA RP11-2B6.2 as a Positive Regulator of Type I Interferon Signalling Pathway in Lupus Nephritis. Front Immunol 10:. https://doi.org/10.3389/fimmu.2019.00975
75. Xu H, Chen W, Zheng F, et al (2020) Reconstruction and analysis of the aberrant lncRNA–miRNA–mRNA network in systemic lupus erythematosus. Lupus 29:398–406. https://doi.org/10.1177/0961203320908927
76. Suo QF, Sheng J, Qiang FY, et al (2018) Association of long non-coding RNA GAS5 and miR-21 levels in CD4+ T cells with clinical features of systemic lupus erythematosus. Exp Ther Med 15:345–350. https://doi.org/10.3892/etm.2017.5429
77. Zhang Y, Yan L, Cao Y, et al (2016) Long non-coding RNA BDNF-AS protects local anesthetic induced neurotoxicity in dorsal root ganglion neurons. Biomed Pharmacother 80:207–212. https://doi.org/10.1016/j.biopha.2016.03.003
78. Gharesouran J, Taheri M, Sayad A, et al (2018) The growth arrest-specific transcript 5 (GAS5) and nuclear receptor subfamily 3 group C member 1 (NR3C1): Novel markers involved in multiple sclerosis. Int J Mol Cell Med 7:102–110. https://doi.org/10.22088/IJMCM.BUMS.7.2.102
79. Dastmalchi R, Ghafouri-Fard S, Omrani MD, et al (2018) Dysregulation of long non-coding RNA profile in peripheral blood of multiple sclerosis patients. Mult Scler Relat Disord 25:219–226. https://doi.org/10.1016/j.msard.2018.07.044
80. Tripathi V, Shen Z, Chakraborty A, et al (2013) Long Noncoding RNA MALAT1 Controls Cell Cycle Progression by Regulating the Expression of Oncogenic Transcription Factor B-MYB. PLoS Genet 9:. https://doi.org/10.1371/journal.pgen.1003368
81. Zhang F, Liu G, Li D, et al (2018) DDIT4 and Associated lncDDIT4 Modulate Th17 Differentiation through the DDIT4/TSC/mTOR Pathway. J Immunol 200:ji1601689. https://doi.org/10.4049/jimmunol.1601689
82. Wang P, Xue Y, Han Y, et al (2014) The STAT3-binding long non-coding RNA lnc-DC controls human dendritic cell differentiation. Science (80-) 344:310–313. https://doi.org/10.1126/science.1251456
83. Dastmalchi R, Omrani MD, Mazdeh M, et al (2018) Expression of long non-coding RNAs (UCA1 and CCAT2) in the blood of multiple sclerosis patients: A case-control study. Iran Red Crescent Med J 20:. https://doi.org/10.5812/ircmj.66334
84. Zhang F, Liu G, Wei C, et al (2017) Linc-MAF-4 regulates Th1/Th2 differentiation and is associated with the pathogenesis of multiple sclerosis by targeting MAF. FASEB J 31:519–525. https://doi.org/10.1096/fj.201600838R
85. Santoro M, Nociti V, Lucchini M, et al (2016) Expression Profile of Long Non-Coding RNAs in Serum of Patients with Multiple Sclerosis. J Mol Neurosci 59:18–23. https://doi.org/10.1007/s12031-016-0741-8
86. Eftekharian MM, Ghafouri-Fard S, Soudyab M, et al (2017) Expression Analysis of Long Non-coding RNAs in the Blood of Multiple Sclerosis Patients. J Mol Neurosci 63:333–341. https://doi.org/10.1007/s12031-017-0982-1
87. Fenoglio C, Oldoni E, Serpente M, et al (2018) LncRNAs expression profile in peripheral blood mononuclear cells from multiple sclerosis patients. J Neuroimmunol 324:129–135. https://doi.org/10.1016/j.jneuroim.2018.08.008
88. Ganji M, Sayad A, Omrani MD, et al (2019) Expression analysis of long non-coding RNAs and their target genes in multiple sclerosis patients. Neurol Sci 40:801–811. https://doi.org/10.1007/s10072-019-3720-3
89. Pahlevan Kakhki M, Nikravesh A, Shirvani Farsani Z, et al (2018) HOTAIR but not ANRIL long non-coding RNA contributes to the pathogenesis of multiple sclerosis. Immunology 153:479–487. https://doi.org/10.1111/imm.12850
90. Piket E, Zheleznyakova GY, Kular L, Jagodic M (2019) Small non-coding RNAs as important players, biomarkers and therapeutic targets in multiple sclerosis: A comprehensive overview. J. Autoimmun. 101:17–25
91. Waschbisch A, Atiya M, Linker RA, et al (2011) Glatiramer Acetate Treatment Normalizes Deregulated microRNA Expression in Relapsing Remitting Multiple Sclerosis. PLoS One 6:e24604. https://doi.org/10.1371/journal.pone.0024604
92. Ahmadian-Elmi M, Bidmeshki Pour A, Naghavian R, et al (2016) miR-27a and miR-214 exert opposite regulatory roles in Th17 differentiation via mediating different signalling pathways in peripheral blood CD4+ T lymphocytes of patients with relapsing–remitting multiple sclerosis. Immunogenetics 68:43–54. https://doi.org/10.1007/s00251-015-0881-y
93. Guerau-De-Arellano M, Smith KM, Godlewski J, et al (2011) Micro-RNA dysregulation in multiple sclerosis favours pro-inflammatory T-cell-mediated autoimmunity. Brain 134:3575–3586. https://doi.org/10.1093/brain/awr262
94. Atabaki M, Shariati-Sarabi Z, Barati M, et al (2020) MicroRNAs as the Important Regulators of T Helper 17 Cells: A Narrative Review. Iran J Allergy Asthma Immunol 19:589–601. https://doi.org/10.18502/ijaai.v19i6.4928
95. Hanieh H, Alzahrani A (2013) MicroRNA-132 suppresses autoimmune encephalomyelitis by inducing cholinergic anti-inflammation: A new Ahr-based exploration. Eur J Immunol 43:2771–2782. https://doi.org/10.1002/eji.201343486
96. Majd M, Hosseini A, Ghaedi K, et al (2018) MiR-9-5p and miR-106a-5p dysregulated in CD4+ T-cells of multiple sclerosis patients and targeted essential factors of T helper17/regulatory T-cells differentiation. Iran J Basic Med Sci 21:277–283. https://doi.org/10.22038/ijbms.2018.25382.6275
97. Yue P, Jing L, Zhao X, et al (2019) Down-regulation of taurine-up-regulated gene 1 attenuates inflammation by sponging miR-9-5p via targeting NF-$κ$B1/p50 in multiple sclerosis. Life Sci 233:. https://doi.org/10.1016/j.lfs.2019.116731
98. Ding H, Wang F, Shi X, et al (2020) LncRNA MALAT1 induces the dysfunction of β cells via reducing the histone acetylation of the PDX-1 promoter in type 1 diabetes. Exp Mol Pathol 114:104432. https://doi.org/10.1016/j.yexmp.2020.104432
99. Yin DD, Zhang EB, You LH, et al (2015) Downregulation of lncRNA TUG1 affects apoptosis and insulin secretion in mouse pancreatic β cells. Cell Physiol Biochem 35:1892–1904. https://doi.org/10.1159/000373999
100. You L, Wang N, Yin D, et al (2016) Downregulation of Long Noncoding RNA Meg3 Affects Insulin Synthesis and Secretion in Mouse Pancreatic Beta Cells. J Cell Physiol 231:852–862. https://doi.org/10.1002/jcp.25175

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 1 July 2022 doi:10.20944/preprints202207.0001.v1

101. Guo QS, Zhu MY, Wang L, et al (2012) Combined transfection of the three transcriptional factors, PDX-1, neuroD1, and MafA, causes differentiation of bone marrow mesenchymal stem cells into insulin-producing cells. Exp Diabetes Res 2012:. https://doi.org/10.1155/2012/672013
102. Arnes L, Akerman I, Balderes DA, et al (2016) βlinc1 encodes a long non-coding RNA that regulates islet β-cell formation and function. Genes Dev 30:502–507. https://doi.org/10.1101/gad.273821.115
103. Akerman I, Tu Z, Beucher A, et al (2017) Human Pancreatic β Cell lncRNAs Control Cell-Specific Regulatory Networks. Cell Metab 25:400–411. https://doi.org/10.1016/j.cmet.2016.11.016
104. Morán I, Akerman I, Van De Bunt M, et al (2012) Human β cell transcriptome analysis uncovers lncRNAs that are tissue-specific, dynamically regulated, and abnormally expressed in type 2 diabetes. Cell Metab 16:435–448. https://doi.org/10.1016/j.cmet.2012.08.010
105. Thorens B (2015) GLUT2, glucose sensing and glucose homeostasis. Diabetologia 58:221–232. https://doi.org/10.1007/s00125-014-3451-1
106. Jin F, Wang N, Zhu Y, et al (2018) Downregulation of Long Noncoding RNA Gas5 Affects Cell Cycle and Insulin Secretion in Mouse Pancreatic β Cells. Cell Physiol Biochem 43:2062–2073. https://doi.org/10.1159/000484191
107. Gonzalez-Moro I, Olazagoitia-Garmendia A, Colli ML, et al (2020) The T1D-associated lncRNA Lnc13 modulates human pancreatic β cell inflammation by allele-specific stabilization of STAT1 mRNA. Proc Natl Acad Sci U S A 117:9022–9031. https://doi.org/10.1073/pnas.1914353117
108. Duan LJ, Ding M, Hou LJ, et al (2017) Long non-coding RNA TUG1 alleviates extracellular matrix accumulation via mediating microRNA-377 targeting of PPARγ in diabetic nephropathy. Biochem Biophys Res Commun 484:598–604. https://doi.org/10.1016/j.bbrc.2017.01.145
109. Wang J, Yan S, Yang J, et al (2020) Non-coding RNAs in Rheumatoid Arthritis: From Bench to Bedside. Front Immunol 10:1–9. https://doi.org/10.3389/fimmu.2019.03129
110. Wang B, Suen CW, Ma H, et al (2020) The Roles of H19 in Regulating Inflammation and Aging. Front Immunol 11:1–11. https://doi.org/10.3389/fimmu.2020.579687
111. Liu W, Sheng L, Nie L, et al (2020) Functional interaction between long non-coding RNA and microRNA in rheumatoid arthritis. J Clin Lab Anal 34:1–6. https://doi.org/10.1002/jcla.23489
112. Imamura K, Imamachi N, Akizuki G, et al (2014) Long Noncoding RNA NEAT1-Dependent SFPQ Relocation from Promoter Region to Paraspeckle Mediates IL8 Expression upon Immune Stimuli. Mol Cell 53:393–406. https://doi.org/10.1016/j.molcel.2014.01.009
113. Kalliolias GD, Ivashkiv LB (2016) TNF biology, pathogenic mechanisms and emerging therapeutic strategies. Nat Rev Rheumatol 12:49–62. https://doi.org/10.1038/nrrheum.2015.169
114. Hosseini A, Teimuri S, Ehsani M, et al (2019) LncRNAs associated with multiple sclerosis expressed in the Th1 cell lineage. J Cell Physiol 234:22153–22162. https://doi.org/10.1002/jcp.28779
115. Mirza AH, Kaur S, Pociot F (2017) Long non-coding RNAs as novel players in β cell function and type 1 diabetes. Hum Genomics 11:1–10. https://doi.org/10.1186/s40246-017-0113-7
116. Stuhlmüller B, Kunisch E, Franz J, et al (2003) Detection of Oncofetal H19 RNA in Rheumatoid Arthritis Synovial Tissue. Am J Pathol 163:901–911. https://doi.org/10.1016/S0002-9440(10)63450-5
117. Ye Y, Gao X, Yang N (2018) LncRNA ZFAS1 promotes cell migration and invasion of fibroblast-like synoviocytes by suppression of miR-27a in rheumatoid arthritis. Hum Cell 31:14–21. https://doi.org/10.1007/s13577-017-0179-5
118. Spurlock III CF, Tossberg JT, Matlock BK, et al (2014) Methotrexate Inhibits NF-κB Activity Via Long Intergenic (Noncoding) RNA–p21 induction. Arthritis Rheumatol 66:2947–2957. https://doi.org/https://doi.org/10.1002/art.38805
119. Mo BY, Guo XH, Yang MR, et al (2018) Long Non-Coding RNA GAPLINC Promotes Tumor-Like Biologic Behaviors of Fibroblast-Like Synoviocytes as MicroRNA Sponging in Rheumatoid Arthritis Patients. Front Immunol 9:702. https://doi.org/10.3389/fimmu.2018.00702
120. Alghasham A, Rasheed Z (2014) Therapeutic targets for rheumatoid arthritis: Progress and promises. Autoimmunity 47:77–94. https://doi.org/10.3109/08916934.2013.873413
121. Wofsy D (2014) Treatment of lupus nephritis with abatacept: The abatacept and cyclophosphamide combination efficacy and safety study. Arthritis Rheumatol 66:3096–3104. https://doi.org/10.1002/art.38790
122. Herrero-Beaumont G, Martínez Calatrava MJ, Castañeda S (2012) Mecanismo de acción de abatacept: Concordancia con su perfil clínico. Reumatol Clin 8:78–83. https://doi.org/10.1016/j.reuma.2011.08.002
123. Cheng LE, Amoura Z, Cheah B, et al (2018) Brief Report: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multiple-Dose Study to Evaluate AMG 557 in Patients With Systemic Lupus Erythematosus and Active Lupus Arthritis. Arthritis Rheumatol 70:1071–1076. https://doi.org/10.1002/art.40479
124. Koriem KMM (2016) Multiple sclerosis: New insights and trends. Asian Pac. J. Trop. Biomed. 6:429–440
125. Faissner S, Plemel JR, Gold R, Yong VW (2019) Progressive multiple sclerosis: from pathophysiology to therapeutic strategies. Nat. Rev. Drug Discov. 18:905–922
126. LaMothe RA, Kolte PN, Vo T, et al (2018) Tolerogenic Nanoparticles Induce Antigen-Specific Regulatory T Cells and Provide Therapeutic Efficacy and Transferrable Tolerance against Experimental Autoimmune Encephalomyelitis. Front Immunol 9:2. https://doi.org/10.3389/fimmu.2018.00281
127. George G, Shyni GL, Raghu KG (2020) Current and novel therapeutic targets in the treatment of rheumatoid arthritis. Inflammopharmacology 28:1457–1476. https://doi.org/10.1007/s10787-020-00757-9

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 1 July 2022 doi:10.20944/preprints202207.0001.v1

128. Tiwari P (2015) Recent trends in therapeutic approaches for diabetes management: A comprehensive update. J Diabetes Res 2015:. https://doi.org/10.1155/2015/340838
129. Pathak V, Pathak NM, O'Neill CL, et al (2019) Therapies for Type 1 Diabetes: Current Scenario and Future Perspectives. Clin Med Insights Endocrinol Diabetes 12:. https://doi.org/10.1177/1179551419844521