Autoimmune Disease-Related Molecular and Cellular Mechanisms

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Abstract

Several autoimmune illnesses are becoming more common in the United States, according to evidence. As a result, the expense of clinical management of autoimmune disorders to the public health is increasing. Both genetic and environmental variables play a role in the onset and course of autoimmune disorders. Autoantibodies can be caused by deficiencies in key proteins that are normally involved in maintaining the internal environment's checks and balances. Autoimmunity has been linked to structural anomalies or a decrease in normal levels of the pentraxins (serum amylase-P protein, acute phase proteins, complement, and C-reactive proteins). The quality and amount of subsequent immune responses are determined by the type of ligand/receptor interactions that promote physical recruitment of various signals within the cell. *CD95*, also known as *Fas/Apo-1*, and its ligand *CD95L* regulate lymphocyte populations, influencing different aspects of immune responses. Mutations in the apoptotic pathways may occur from aberrant protein synthesis by *CD95* and/or its receptor *CD95L*. Apoptosis can be prevented fully, triggered partially, or partially stimulated. Apoptosis modulation may result in the buildup of self-antigens. Through lymphatic hyperplasia, the immune system may be prompted to react to self-molecules. Proliferative diseases and increased vulnerability to autoimmune syndromes may result from this process. The mechanisms of autoimmunopathogenesis at the cellular and molecular levels are discussed in this research. The importance of T and B cell receptor/ligand interactions, functions, and malfunctions as a result of structural and quantitative changes in the T-B-cell cluster of antigen determinants is highlighted. The etiological factors implicated in the initiation and subsequent dissemination of autoimmune disorders is reviewed in genetically sensitive patients who acquire spontaneous autoimmune diseases.

Keywords: T cell receptor • B cell receptor • Apoptosis

Introduction

T cells are essential components of the adaptive immune system and are responsible for determining the functional outcome of immune responses. The TCR on CD4 helper or CD8 cytotoxic T cells is responsible for the specificity of T-cell-mediated immune responses. The TCRs recognise a peptide in target cells that is associated with MHC class II or class I molecules. CD4 T cells regulate the actions of other immune cells, such as B cells, to govern ongoing immunological responses, whereas CD8 T cells attack and kill target cells directly. Tcell activities during immunological responses are crucial in starting and controlling T-cell-mediated immune functions in both cases, and even more so in many people who are prone to autoimmunity. Various methods are known to govern and stop an ongoing immune response, and TCR signalling abnormalities inevitably impede T-cell growth and/or induce T-cell function deviation [1, 2]. In these pathways, costimulatory molecules play a key role [3]. The destiny of individual T cells and the immunological response is determined by the balance of positive and negative signalling costimulatory pathways. Various methods are known to govern and stop an ongoing immune response, and TCR signalling abnormalities inevitably impede T-cell growth and/or induce T-cell function deviation [1, 2]. In these pathways, costimulatory molecules play a key role [3].

The destiny of individual T cells and the immunological response is determined by the balance of positive and negative signalling costimulatory pathways. The antigen-specific receptors on T- and B-lymphocytes, as well as most cytokine receptors whose ligands regulate proliferation and differentiation in the haematological system and several hormones, belong to a family of heterogeneous receptors that lack an evident catalytic domain. When a receptor interacts to its ligand, it activates tyrosine kinases, which phosphorylate a variety of target proteins. They are either member of the Src or Janus families of nonreceptor protein kinases [4]. Their kinase domain, on the other hand, is expressed by a different gene than the receptor tyrosine kinases and is noncovalently linked to the polypeptide chain of the receptor. Like the other tyrosine kinases, these family members are activated by ligand-induced dimerization. Src, Yes Fgr, Fyn, Lck, Lyn, Hck, and Blk are the eight members of the Src family of nonreceptor protein tyrosine kinases. They have two highly conserved noncatalytic domains called SH2 and SH3 (for Src homology regions 2 and 3, because they were first discovered in the Src protein) that interact with transmembrane receptor proteins and, in part, covalently attached lipid chains on the cytoplasmic face of the plasma membrane. SH2 domains recognise phosphorylated tyrosines and allow proteins with them to bind to activated receptor tyrosine kinases (*RTKs*) and other intracellular signalling proteins that have been transiently phosphorylated on tyrosines. The SH3 domains' function is unknown; however they are thought to bind other proteins in cells lacking the SH3 domain. Different varieties of the group bind to various receptors and phosphorylate overlapping but unique groups of target proteins.

Some receptors are Protein Tyrosine Phosphatases (*PTPs*), which may rapidly dephosphorylate tyrosine residues from specific phosphotyrosines on proteins [5, 6]. PTPs are known to have high specific activity, which makes their tyrosine phosphorylation actions highly short-lived. Phosphorylation is likewise quite low in resting cells. They have distinct functions in cell signalling and the cell cycle. The Cluster of Differentiation Antigen 45 (CD45) is an example of a Regulated Protein Tyrosine Phosphatase (RPTP) attached to the surface of leucocytes that plays a key function in T- and Blymphocyte activation. It's a single-pass transmembrane glycoprotein whose phosphatase activity is inhibited by dimerization, and it's been linked to autoimmune induction in humans and animals, with severe effects. Several of the genes that encode the proteins that stimulate intracellular signalling cascades activated by receptor tyrosines were discovered as oncogenes in cancer cells or tumour viruses. Excessive cell proliferation is caused by improper activation of these signalling proteins. Adaptor proteins, which are found between signalling tyrosine kinases and nonspecific cellular regulatory circuitry, act as major regulators of downstream signalling pathways following ligand binding to the TCR. To offer binding sites for some soluble intracellular adaptor polypeptides, Lck and Fyn phosphorylate TCR. As a result of the adaptor proteins, the TCR has several activation routes. The presence of adaptor proteins, their relative affinities for receptor polypeptides, and the time required for binding to related ligands may all have a significant impact on the type of TCR signalling. This indicates that during T cell activation, changes in the phosphorylation of each immunoreceptor's tyrosine-based activation motif can result in a mix of signals. The TCR signal transduction machinery can then give out many separate signals in this manner. *TSAd* is a T cell-specific adaptor protein that is known to play a role in the formation of intracellular signalling complexes in T cells as well as the activation of T cell interleukin 2 productions and proliferation.

Autoimme reaction: Cells and molecules

Lymphocytes are the primary cellular carriers of immunological responses. Memory, specificity, and discrimination between'self' and 'non-self' are all implemented via different functional categories. T and B lymphocytes are the two main lymphocyte populations involved in antigen recognition and response. They have a significant number of self- and non-self-identification recognition molecules on their surface membrane. Each cell has only one type of specificity [7]. Clonal expansion occurs in response to antigen interaction, allowing the offending substance to be eliminated while also preserving memory for future encounters with the same or roughly related epitope. Lymphocytes can thus display clonal diversity, which provides an evolutionary advantage in an equally complicated environment.

Under normal conditions, the immune system is capable of responding to a wide range of foreign antigens and providing effective defence against pathogens ranging from viruses and bacteria to complex multicellular parasites. Random somatic recombination of genes coding for antigen-binding domains of lymphocyte receptors generates diversity to combat all types of antigens. Similarly, the generation of membrane receptors that are potentially reactive with self-antigens is unavoidable. Normally, immune system cells communicate with one another and with other cells in the body using a variety of signalling molecules that are secreted by exocytosis, diffuse through the plasma membrane and into the extracellular fluids, remain adhered to the cell surface, and only influence cells that come into contact with the signalling cell, a process known as autocrine and/or paracrine signalling. Immunocytes react to the target cell's surface via particular receptors, which are transmembrane proteins. T lymphocyte activation requires interactions between the multimeric TCR and a molecular complex found on Antigen Presenting Cells (APC), most commonly a macrophage. The molecular components are processed antigen in combination with MHC II or I molecules. This *Ag-MHC* complex is critical for intercellular self/nonself distinction because it directs the TCR to recognise "self" and Ag. Both humoral and cell-mediated immune responses rely heavily on the MHC. They provide antigenic peptides to the T cell repertoire for recognition. These receptors bind signalling chemicals, causing the target immune cells to respond. The nucleus receives signals from such associations, which result in gene expression. This is accomplished through a complex system of intracellular signalling proteins that are phosphorylated by protein kinases, dephosphorylated by protein phosphatases, or bind triphosphate nucleotides to form activated proteins. As part of the cascade, downstream proteins may also be phosphorylated.

Autoimmune disease genetic determinants

Many genes play a role in lupus susceptibility. Mutations in these genes either increase or decrease the severity of lupus-like disorders. Predisposition to autoimmune illnesses is influenced by MHC and non-MHC genes, as well as vulnerability to spontaneous lupus. Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease with a wide range of clinical symptoms and pathogenicity. Epidemiological evidence suggests a strong hereditary component to SLE susceptibility, and numerous genes involved in immune complex deposition play a role in pathogenesis. In general, people with certain HLA alleles have a higher risk of developing autoimmune disorders than people who don't have these alleles. Findings from genetic investigations frequently provide useful information for clinical care of autoimmune disease patients. A study of the literature on rheumatoid arthritis, for example, reveals that mechanisms are involved in the induction of RA in the synovium. Several cytokines are produced in the course of the disease, according to animal models of inflammatory arthritis and data from humans with rheumatoid arthritis. Cytokines are factors that mediate cell-to-cell communication and are important in drawing inflammatory and immune cells to the joints, where they release tissue-damaging chemicals. Cytokines bind to receptors on cell surfaces and drive signal transduction pathways that lead to high or low transcription [8].

Pathways that lead to autoimmunity predisposition or resistance

Animal studies established the groundwork for later floods of research into how some people are prone to acquiring an autoimmune disease. Anti-C1q antibodies are notably associated with glomerulonephritis and are largely linked with several spontaneous murine models of SLE. Anti-C1q antibodies are particularly associated with glomerulonephritis and are predominantly related with several spontaneous murine models of SLE. This molecule's diversity permits it to play a universal role in a variety of physiological and immunological pathways that are currently unknown. The most interesting aspect of this molecule is its role in apoptotic cell clearance. Failure to do so due to a deficient status may result in the induction of autoimmune disease. The classical pathway deficiency leads to the development of SLE because of a decreased capacity to clear antigenantibody complexes in tissue damage and release of autoantigens, according to the notion associating complement deficiency with faulty apoptotic cell clearance. This is one mechanism through which apoptotic bodies containing self-epitopes might accumulate and overwhelm the immune system, leading to autoimmune illness. This hypothesis, on the other hand, supports the idea that C1q is involved in the maintenance of immunological tolerance by clearing auto antigen-containing surface blebs produced by apoptotic cells; animal models back this up. The C4 complement protein, which plays a role in the early stages of the cascade, is made up of two isoforms: C4A and C4B, which are both polymorphic, and the quantity of C4 genes present on a haplotype varies. The 8.1AH is made up of a single segment with a short C4B gene but no C4A gene. The CD45 protein appears to play an important role in lymphoproliferation control, according to recent discoveries.

A Regulated Protein Tyrosine Phosphatase (*RPTP*) attached to the surface of all nucleated hematopoietic cells is CD45 protein, a one-pass transmembrane glycoprotein. Each cell type produces its own *CD45* isoform, which ranges in molecular weight from 180 to 235 kilodaltons. The different isoforms contain the identical intracellular *RPTPase* domain, but their extracellular domains differ in length and glycosylation pattern. *CD45* is required for signal transduction via antigen receptors, which are involved in the activation of both T and B cells by foreign antigens. The *RPTPs* are a broad family of signal transduction molecules that are extensively expressed [9, 10].

Conclusion

Most *RPTPs*' key metabolic substrates and physiological activities are unknown, but the isoform *CD45R*, often known as *B220* because of its molecular weight of 220K, is specific to the B-cell lineage. *CD45* is thought to act on a wide range of various substrates, favourably or negatively regulating numerous receptor proximal components. Extracellular antibodies, on the other hand, create crosslinks with T and B cells, causing polyclonal activation in these cells. When external antibodies cross-link T- and *BCRs*, the catalytic domain of CD45 is activated, removing phosphate groups from tyrosine residues on particular proteins. In lymphocytes, proteins like lck, a tyrosine kinase, are then driven to phosphorylate other proteins. It should be highlighted; however, that majority of the genes that code for proteins required for intracellular signalling cascades initiated by receptor tyrosine kinases are deemed oncogenes in cancer cells or tumour viruses. *CD45*-deficient animals suffer significant delays in T and B cell growth and function, while CD45-deficient humans have severe autoimmune disease. SCID (severe combination immunodeficiency) phenotype *CD45*-deficient animals showed similar results. Negative phosphorylation of the C-terminal site RTP within kinases of the SRC family *CD45* T and B cells are kept in a "primed" state, allowing them to function fully. Following interaction with an antigen receptor, the cell is activated. CD45 has an extracellular domain, a single transmembrane domain, and a cytoplasmic domain with tandemly duplicated PTPs, just like all other *RPTPs*. Within the extracellular domain, alternative splicing of exons 4, 5, and 6 produces a variety of *CD45* isoforms. The extracellular structure and overall charge of the high molecular weight isoform (*CD45RA*+) differs from the low molecular weight isoform (*CD45RO*), which lacks the three exons that code for O-linked glycosylation.

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