

MOLECULAR NATURE OF T-CELL RECEPTORS

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INTRODUCTION

The immune system is crucially involved in a number of diseases including microbial infections, allergies, cancer, rheumatism, autoimmunity and degenerative disorders of ageing. While the T-lymphocytes play a key role in the body's immune defence mechanism, they also act to reject grafted or transplanted tissues.

The T-cells comprise only about half the population of lymphocytes; the other half, the B-lymphocytes being involved in secretion of antibody (immunoglobulin) molecules which also act as receptors when still bound to the B-cell surface. Since T-cells are antigen-specific, they must exhibit receptor molecules on their surface analogous to the membrane-bound immunoglobulins on the B-cells. The T-cell receptor (TCR) is membrane-bound and, unlike immunoglobulins, is not secreted from the cell¹. Again unlike immunoglobulins, the TCRs do not bind soluble antigens like bacterial toxins².

The structure of the TCRs is now rapidly coming into focus and the structural clarification is increasing our knowledge of the interactions of T-cells with other elements of the immune system.

SUBSETS OF T-CELLS

The T-lymphocytes can be distinguished from the remaining haemopoietic cells by a marker called the CD3 complex, associated with the TCRs for antigen³, which can be identified by a monoclonal antibody OKT3^{4,5}.

The CD3 + T-cells can be further divided into sub-populations according to their expression of CD4⁶ and CD8 proteins. About two-thirds of the CD3 + cells express CD4 but not CD8 and one third CD8 but not CD4 proteins. They are referred to as CD4+ (CD4+ 8-) and CD8+ (CD4- 8+), respectively. A very small proportion of CD3 + cells, however, neither express CD4 nor CD8 and may be referred to as CD4+ 8⁷.

A unique and important property of the TCRs is that they only recognize the antigens (peptides) which are associated with the major histocompatibility complex (MHC) molecules on the cell surface⁸. MHC molecules are proteins encoded by the genes of the MHC chromosomal region⁹. The two classes of MHC molecules involved are the class I MHC proteins expressed on most nucleated cells and class II MHC proteins which are expressed only on B-lymphocytes, macrophages, dendritic T-cells and epithelial cells of the thymus. The class I proteins usually associate with peptides present in the cytosol including degraded products of viral proteins in virally infected cells¹⁰ which are transported to the cell surface by an unknown mechanism⁷. The class II MHC proteins bind peptides derived from external proteins which are endocytosed by macrophages, dendritic T-cells or B-cells and are cleaved in lysosomes. The CD4+ cells bind peptides associated with class II MHC molecule while the CD8+ cells bind peptides associated with class I MHC molecule⁷. Antigen recognition by T-cells is therefore considered MHC-restricted.

The T-cells produce lymphokines¹¹⁻¹³ and also express receptors which bind these lymphokines and

hence regulate their growth and differentiation⁷. The best characterized of these receptors is the IL-2 (interleukin-2) receptor which is expressed by both activated CD4+ and CD8+ cells⁷. The CD3+4'8' cells can also be induced to produce IL-2 and become cytolytic¹⁴ but their antigen-specificity is not known.

TYPES OF TCRS

Based on their structural components, TCRs can exist as heterodimers (with 2 non-identical chains) or homodimers (with 2 identical chains). Two heterodimer forms and one homodimer form have been detected. The two heterodimeric forms either consist of an alpha chain and a beta chain (alpha/beta TCR) or a gamma chain and a delta chain (gamma/delta TCR)¹⁶⁻¹⁸ of proteins. A homodimer TCR, the gamma/gamma TCR has also been described¹⁹.

The alpha/beta TCR recognizes protein fragments presented by class I or class II MHC-encoded molecules but the antigens recognized by the gamma/delta TCR are still being defined¹⁵ and the physiologic significance of gamma/delta TCRs remains unclear^{20,21}.

In man, gamma/delta TCRs comprise majority of the dendritic epidermal T-cells and 1-10 per cent of peripheral blood T-cells' evenly distributed throughout the lymphoid organs and skin- and gut-associated lymphoid tissue, with no discernible local preference^{18,22,23}. Some local preference in certain species and the limited TCR diversity of gamma/delta TCRs lead to the hypothesis that gamma/delta TCRs are a phylogenetically very old surveillance system to monitor cell integrity and to destroy transformed or infected cells²⁴.

The alpha/beta TCR binds to both the peptide as well as the polymorphic residues of MHC molecules. The antigen recognition by the alpha/beta TCR is facilitated by the CD4 and CD8 co-receptors expressed in a mutually exclusive fashion on mature T cells²⁵. The CD4 and CD8 co-receptors bind to the nonpolymorphic residues of the class II and class I MHC molecules, respectively¹. Unlike the alpha/beta TCR, both the gamma/delta TCR and the gamma/gamma TCR are not MHC-restricted²⁶.

STRUCTURE OF TCRS

The TCRs, like the MHC molecule, consist of two disulfide linked variable glycoproteins^{27,28}. In the alpha/beta TCR, the alpha glycoprotein has a molecular weight of 43-49 kd while the beta glycoprotein is 38-42 kd, both of which are heterogeneously charged glycoproteins^{27,28}. The TCR alpha chain contains nitrogen-linked oligosaccharides of the complex type and TCR beta chain comprises of both high mannose and complex nitrogen-linked glycan side chains^{26,27}.

The organization of the TCR proteins is very similar to the antigen binding fragment (Fab segment) of immunoglobulins^{1,26,29}. As in the immunoglobulin molecule, all TCR proteins have a variable (V) region and a constant (C) region which are linked by a short joining segment (J) while the TCR beta and TCR delta chains also have a diversity (D) segment⁷.

The TCR proteins also have a transmembrane region and a short cytoplasmic tail of 5-12 amino acids extending into the cytoplasm of the T-cell. The two cysteine residues in each of the V and C regions indicate an interchain disulfide loop in each region. The TCR alpha chain and TCR beta chain have cysteine residues proximal to the transmembrane region that form an inter-chain disulfide bond²⁶. The gamma TCR chain which is a 55 kd protein product and the delta TCR which is a 40 kd protein¹⁷ are also covalently linked to form a gamma/delta TCR heterodimer or a gamma/gamma TCR homodimer^{16,19,30}.

The chromosome location of the CD3 gene is at 11q23, that of alpha TCR at 14q11, beta TCR at 7q32-35 and gamma TCR at 7p15 while the delta TCR gene is still under study²⁶. The TCR genes are first rearranged and expressed in the thymus during the T-cell differentiation. The TCR beta, gamma and delta genes are rearranged and transcribed first, followed by the alpha chain gene¹.

The appearance of gamma/delta heterodimers precedes the alpha/beta TCR expression by one or two days in fetal ontogeny, as studied in the mouse. It has been suggested that only those cells that cannot produce a gamma/delta heterodimer proceed to alpha and beta expression. Alternatively, these two different types of T cells represent separate compartments and express their respective TCR chains independently¹.

FUTURE PROSPECTS

The structural clarification of the TCR has brought about a far better understanding of the complex physiology of the T-cells, and the medically important properties of the cell mediated limb of immunological response. This revolutionary advance in knowledge is expected to aid in improving the management of various diseases, especially viral infections, allergies, autoimmunity and cancer.

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