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# Clinical, Cellular & Molecular Biology of Autoimmune Disorders – Introduction

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Autoimmune disorders are heterogeneous group of diseases believed to arise from immune-mediated attack against self-antigens. Autoimmunity is triggered by a variety of factors whereas interplay between several regulating molecular and cellular pathways makes the process more complicated. Major factors in initiation and regulation of autoimmune diseases are improper major histocompatibility complex (MHC) control to present autoantigens, antigenic mimicry, altered proteins of the host, apoptosis and aging [1]. Beside this, several genetic factors and loci like non-HLA genes and autoimmune susceptibility loci, tumor necrosis factor-alpha (TNF-α) and forkhead box P3 (FOXP3) have been associated with susceptibility to autoimmune diseases [2]. Some common autoimmune diseases are rheumatoid arthritis, multiple sclerosis, diabetes, cardiomyopathy, antiphospholipid syndrome, myasthenia gravis, Crohn's disease, Graves' disease, psoriasis and alopecia. Moreover, such disorders may influence other non-autoimmune diseases as well e.g., Duchenne's muscular dystrophy and arthrosclerosis [3]. Autoimmune disorders as a group are among the most expensive diseases faced by society today however, the total societal disease burden is difficult to evaluate due to their diverse effect on human health from most debilitating and chronic to less serious and temporary.

Autoimmune diseases usually go undetected for long periods, before the appearance of detectable symptoms, progressive tissue damage and lead to the total tissue destruction. Techniques of analytical biochemistry, cell biology, immunology and molecular biology are being applied to identify and characterise autoantigens, to determine their subcellular localisation, to examine the effects of environmental agents on autoantigen expression, and to identify the antigenic epitopes recognised by autoantibodies. As the understanding of the molecular and cellular aspects of autoimmunity increases, more effective treatments for these diseases are being explored. In order to reduce the specific action of the immune cells and factors, current therapeutic approaches try to use general immunosuppressant to down-regulate the whole immune system. Although this approach is being extensively used in the absence of better options, however, generalized immunosuppression has not met with the success expected. Therefore, new strategies attempt to use immunomodulation today rather than immunosuppression [4]. Currently, clinical and molecular approaches involve vaccines, administration of antibodies and cytokines, gene therapy and use of antisense technologies. Refinements in understanding of the effects of immunomodulation versus more drastic measures will no doubt help to devise even more effective therapies [3].

This special issue of "*Clinical, Cellular & Molecular Biology of Autoimmune Disorders*" is devoted to describe the various aspects of autoimmune disorders. It comprises a set of reviews and original peer reviewed research articles that represent a diverse analysis of specific immune cells pathogenesis, role of receptors and autoantibodies in autoimmunity, molecular biomarkers and genetic loci involved in autoimmune disorders.

Diagnosis of autoimmune diseases may present difficulties to the clinician. There is no single definitive laboratory test and it remains mostly on clinical diagnoses which are not disease-specific. Molecular analytical approaches that are linked to disease pathogenesis are mostly focussed on the extraction of actionable biomarkers that will be useful for diagnosis, prognosis, clinical subtyping, and selection and monitoring of therapy. Keeping in view the complex immune system and its cross-reacting components, biomarkers would be expected to use for relationship between different parameters rather than a single measure [5]. These biomarkers may be genetic loci, distinct RNA types or several protein species including receptors and autoantibodies. Brigitte Katrin Paap, Michael Hecker, Dirk Koczan and Uwe Klaus Zettl summarize proposed biomarkers associated with multiple sclerosis (MS) etiology, its clinical manifestation, disease course, and treatment response. They discussed the possibility of different biomarkers based on multiple sample types and technical approaches with special reference to biomarker candidates in the central nervous system. Among the MS biomarkers, a number of HLA alleles and non-HLA single nucleotide polymorphisms (SNP) are considered as potential risk factors for MS development [6]. A number of discovery platforms are available for the identification of disease-specific autoantibodies in easily accessible biological fluids including sera, plasma, and urine. The focus of clinical proteomics is on the analytical and clinical validation and implementation of novel diagnostic or therapy related markers [7].

Natural autoantibodies are produced mainly by (CD5þ) B-1 cells, the predominant lymphocytes in the neonatal B cell repertoire, and marginal zone B cells [8]. These cells would play an important role in the production of pathogenic autoantibodies in several autoimmune diseases [9]. In a study of antitesticular autoantibodies detection by Batool Mutar Mahdi and colleagues in cryptorchid patients, it is shown that autoantibodies are directed against seminiferous tubules and degenerated germinal epithelium. Development of these autoantibodies may contribute in the late descent of a testicle into the scrotum ending in reduced fertility because of atrophy [10]. Phillip Ferdinand and Lauren Mitchell covers the autoimmune encephalitides disorders particularly focussing on anti-N-methyl-D-aspartate receptor encephalitis, one possible cause of which are the antibodies against the NR1 subunit of the receptor. They propose that treatment by induction of immunosuppressive therapy and management of long

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term residual deficits with the following remission of the autoimmune process could be beneficial [11].

Specific gene expression profiles have been studied in affected tissues of individuals with autoimmune diseases, such as the white matter in the brain in MS or synovium in rheumatoid arthritis as well as peripheral blood mononuclear cells of individuals with different autoimmune diseases [12]. This type of gene expression is may be unique or shared among several autoimmune diseases [13]. In recent years, genome wide analysis studies have provided a broad view of the relative contributions of various genomic loci and have substantially improved the understanding of the molecular pathways. Bouzid and colleagues presented a replication study in a cohort of inflammatory bowel diseases (IBD) patients from Tunisia. They tested previously identified genetic markers involved in adaptive immunity and proved genetic heterogeneity at Crohn's disease (CD) and ulcerative colitis (UC) loci [14]. A number of genetic factors have already been explored through SNP array technology implicated in IBD pathogenesis to include over seventy genes and loci associated with UC/CD, spanning pathways involved in adaptive and innate immunity [15]. A comprehensive review on autoimmune disease is given by Sayantan Ray et al., with detailed molecular and cellular mechanisms of autoimmune responses and their diverse origins [16].

A fundamental task in autoimmunity research is to identify those cell types and molecules that promote the initiation and progression of specific diseased condition through their anomalous function. Bimonte Sabrina and colleagues focused on the regulatory role of natural killer T (NKT) cells in autoimmune diseases. NKT are a heterogeneous group of T cells that share properties of both T cells and natural killer (NK) cells and hence play role both in innate and adaptive immune response. They can recognise antigen-presenting CD1d molecule that binds self and non-self glycolipids and lipids and are considered critical cells in regulatory events during autoimmune inflammatory responses. Studies in mice model created a paradox for the enhancing or suppressive role for NKT cells, however, it was found that cross regulation between the two distinct types of NKT cells suggests an immunoregulatory axis [17].

The next two reviews examine the role of another distinct type of IL-17-producing CD4+ population of T helper cell lineage named Th17 cells that are critically involved in the development of many autoimmune diseases on the basis of evidence from human and mouse studies. Yaochite J.N.U and Carlos D presented controversial role of Th17 cells in development and progression of type1 diabetes pathogenesis [18]. Shinji Maeda et al., further elaborated the Th17 cells contribution in the pathophysiology of rheumatoid arthritis (Bone destruction), psoriasis, psoriatic arthritis (Cutaneous inflammation), and Behcet's disease (neutrophilic inflammation) [19]. Both articles consider the possibility to use Th17 as a potential therapeutic target for these diseases.

Another challenge is to explore the aberrant function of specific receptors or intracellular signalling molecules that influence immune cell development and function, finally result in loss of self-tolerance or generalized inflammatory conditions [2]. Chiharu Kishimoto and Zuyi Yuan review the contribution of Fcγ receptors to the regulation of immune and inflammatory responses that are expressed by major cell types during cardiovascular diseases. They described that immune complexes and C-reactive protein have been shown to activate FcγRs signal pathway that may provide a possible therapeutic target for the prevention and therapy [20].

Together these articles provide a variety of valuable points about cellular and molecular pathways involved in the disease progression and interplay between different autoimmune diseases. We hope that these articles motivate new approaches and stimulate scientists and clinicians to experiment new ideas in the field of autoimmunity research. We are of opinion that mysteries of autoimmune disorders will be explored only on the cellular and molecular backgrounds.

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