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ANTIGEN PROCESSING AND PRESENTATION AN OVERVIEW

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The purpose of the immune system is to defend the body against foreign microbial invasion. To this end the immune system has been armed with some very powerful weapons that enables it to kill or neutralize virtually any invader. Without this defence we would succumb to invasion by otherwise harmless and opportunistic microorganisms. However, like any army – no matter how powerful it is – it is worthless, if not downright dangerous, to its own kind if it cannot distinguish between friend and enemy. The immune system can if misguided launch an attack on healthy tissue as though it represented a pathogenic invader and ultimately destroy it and the body. Such so called autoimmune diseases are common; well-known examples include diabetes, sclerosis, rheumatoid arthritis – and they are often seriously debilitating to the patient. Thus, the single most important quality about the immune system is its ability to distinguish between friend and enemy – i.e. between self and non-self.

The constantly raging battle against invading microorganisms is led by the white blood cells, also known as the lymphocytes, in particular the so-called B and T lymphocytes. These are the only cells known so far that have receptor molecules on their surface which allows them to specifically examine their surroundings. A very large number of receptors exists, but any given B or T cell only express receptors of one specificity; the receptors are clonally distributed. The sum of all the B or T cells – each expressing one single receptor – constitutes the B or T cell repertoire. If you can control the individual B or T cell clones you control the repertoire. The receptors are randomly generated and the repertoire is potentially omnipotent. Subsequently clones with self-reactive receptors are deleted or inactivated from this omnipotent repertoire and we are left with the desired repertoire that responds to anything foreign, but leaves self unharmed (reviewed in Bohemer & Kisielow, 1991).

Now, how do the B and T cells actually recognize foreign in molecular terms. The two cell types although they use similar, but not identical, receptors, recognize their surroundings in completely different ways. The B cell receptor, the immunoglobulin, directly recognizes three-dimensional structures of virtually any kind – proteins, sugars, lipids, nucleic acids etc. After the B cell has differentiated into a plasma cell it secretes soluble immunoglobulin and the recognition event can take place in the extracellular space far away from the B cell. In contrast, the T cell receptor is always cell-bound and it always recognizes its target on the surface of another cell, the so-called antigen presenting cell (APC). Two subtypes of T cells exist. The CD4 positive T helper cells regulate other cells participating in the immune response, whereas the CD8 positive T cytotoxic cells are effector cells capable of eliminating host cells expressing foreign proteins. T cells may well be the most important of the immune cells because they regulate a great number of immune responses. Interestingly, T cells focus their attention on proteins – the functional and structural basis for all life as we know it. Throughout the rest of this review I will deal with the molecular aspects of T cell recognition.

T cells cannot recognize anything in the absence of APC's. To function as an APC a cell must meet certain requirements. Of interest here the APC must possess an intact antigen processing apparatus and it must possess MHC molecules. Ten years ago the function of the MHC was unknown, the T cell receptor had not been identified and the antigen that it was supposed to recognize was elusive, too. The complexity of T cell recognition long resisted all scientific investigations. However, due to tremendous advances in cellular and molecular immunology we now have a much better understanding of what T cells recognize (reviewed in Grey et al., 1989). The cell receptor and its specificity is now well known.

The cell receptor is not specific for the native protein antigen, but rather for a complex ligand presented on the surface of the APC. This ligand consists of antigenic peptide and MHC. The interaction between peptide and MHC is specific and only the peptides which are bound to a MHC molecules are presented to T cells (Babbitt et al., 1985; Buus et al., 1986; Schaeffer et al., 1989). The cells are consequently said to be MHC restricted. Each MHC molecule binds a fairly large fraction of the universe of antigenic peptides. MHC molecules cannot distinguish between peptides derived from autologous or foreign proteins, and they largely preoccupied with self-peptides (Babbitt et al., 1986; Buus et al., 1988). This is consistent with the very broad specificity of MHC molecules and places the important self-non-self discrimination solely at the level of the T cell. This broad specificity is created through the recognition of structural motifs (Sett et al., 1987). MHC is the most polymorphic molecule known and the polymorphism is generally found near the peptide binding groove (Björkman et al., 1987a). Polymorphism thereby affects the specificity of peptide-MHC interaction. The reason for the enormous polymorphism is not quite understood, but one obvious consequence of the polymorphism of MHC is that it secures that T cells from a given individual recognize their surroundings in a manner completely different from T cells of any other individual. Thus, no parasite knows what to except when it invades a new host. In molecular terms the function of the MHC molecule is to select samples of all proteins in the body, self as well as foreign derived, and submit these samples to the scrutiny of the T cells.

An apparent dichtomy exists. CD4 positive T helper cells, regulating other immune cells, predominantly recognize exogenous antigen presented by MHC class II molecules. CD8 positive T killer cells, mediating direct cell killing, predominantly recognize endogenous antigen presented by MHC class I molecules. Thus, although MHC is unable to distinguish between self and non-self, it appears that MHC molecules of class I and II to some extent can distinguish between antigens derived from endogenous or exogenous sources (Morrison et al., 1986). This skewing of the MHC repertoire is not due to the specificity of the MHC itself, but rather to antigen processing events preceeding peptide binding and presentation. MHC molecules, at least MHC class I molecules, are inherently unstable when empty and must bind a peptide to obtain the stability needed to reach the cell surface functionally intact (Townsend et al., 1989). For this reason MHC class I molecules must bind antigens during or right after their synthesis in the ER and as a consequence they predominantly present endogenously derived peptides. In contrast, MHC class II molecules are thought to be stable and, due to the blocking action of the so-called invariant chain, unavailable for peptides in ER (Teyton et al., 1990). The class II molecule is diverted to the endocytic pathway where the invariant chain is split off and only then does the MHC class II become available to peptides. Since this occurs in the endocytic pathway MHC class II molecules predominantly obtain peptides derived from exogenous antigens.

MHC molecules are mostly preoccupied with self molecules (Björkman et al., 1987b; Buus et al., 1988). These peptides can be eluted off the MHC and characterized (Buus et al., 1988). A revolutionizing technique that allows one to directly sequence such peptides and thereby determine the motif of the MHC molecule in question has recently been introduced (Falk et al., 1991). This technique has subsequently been extended to MHC class II molecules (Rudenski et al., 1991).

The function of the MHC is thus relatively well characterized. In contrast, the molecular mechanisms of antigen processing is still very much unresolved. However, an explosion in our knowledge of antigen processing is taking place presently. As mentioned above, two separate pathways of antigen processing exist; one for MHC class I presentation and one for MHC class II presentation. In both cases the final outcome of antigen processing is the generation of peptide fragments derived from the intact antigen (Shimonkevitz et al., 1983; Townsend et al., 1986). The presentation of exogenous antigens via MHC class II involves endocytosis. The native antigen is taken up by the APC and fragmented intracellularly where some of the resulting fragments are bound to MHC molecules. The late endosomes and the lysosomes are acidic compartments of the endocytic pathway possessing powerful proteolytic enzymes. It is now known that the optimal pH for peptide binding to MHC class II is quite acidic suggesting that fragmentation and binding might occur in the same endocytic compartment (Jensen, 1990). Further strength-

ening this idea is the finding that peptides once bound to MHC molecules are effectively protected against further proteolysis (Donermeyer & Allen, 1989). Thus, the MHC class II molecule itself may serve as the molecule that rescues the immunogenic peptide from complete degradation in the proteolytic inferno of antigen processing. The resulting peptide-MHC complexes are exocytosed to the cell surface and presented to T helper cells. The presentation of endogenous antigens via MHC class I involves cytosolic processing. The findings of mutant cells lines that produce normal amounts of class I molecules, but are unable to support correct assembly of class I molecules, unless they are supplied with large amounts of specific peptides, have illuminated the role of the peptide in class I assembly and folding (Townsend et al., 1989). They have also yielded an assay which can be used to probe for the mechanisms of antigen processing. It appears that the immune system is using some very old and basic mechanisms to generate the antigenic peptides. These mechanisms involve cytosolic proteolysis, transport and translocation of the resulting peptides across the ER to the de novo systhesised class I. Tandem repeats of genes encoding molecules thought to be involved in such processes has recently been localized to the MHC gene region (Monaco et al., 1990; Oritz-Navarrete et al., 1991; Trownsdale et al., 1991). Whether these processes are specific with respect to peptide generation and/or transport is not yet known.

Antigen processing and MHC mediated presentation are intimately related. An antigen, once bound to its MHC restriction element, is protected against further proteolytic degradation, and conversely, a MHC molecule which binds a peptide, is protected against denaturation.

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