Antibody Production and Autoimmune Response in Lupus

By Group #6: McKenna Dunn, Shahnaz Ghahremani, Daniel McDonough, Tenny Oguntolu, Wesley Paul

INTRODUCTION/BACKGROUND:

Cell biology is the study of cell structure and its function. Revolving around the concept that the cell is the fundamental unit of life, and focuses on a detailed understanding of the tissues, organisms, and how cells compose and message one another. The immune system is a core construct of multicellular organisms, and a key concept of cell biology. The immune system relies on several cells signaling to one another and passing information, but when distorted, this signaling can result in unintuitive processes. Systemic Lupus Erythematosus (SLE), the topic we will be focusing on, tricks antibodies into attacking healthy cells. This phenomenon has been known of and studied about for several decades, yet only slow advances have been made.

Lupus is known to be the multisystemic inflammation that results from abnormal immunological functions. Over 1.5 million people in the U.S. alone have lupus, or simply SLE. Such a common phenomenon that lurks within the genetic material that makes up all life can be fatal (although rare) and is a danger to the human population. Causing fatigue, rashes and joint pain, this disorder causes a great weight on the American people and the world's state of productivity. It's hereditary nature through passing down predisposition to itself shows no signs of stopping and is carried throughout the carriers lifetime. This disorder has been reported by journalists to decrease the chances of women in the workplace of higher education and reportedly results in several cognitive symptoms such as headaches, dizziness, behavior changes, vision problems, and even strokes or seizures. This disorder affects the world not only through the individual but also takes a toll on others around them. Being studied for several decades, it is imperative that we as a species find preemptive measures for this disorder[6].

The state of the current cell biological research regarding individuals afflicted with SLE shows that there are many unresolved questions and problems that still exist. Measuring the activity of lupus in patients that are

affected remains a challenge, due to the complexity of the disease. And although, few disease-producing factors have been identified, there has not been any research that has focused in isolating and removing these factors. Currently, novel research has been conducted with the intention of understanding the pathological workings of SLE. Characterised by a myriad of immune system aberrations, involving B cells, T cells, and cells of the monocytic lineage it often results in polyclonal B cell activation, increased numbers of antibody producing cells, autoantibody production, and immune complex formation. We wish to examine closer to find a common factor of lupus causation, so more effective and efficient targeted treatments can be discovered and improve the quality of life for those who suffer from this autoimmune disease. By shifting focus towards the development of new diagnosis methods, we hypothesize that a universal treatment for lupus could be possible in theory.

RESULTS AND INTERPRETATION

Systemic lupus erythematosus (SLE), a systemic autoimmune disease is already known to be linked with B-cell and T-cell overreactivity. Causes of the diffusal of B-cell over-reactivity are unclear, but studies have shown that candidates include; disturbed activation thresholds and ineffective negative selection of B-cells, lack of immunoregulatory functions, secondary effects of an overactive inflammatory environment, and disturbed cytokine production by non-B immune cells. These mechanisms are not mutually exclusive and may operate to varying extents and at varying times in SLE. However as stated previously, T-Cells are also involved and the tested causes were only involved in B-cells. So, in order for a universal fix if must also alleviate the T-Cell factor. The possibility of a common tunnel for autoimmunity between the two cells lie in the abnormal selection during T cell-dependent B-cell responses on the other[1]. Studies have shown that there is a chance that some "apoptotic material" bound to the surface of follicular dendritic cells positively selects autoreactive B cells that arise from non-autoreactive B-cell precursors as a result of somatic hypermutation and thereby promotes the peripheral emergence of autoimmunity. This discovery however only affects the interaction of T-cell and B-cells and does not solve the problem of direct Antigenic Stimulation.

In addition, genomic studies have identified a number of candidate genes, such as BANK1, BLK, IL-21R, CD40, Lyn, PTPN22, TNFAIP3, FcγRs, and Blimp-1, that are associated with SLE and other autoimmune diseases and could predispose to increased B-cell responsiveness[1]. Another genomic was performed in 2013 to test whether anti-dsDNA or anti-nucleosome antibodies were better indicators of SLE for the purpose of diagnosis (Saigal et al. 2013). The researchers performed statistical analysis on the presences of these antibodies in patients with both SLE and other autoimmune diseases. Researchers collected blood samples from an observational sample of hospital patients, 40 of which were cases of SLE and 80 of which were the control group that of which consisted of 40 healthy blood donors and 40 cases of other systemic autoimmune diseases (SAD). To test the detection of antibodies in the blood samples, "commercial quantitative enzyme linked immunosorbent assay" (ELISA) was used. Samples were incubated and a substrate solution was added to identify the concentration of the antibodies within the sample. The SLE Disease Activity Index (SLEDAI) was used to assess SLE activity. Statistical analysis for sensitivity and specificity of anti-nucleosomes and anti-dsDNA was then performed for the diagnosis of SLE and lupus nephropathy, inflammation of the kidney[2].

The results of the study for diagnosis of SLE by anti-dsDNA showed a sensitivity of 37.5% and specificity of 97.50%. The diagnosis of SLE by anti-nucleosome was a sensitivity of 47.50% and specificity of 100%. In the population sample, the anti-nucleosome antibodies showed better positivity, but when SLEDAI was used to assess the SLE activity anti-dsDNA showed a better positive correlation with the SLEDAI score. Both antibody-SLEDAI correlations were positive. There was not a significant difference in the statistical analysis to prove one antibody a stronger indicator of SLE[2]. By identifying the better indicator of SLE further research can focus on the mechanisms of action of the antibodies to further understand how their function is initiated to cause the disease and its function. Further studies can be done on how anti-dsDNA and anti-nucleosomes are affect cell signaling. In addition, further research will help find a standard to define and measure the disease.

A study in 2005 was performed to assess the role, efficiency, and safety of T cell vaccinations (TCV) in humans affected by SLE (Z-G Li et al. 2005). The assumption was that autoreactive T cells might induce the autoimmunity of human SLE, and the inhibition of these T cells might decrease the severity of the disease. This led to a group of scientists exploring the use of TCV to treat patients afflicted with SLE in a similar approach to other autoimmune diseases. TCV is a unique type of immunization where patients are injected with inactive autoreactive T cells to reduce severity of an autoimmune disease. At the time that this research was published, this was the first study to consider the application of inactivated autoreactive TCV for human SLE. The results from this article, had shown that T cell immunization was safe since no anti-T cell antibodies were produced in five of the six patients with SLE[3]. This use of TCV may have many benefits if further research regarding its mechanisms are explored in greater detail. This article represents the first example of how the applications of new treatments could improve the quality of life for those suffering from SLE.

In 2009, research was performed to investigate the prevalence of CD4 T cells in the development in SLE (Bubier et al. 2009). *BXSB* mice bearing the Yaa mutation (Y chromosome-linked autoimmune acceleration) were used as the model system of the research. These affected mice present the most severe disease characteristics and have elevated IL-21 at the transcriptional and protein levels. IL-21 is a cytokine produced by CD4 T cells that affects the differentiation and function of multiple cell types such as T and B cells. The study was conducted by comparing deficient IL-21 receptors to *BXSB*-Yaa mice to test for multiple parameters that are characteristic in SLE[4]. After further isolation testing on the mice, it was discovered that IL-21 had been specifically produced by ICOS+ CD4+ splenic T cells[5]. The results showed that incorrect signaling and receptors of IL-21 increase the chances of SLE characteristics.

The results from this article show that an abnormal population of CD4 T cells is stemmed from IL-21 and thus further research in the future should be focused on the how IL-21 is specifically originated in different people and what factors cause IL-21 to produce an abnormal population of CD4 T cells. The abnormal population of CD4 T cells is what spurs the development of life-threatening autoimmune diseases such as

systemic lupus erythematosus (SLE). Further research could also be conducted on how signaling in B cells effects the differentiation and function of T cells.

Clinical studies are currently being run to focus on targeted therapy for patients that suffer from SLE. Many of these studies focus on cell-depleting therapies, cytokine blockade, and anti-tumor necrosis factor therapy (Anolik et al. 2005). It has been identified that B lymphocytes play a critical role in SLE by both auto-antibody dependent and independent systems. Researchers have emphasized focusing on interactions between B and T cells since they are critical to the development of SLE. Many treatments options focus on managing the severe symptoms of SLE and not eradicating the origin of the disease itself. Many patients with SLE suffer from lupus nephritis, which is the inflammation of the kidneys. Medication can be administered to reduce the harmful effects of symptoms like lupus nephritis, however, there is still no cure for the lethal autoimmune disease of SLE.

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