On the logic of positive selection

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This is a comment that questions the almost unanimous assumption that the T-cell antigen receptor (TCR) delivers distinctly different signals dependent on the level or duration of occupancy.

When the TCR of the thymic precursor ($CD4^+$ $CD8^+$) (referred to here as oT) docks on the major histocompatibility complex-encoded restricting element (referred to here as R_T) that is expressed by the positively selecting thymic cell, the oT-cell receives three bits of information:

1 That it has recognized an allele-specific marker on thymic-R_T and will therefore be saved from death-by-neglect.
2 That it should differentiate to become a cytotoxic ($CD8^+$) or helper ($CD4^+$) cell dependent on whether the allele-specific determinant is on a Class I (RI) or Class II (RII) restricting element.
3 Whether its specificity for peptide is anti-self (Ps), which results in its deletion (i.e. negative selection), or anti-non-self (Pns), which is the residue that provides the functional protective repertoire.

The second bit of information includes the first but it is separated in order to stress that it is restrictive recognition that is under analysis.

The discussion requires that two questions be separated:

1 How does the thymic selecting cell that expresses R_T, signal the oT-cell (a) that its TCR is of a matching allele-specific recognition and (b) what its lineage should be?
2 How is this signal from the thymic selecting cell read or interpreted by the oT-cell?

Under the Standard Model (e.g. as reviewed in 1–6) the TCR delivers three qualitatively distinct signals dependent on occupancy (level or duration) that are read by the oT-cell as initiating three distinct pathways: inactivation (negative selection), cytotoxic, helper. This three signal Standard Model is derived from the assumption that the TCR is B-cell receptor-like in that it has a unique combining site that recognizes a determinant formed by a meld (Q) between peptide (P) and restricting element (R) (i.e. $P + R \rightarrow Q$). Buried in all of this is the assumption that selection for intermediate occupancy anti-self specificity is the source of the high occupancy anti-non-self repertoire that functions to protect the host. This has to be questioned as occupancy is multifactorial and an adequate degree of specificity is key to a self–non-self discrimination. This model of TCR signalling is sufficiently improbable to warrant consideration of a competing proposal, the Tritope Model.[7–9]

Under the Tritope Model, one receptor can only deliver a single signal, which in this case is peptide-specific and read by the oT-cell ($CD4^+$ $CD8^+$) as inactivation (negative selection). No signal to the oT-cell via the TCR upon interaction with R_T can tell that cell if its TCR is RI_T- or RII_T-restricted. The only component that can be a decision-maker in positive selection is the thymic restricting element, RI_T or RII_T, itself. Therefore, the signal determining the relationship between function and restriction specificity must originate from the RI and RII elements on the thymic selecting cell and not be delivered via the TCR.

Now we can address the first question. What minimal scenario might be envisaged?

In the Tritope framework positive selection is P-unspecific (anti-P independent). It is dependent solely on an interaction of the TCR with R_T, which, of course, is allele-specific. The TCR docking on R_T induces a concerted conformational change in both the TCR and R_T that initiates a signal via the thymus selecting cell to the oT-cell. In other words, it is the TCR acting as a ligand for R_T acting as a receptor that initiates the differentiative signal. The oT-cell receiving an R_T-initiated signal has two pathways open to it. The choice between two pathways requires two qualitatively distinct signals. In the previously presented model[8] an RI-signal for the cytotoxic lineage ($CD8^+$) and an RII-signal for the helper lineage ($CD4^+$) was proposed that passes from the RI- and RII-elements via CD8 and CD4, respectively, to the oT-cell.

This proposal now needs tweaking by separating the signal for survival (rescue from death-by-neglect) from the signals for lineage commitment. The survival signal can either be delivered via the TCR which undergoes a conformational change when docking on R, or via an interaction of oT with a RI/II activated ligand on the thymic selecting cell. In either case, the survival signal cannot determine lineage commitment.

Collins and Littman[4] have pointed out the possibility of a default pathway to the CD8 lineage that can be diverted to the CD4 lineage. In this event, the survival signal might be viewed as initiating the differentiation to $CD8^+$ and an RII-initiated signal would trigger diversion to $CD4^+$. Even were the survival signal to pass via the TCR, it would be unable to distinguish RI from RII. The diversion of the default CD8 pathway to the CD4-lineage would require an RII-specific signal initiated by the interaction of the TCR with RII and delivered via CD4. A default pathway to the CD8-lineage would obviate the need for an RI-specific signal. The default pathway is favoured by the finding that (1) CD8 lineage commitment occurs in the absence of CD8;[10] and (2) RII-restricted cytotoxic T-cells are generated in the absence of CD4[5,11] or in *hd* mutant mice.[2,12] Whichever scenario is envisaged, a default plus an RII-signal or an RI and an RII signal, the TCR occupancy (level or duration) does not determine the lineage commitment and the survival signal does not engage the self-peptide as a specificity element. A signalling engagement of self-peptide would result in deletion (negative selection).

This introduces the second question, which has been discussed in detail.[1–6] It is not germane to this comment as no TCR-specific interactions are involved. What is involved is a cascade of signal transducing factors that focus on the Th-POK[6] as a master switch in the oT-cell.[1,2,6]

If the eventual functional presence or absence of the Th-POK transcription factor is the switch between the oT-cell becoming a helper ($CD4^+$) or a cytotoxic ($CD8^+$) cell,[1,2,6] then an RII-initiated signal from the thymic selecting cell must, in the end, determine the functional presence of Th-POK and an RI-initiated or a survival signal must determine its functional absence. Transmission of these two signals from the thymic selecting cell to the oT-cell is a reasonable alternative to the presently popular model of a multiply signalling TCR. This model is lacking because no signal via the TCR, whether it occurs or not[1–6] can determine the class of R/effector function relationship.[7–9]

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