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Can two different TCRs that react with the same peptide-MHC complex influence the differentiation of naive CD4 T cells?

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Keywords

Differentiaton, T cell, TCR, transgenic mice

Context

Several studies have demonstrated that antigenic peptides can modulate the magnitude of T cell activation by influencing the rate of phosphorylation by protein kinases in the T cells and by controlling the direction of the functional immune response. For example, high doses of moth cytochrome *c* peptide induced a Th1 commitment *in vivo*, while low doses of the peptide drove Th2 differentiation. Likewise, agonist peptides forming high affinity interactions with the MHC molecule favored Th1 differentiation of naive $CD4^+$ T cells, whereas altered peptide ligands with affinities either for the presenting MHC or for the TCR favored Th2 differentiation. Moreover, the MHC haplotype itself might influence T cell differentiation as MHC molecules that bound to a peptide with high avidity promoted Th1 differentiation, in contrast to MHC molecules expressing a lower avidity for the given peptide, which favored Th2 differentiation. To investigate whether a single amino acid alteration in the TCR's peptide contacting residues affects the differentiation of naive $CD4^+$T cells in response to priming with antigenic peptide.

Significant findings

Alteration of the TCR a chain at position 51 led to a striking reduction in the number of $CD4^+$ T cells that expressed the transgenic TCR in secondary lymphoid tissue and resulted in lower proliferative responses to both peptides, with a more prominent effect on the response to the wild-type peptide CA-WT. Interestingly, after priming with CA-WT peptide 33% of sorted L51S naive $CD4^+$ T cells became IL-4-producers compared to 7% in D10.BR T cells. In contrast, 12% of the L51S cells secreted IFN-? after priming with CA-WT compared to 28% in D10.BR T cells. Different doses of CA-WT did not result in significant IFN-? production by L51S $CD4^+$ T cells. In contrast, high doses of both peptides, R2G and CA-WT, promoted Th1 differentiation of D10.BR $CD4^+$T cells, whereas low doses favored Th2 commitment.

Comments

T cell differentiation is regulated by a variety of mechanisms, such as cytokines and signals delivered through costimulatory molecules on T cells. The effect of antigenic peptides presented by MHC II molecules on T cell commitment has been well documented, but the role of the T cell receptor (TCR) in determining Th1/Th2 differentiation has been less well delineated. In this paper the effect of a single amino acid substitution in the second complementarity-determining region (CDR2) of the a chain of the TCR on T cell differentiation was investigated using purified naive $CD4^+$ T cells from transgenic mice bearing either the parent or the altered TCR. Whereas high doses of peptide favored Th1 differentiation of the parent TCR $CD4^+$ T cells, the altered TCR bearing $CD4^+$ T cells became interleukin (IL)-4-producers. Thus, a single amino acid alteration in the TCR influenced the outcome of T cell differentiation. This observation confirms the important role of TCR-peptide-MHC II ligation not only for T cell activation and T cell proliferation, but also for distinct cytokine secretion.

Methods

$CD4^+$ T cells from TCR transgenic mice, expressing either a wild-type TCR specific for chicken conalbumin (D10.BR mice) or an altered TCR bearing a leucine-to-serine substitution at position 51 in CDR2 of the TCR a chain (L51S mice), were isolated from lymph nodes and spleen. Function and differentiation of naive $CD4^+$ T cells into Th1 or Th2 effectors was assessed after primary and secondary stimulation with two peptides from chicken conalbumin, the wild type (CA-WT) and a mutated peptide, R2G.

References

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