T Cell Activation as Starter and Motor of Rheumatic Inflammation

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Abstract Rheumatic inflammation is driven by sustained specific immunity against self-antigens, resulting in local inflammation and cellular infiltration and, subsequently, in tissue damage. Although the specific autoantigen(s) eliciting the detrimental immune reactions in rheumatic diseases have rarely been defined, it has become clear that the mechanisms resulting in the destruction of tissue and the loss of organ function during the course of the diseases are essentially the same as in protective immunity against invasive microorganisms. Of fundamental importance in initiating, controlling, and driving these specific immune responses are CD4 T cells. Currently available data provide compelling evidence for a major role of CD4 T cells in the initiation and perpetuation of chronic rheumatic inflammation. Consequently, T cell-directed therapies have been employed with substantial clinical success in the treatment of rheumatic diseases. Here, we review current knowledge based on which CD4 T cells can be implicated as the motor of rheumatic inflammation.
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T Cell Development and T Cell Subsets

The peripheral T cell repertoire consists of T cells that have survived dual selection in the thymus and comprises several distinct T cell subsets that can be identified based on their characteristic cell surface molecule expression (Germain 2002; Spits 2002; Weiss 1993). All T cells express a disulfide-linked heterodimeric T cell receptor (TCR), which confers antigen specificity to the T cell. Associated with the TCR and required for its surface expression is the CD3 complex, which consists of four invariant transmembrane polypeptides (designated γδεε). The CD3 complex mediates signaling and is linked to a largely intracytoplasmic homodimer of ζ-chains, which are critical for maximal signaling (Chan et al. 1992). CD4 or CD8, co-receptors, whose expression is mutually exclusive on mature post-thymic T cells, bind to invariant sites of the major histocompatibility complex (MHC) class II or I molecules on antigen-presenting cells (APCs), respectively, stabilize the MHC/peptide/TCR complex during T cell activation, and thus increase the sensitivity of a T cell for activation by MHC-presented antigen by approximately 100-fold (Weiss 1993).

In humans, the great majority of peripheral blood T cells expresses TCRs consisting of α and β chains (αβ T cells). αβ T cells can be divided into two subgroups, characterized by the expression of either CD4 or CD8 (Table 1). CD4 αβ T cells primarily function as regulators of other immune cells either through secreted cytokines or by direct cell–cell contact. Consequently, CD4 αβ T cells mediate the classical helper T cell responses. CD8 αβ T cells, on the other hand, are programmed to become cytotoxic effector cells that kill infected target cells. CD8 T cells are therefore named cytotoxic T cells. As the αβ TCR does not bind antigen directly, T cell activation is dependent on

<table>
<thead>
<tr>
<th>TCR</th>
<th>Frequency</th>
<th>Co-receptor</th>
<th>Function</th>
<th>Restriction</th>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>αβ</td>
<td>95%–98%</td>
<td>CD4 helper</td>
<td>Regulators of other immune cells; cytokine secretion; cell–cell contact;</td>
<td>MHC class II</td>
<td>Exogenous peptides</td>
</tr>
<tr>
<td></td>
<td>(50–80%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>γδ</td>
<td>2%–5%</td>
<td>None, CD8α</td>
<td>Cytolysis of target cells</td>
<td>MHC class I</td>
<td>Endogenous peptides</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unknown, peptides?</td>
</tr>
</tbody>
</table>

TCR, T cell receptor; MHC, major histocompatibility complex