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REVIEW

Modulation of T cell function by TCR/pMHC binding kinetics

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Abstract

The interaction between the T cell receptor (TCR) and the peptide-MHC complex (pMHC) at the interface between the T cell and the antigen presenting cell (APC) is the main event controlling the specificity of antigen recognition by T cells. It is thought that TCR/pMHC binding kinetics are critical for the selection of the T cell repertoire in the thymus, as well as the activation of mature T cells in the periphery. One of the binding parameters that conditions T cell activation by pMHC ligands is the half-life of the TCR/pMHC interaction. This kinetic parameter is highly significant for the regulation of T cell activation and therefore determines the capacity of T cells to respond against pathogen- and tumor-derived antigens, avoiding self-reactivity. Several studies support the notion that T cells are activated only by TCR/pMHC interactions that are above a threshold of half-life. pMHC complexes that bind TCRs with half-lives below that threshold behave as null or antagonistic ligands. However, since prolonged half-lives can also impair T cell activation, there seems to be a ceiling for the TCR/pMHC half life that leads to efficient activation of T cells. According to these observations, efficient T cell activation would require an optimal half-life of TCR/pMHC interaction. These kinetic restrictions for T cell activation are important to generate a protective adaptive immune response minimizing cross-reactivity against self-constituents. The nature of the TCR/pMHC interaction defines in the thymus whether a thymocyte develops into a mature T cell or is eliminated by apoptosis. In addition, the kinetics of TCR/pMHC binding can determine the type of response shown by mature T cells in the periphery. Although several studies have focused on the modulation of T cell function by the affinity of the TCR/pMHC interaction, the binding kinetics rules governing T cell activation remain poorly understood. Here we review recent data and propose a new model for the regulation of T cell function by TCR/pMHC binding kinetics.

Keywords: APC; T cell; TCR; TCR/pMHC kinetics; Immunological synapse; Thymocyte selection

Abbreviations: APC, antigen presenting cell; APL, altered peptide ligand; CTL, cytotoxic T lymphocyte; IS, immunological synapse; ITAM, immunoreceptor tyrosine-based activation motif; MHC, major histocompatibility complex; pMHC, peptide-MHC complex; cSMAC, central supra-molecular activation clusters; pSMAC, peripheral supra-molecular activation clusters; TCR, T cell receptor

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Introduction

Development of T cells in the thymus, as well as activation of mature T cells in the periphery are two central processes in adaptive immunity that depend on the interaction between the T cell receptor (TCR) and cognate peptide-MHC complex (pMHC) complexes on the surface of antigen presenting cells (APCs). The TCR is a clonotypic type I integral membrane protein composed by one α and one β chain, which form a disulfide-bound heterodimer (Fig. 1) (Chothia et al., 1988; Davis and Bjorkman, 1988; Haskins et al., 1983). The $\alpha\beta$ heterodimer associates with accessory molecules, the CD3 elements (ξ, ε, γ, η and δ), which specialize in signal transduction (Brattsand et al., 1990; Irving and Weiss, 1991; Kalergis, 2003; Pitcher and van Oers, 2003; Weissman et al., 1988). TCR molecules show an enormous variability at the amino acid sequence level for both α and β chains (Bentley and Mariuzza, 1996; Ishiguro et al., 1990; McIntyre and Allison, 1983; Tanaka et al., 1990). The TCR sequence diversity is mainly localized at the variable domains of the α and β chains and defines the TCR repertoire of a particular individual (Tanaka et al., 1990; Thompson et al., 1992; Tillinghast et al., 1986). The amount of different foreign antigens that can be recognized by the adaptive immune system is determined by the TCR repertoire, which has been estimated to potentially reach approximately 10^{14} different TCR combinations (Davis and Bjorkman, 1988; Fanning et al., 1996). The diversity of the TCR repertoire results from genetic recombination events occurring during T cell development in the thymus and involves genes coding for the TCR α and β chains (Bluthmann et al., 1988; Schatz et al., 1992; Sebzda et al., 1999). The ligand for the TCR consists of foreign- or self-derived peptides bound to major histocompatibility complex (MHC) of the host. These pMHC complexes locate at the surface of APCs, such as dendritic cells, and derive from the intracellular processing of protein antigens (Rock and Goldberg, 1999). While MHC class I molecules mainly present peptides derived from cytosolic proteins degraded by the proteosome, MHC class II molecules present peptides derived from extracellular proteins degraded by the endocytic pathway (Nathenson et al., 1986; Neefjes et al., 1991). However, presentation of extracellular-derived proteins on MHC class I molecules can occur in a process known as cross-presentation as carried out by professional APCs, such as dendritic cells (Ackerman et al., 2005; Guermonprez and Amigorena, 2005). Normally APCs bear on their surfaces about 10^5 pMHC complexes of different nature, from which only very few have bound the peptide that specifically is recognized by a particular TCR (de Jong, 1998; Falk et al., 1991; Hunt et al., 1992a, b). Thus, the TCR/pMHC interaction is an

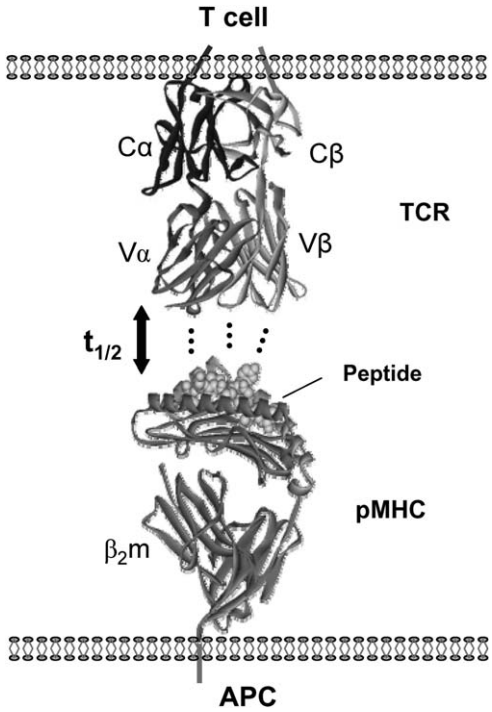

Fig. 1. The T cell receptor (TCR) is a heterodimer composed by one α and one β chain. Recognition of pMHC ligands by the TCR is mediated by complementarity determining regions (CDRs) located on both α and β chain variable domains (Vα and Vβ). TCR constant domains (Cα and Cβ) are located proximal to the membrane. The pMHC complex located on the antigen presenting cell surface bears an antigenic peptide presented on self-MHC molecules. Although the structure of the TCR and the pMHC complex has been resolved, the effect of TCR/pMHC binding kinetics on T cell activation remains controversial.