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Introductory Chapter: Autoantibodies and Their Types

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1. Introduction

Autoantibodies are groups of antibodies that are directed against body's own antigen. These autoantibodies are generated against different types of antigens in various autoimmune diseases. Clinical symptoms of systemic autoimmune diseases are characterized by the involvement of various organs in addition to the production of non-organ specific autoantibodies. These autoantibodies in autoimmune diseases are associated with a specific clinical symptom within a spectrum [1]. Most of the autoantibodies have diagnostic and prognostic importance with respect to their associated disease and all of these are not involve in the pathogenesis of these diseases. Most autoantibodies are mainly used as biological markers for certain disease but they do not actually reflect the pathophysiological process underwent during the course of the disease, **however, many autoantibodies also have a pathogenetic roles such as anti-nuclear antibodies and anti-tTG antibodies in celiac disease**. For example, autoimmune hepatitis is a chronic disease which is characterized by various clinical, histological as well as immunological characteristics including production of circulating autoantibodies and high serum concentration of gamma globulin [2]. These autoantibodies are very important for the correct diagnosis and classification of autoimmune liver disease [3] and they are not related with the pathogenesis of autoimmune hepatitis. However, some of the systemic autoimmune disease relating these autoantibodies in the sense that their levels are changes during the course of the disease. These include anti-double stranded DNA antibodies in systemic lupus erythematosus (SLE) and anti-neutrophil cytoplasmic autoantibodies in the vasculitis [4]. Other types of antibodies like anti-nucleosome and anti-CIq autoantibodies can function as both markers of the disease activity as well as pathogenic autoantibodies in SLE [5, 6].

The history of the autoantibodies goes back to 1940s, when two types of antibodies (anti-nuclear antibodies; ANA and rheumatoid factors; RF) were discovered as the serum factors that bind to nuclear antigen IgG, respectively [7, 8]. ANA and RF considered being a diagnostic

feature of SLE but their role in disease pathogenesis remains elusive. In the last two decades, the effects of autoimmune diseases have been gown up to such an extent that it can explains both points of views, as clinically and diagnostically. The pathogenic mechanisms of these autoimmune diseases help to contribute to the discovery of new autoantibodies and new area of research, based on diagnostic and prognostic value, have been developed. Determination of these autoantibodies in the diagnosis of autoimmune disease is important because they are sometime showing nonspecific, unclear character and even shared by different autoimmune diseases [9]. For most of the autoimmune diseases, classification criteria include the determination of autoantibody that helps in final diagnosis. They are important not only for diagnostic perspective but also for prognostic value. Some of these autoimmune have been associated with the clinical manifestation of the disease, therefore estimation of these autoantibodies pattern in the patients might helpful to detect severity of the disease that can be useful for the need of correct therapy [10].

Several autoimmune diseases show chronic conditions that develop over the period of years and are characterized by the production of autoantibodies that actually present much before the actual onset of the disease. These autoantibodies are called as predictive autoantibodies that are present (or appear) in the blood much before systemic pathological conditions arise during the course of the disease. Detection of specific autoantibodies is the most important clinical and experimental evidence to predict any autoantibodies as biomarker for that autoimmune disease [11]. The levels and variety of autoantibodies may vary according to the disease that may function as predictive biomarker. While the experimental importance of autoantibodies has been well recognized in many clinical conditions, its clinical utilization remains to be short for most of the diseases [12]. Autoimmune diseases are caused by various autoimmune responses, generated during the course of the disease. The generations of immune responses are characterized by the appearance of the autoantibodies in the serum, therefore recognition of a particular autoantibody showed the path to recognize an autoimmune disease. Initially, the clinical symptoms of the disease are not emerges in full flash although these autoantibodies may arises much before these symptoms and actual onset of the disease. So, the symptoms are not visible, so the physician did not think to test these autoantibodies initially [13]. Therefore, test for these autoantibodies could be done in pre-screening on various groups of population to identify the individuals who are susceptible for the development of the disease at an early stages and treatment should be given to prevent the actual occurrence of the disease. Multiple tests have been given for these patients for different autoimmune diseases, and recommendations are given to done multiple test for the patient who are having autoimmune disease [14]. However, disease related autoantibodies cannot develop simultaneously, although they are present much before the actual disease onset, and many of these autoantibodies are antigen specific, so using a panel of different autoantibodies set, might helpful to increase the sensitivity and prediction of the test [15].

Autoimmunity arises due to the failure of the immune system to be self-tolerance, which is mediated through the involvement of T and B cells [16]. Most of the autoimmune disease involves T cell, which play an important role in dysregulation and autoimmune aggression and during this process large amount of autoantibodies are also produced. These

autoantibodies plays not only in key pathogenic role in some diseases including SLE and Graves' disease but also found in some disease in which they play minor pathogenic role and can act as important biomarker [17, 18]. Cytokines, in addition to the production of autoantibodies, play important role in the generation of autoimmune response (especially pro-inflammatory cytokines: except multiple sclerosis), they are produced in response to the viral invasion and are deeply involved in various autoimmune process. Under normal condition, anti-cytokine antibodies response have been develop in healthy normal individual that is consider to be normal physiological process to control various immune response. These responses are for limited time initially, and then the concentration of these autoantibodies increases, reaching a threshold and then coming up to its normal concentration after few weeks. This process also occurs in some pathological conditions including autoimmunity and autoantibodies develop as a result of these processes might be used as prognostic marker for monitoring the disease [19].

2. Different types of autoantibodies

2.1. Anti-cytokine autoantibodies

Autoantibodies against various types of cytokines have been described not only in normal individuals but also in patients with different infectious and immuno-inflammatory disease [20]. These include interferon (α, β, and γ), interleukin (α, 2, 4, 6, 8 and 10), nerve growth factor, chemokine (α and β), leukemia inhibitory factor, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor (α and β) and receptor, which are found to be in normal individuals and patients with various disorders. In autoimmune disease, these autoantibodies can function as prognostic biomarkers that may even show negative (auto-antibodies against IL-18 and IL-1α in RA) or positive (autoantibodies to IL-6 in systemic sclerosis) results [21]. The autoantibodies against cytokines found to be pathogenic that makes autoimmune patients more susceptible to other diseases. There are various autoimmune diseases including rheumatoid arthritis, multiple sclerosis, systemic sclerosis, SLE, autoimmune polyendocrine syndrome type 1, in which neutralizing autoantibodies against cytokines have been described. The affinity of anti-cytokine autoantibodies may depend on the function of cytokine during various immune responses. For example, pro-inflammatory cytokines such as interleukin-1α, -6, -8, TNF-α and GM-CSF, have more frequently autoantibodies, whereas anti-inflammatory cytokines like interleukin-10 and TGF-β, have autoantibodies that were reported rarely [22–24]. However, most of these studies does not provide sufficient evidences for the functional effects of these autoantibodies, which might helpful to describe their role in various autoimmune diseases and capitalize them for future therapies. There are few pro-inflammatory cytokines that play important role in joint aggression in rheumatoid arthritis [25, 26]. Autoantibodies against IL-1alpha can be worked as an important prognostic marker for early detection of RA [27] and several parameters of RA disease activity and severity was found to be significantly lower in those patients who have high levels of anti-IL-1α autoanti-bodies in comparison to those who have low levels of these autoantibodies. Autoantibodies

showed neutralizing effects on the function of IL-1α by inhibiting thymocytes proliferation in the sera of RA patients [28]. These autoantibodies were also detected in the patients with systemic sclerosis. Autoantibodies against IL-1α have been secreted in high amount in the skin [29]. These autoantibodies have also been found in other dermal diseases; for example, psoriasis and pemphigus, that are supposed to be involve in the regulation of inflammation of skin [30].

2.2. Antinuclear autoantibodies (ANA)

Autoimmune hepatitis is the first disease in which autoantibodies had been clearly associated. In 1960s, these autoantibodies were detected by indirect immunofluorescence assay in the diagnosis and prognosis of autoimmune hepatitis. ANA directed against various nuclear components including single or double stranded DNA (s- or ds-DNA), transfer RNA, histone and other nuclear components [31–33]. There are various other nuclear components which are targeted by these autoantibodies but are not related with autoimmune hepatitis including s-DNA and ds-DNA, chromatin, histones, hnRNP, A_2/B_1, cyclin A, and centromere of the chromosomes [34]. These autoantibodies may arise due to the mistake in identifying normal nuclear components as foreign and dangerous. Once this happen, they identify natural occurring protein as foreign and they are called as autoantibodies because they are produce against own antigen. These autoantibodies start chains of reactions causing inflammation and attack itself. So they also start to target normal protein in the nucleus of the cell and they are called antinuclear antibodies. Although, we all have autoantibodies but they are present in very small amount and they remain silent in the body until and unless some factors may trigger these autoantibodies to be active against normal nuclear components. Once these autoantibodies attack on the self nuclear components, they may trigger various diseases including systemic lupus erythematosus, scleroderma, Sjogren's syndrome, polymyositis/dermatomyositis, etc. Increased level of ANA is seen in almost all the systemic rheumatic disease which either showed sometime high, sometime loose association between a particular type of ANA and a particular type of rheumatic disease. Most of these autoantibodies directed against either nucleic acids or protein close to the nucleic acid. For example, the most common antigen in SLE is nucleosomes. Nucleosomes form the building blocks of chromatin molecule and play an important role in the compaction of DNA in the nucleus. ANA directed against DNA, considered to be as diagnostic maker and hallmark of SLE. Antibodies against histones were also reported in various studies that also proven to be an important marker for SLE. Other important antigen for ANA is small nuclear ribonucleoprotein (snRNP) particles that are formed from a capped small nuclear RNA molecule and polypeptide. In addition, other antigens from the cytoplasmic relevance to ANA binding are ribosomal RNP and aminoacyl tRNA synthetase [35]. ANA play an active role in SLE since these autoantibodies bind to the antigen that may be present in the circulation or their immune complexes are deposited in the tissue that leads to inflammation and subsequent disease features. Either anti-DNA or anti-DNA complexes were involved in the induction of lupus nephritis. In addition, anti-DNA antibodies against various protein molecules are also found in SLE that plays an important role in the etiopathogenesis of this disease [36–40].

2.3. Anti-citrullinated protein antibodies and anti-CCP antibodies

These are the autoantibodies that are induced against any peptide or protein that are citrullinated. They are present in the majority of the patients suffering from RA. Clinically, this antigen can be frequently used to detect antibodies in the serum of RA patients. It has been assumed that high titers of these autoantibodies are correlated with high risk in the development of RA [41]. These autoantibodies were found to be highly sensitive and specific in comparison to rheumatoid factor. In addition, combined estimation of rheumatoid factor and anti-citrulline antibodies can increase the assessment of both tests [41]. Anti-CCP antibodies can function not only as diagnostic marker but also have prognostic value, they might be used to predict the development of the disease and can be present much before the actual onset of the disease. These autoantibodies are also associated with other diseases such as cardiovascular as well as pulmonary complications. Anti-CCP antibodies can be useful in the diagnosis and prognosis of RA and have been included as one of the major criteria for the classification of this disease [42].

2.4. Rheumatoid factor (RF)

Rheumatoid arthritis is one of the disease in which the option for diagnosis and prognosis is more advance in the field of autoimmunity [43]. Since RA have nonspecific symptoms, therefore the diagnosis could be difficult but early diagnosis is important to have more option for therapy and cure. However, as this disease is characterized by radiological progression during early phase of the disease, so there might be good opportunity to initiate for early and effective treatment [44]. In early studies, serological diagnostic tool for RA were limited and the only autoantibodies related with the diagnosis of RA was rheumatoid factor that showed low sensitivity and specificity [43, 44]. Some patients can even showed negativity for RF and RF may be positive in various other autoimmune diseases that are showing nonclinical conditions and are positive even with other types of autoantibodies in these diseases. If the RF is falsely positive, it is interesting to mention that the complementary diagnostic test is antistreotolysin O (ASO/ASLO) test. Earlier studies have shown that smoker have elevated incidence of RA because of high RF [45]. Studies also indicated that elevated level of RF was found to be twice in comparison to both current and ex-smokers than nonsmokers and the level of RF was more in these individual [46]. Studies also have shown that smoking somehow effect the progression of RA [47].

Besides that, there are large groups of autoantibodies that are causing various types of autoimmune diseases including Anti-transglutaminase antibodies-celiac disease, dermatitis herpetiformis; Anti-ganglioside antibodies-Miller-Fisher syndrome, acute motor axonal neuropathy; Anti-actin antibodies-coeliac disease; Anti-thrombin antibodies-SLE; Anti-neutrophil cytoplasmic antibody-polyangiitis; Anti-smooth muscles antibodies-hepatitis; Anti-mitochondrial antibodies-primary biliary cirrhosis; Anti-SRP-polymyositis; Anti-SRP & Anti-AChR-myasthenia gravis; Anti-thyroid antibodies-Hashimoto's thyroiditis, Graves' disease; Anti-SLA/LP, perinuclear anti-cytoplasmic antibodies, Anti-LKM, Anti-LC-1, Anti-mitochondrial antibodies, Anti-asialoglycoprotein receptor antibodies-liver disease, etc. (**Figure 1**).
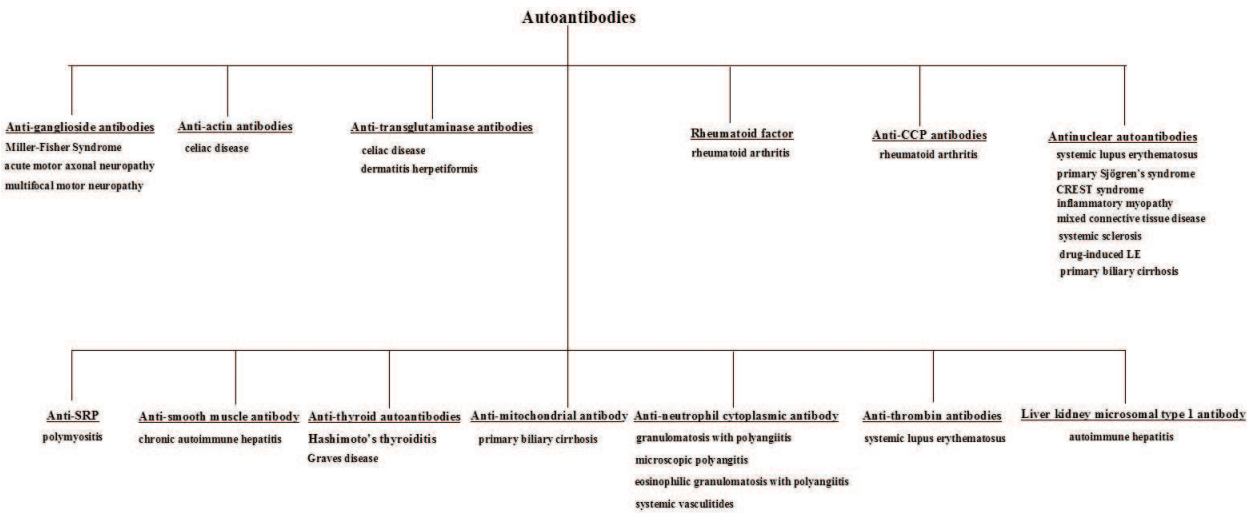
Figure 1. List of some common autoantibodies and their associated diseases.

3. Conclusion

Autoantibodies are group of antibodies that are directed against self antigen. These antibodies recognized normal molecules in the cells as foreign and dangerous. As a result of that, large group of reactions take place in which these autoantibodies recognized normal molecules and generate various immunological response against them. In consequence, these autoantibodies also interact with other protein molecule in order to generate a series of reactions causing binding to the self molecules. Binding of autoantibodies to self molecules can be recognized by various immune cells that mainly responsible for the damage and excretion of these molecules. For examples, there are various types of autoantibodies and their associated antigens found in in SLE (**Table 1**). These self damaged molecules are called as auto-antigen and finally treat as foreign molecule and damage by various immune cells.

Antinuclear autoantibodies (ANA)	Various nuclear components
Anti-ds DNA	Double stranded DNA
Anti-Sm	Protein with nuclear U1 RNA
Anti-RNP	Protein with U1 RNAγ
Anti-R$_o$ (SS-A)	Protein with hYRNA
Anti-La (SS-B)	Protein with hYRNA
Anti-histone	Histones
Anti-phospholipids	Phospholipids
Anti-neuronal	Neurons and lymphocytes
Anti-ribosomal	Protein in ribosomes

Table 1. Major types of autoantibodies and their associated antigens in SLE.

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