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THE ROYAL SOCIETY

The terminology problem for T cells: a discussion paper

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The school of thought that owes allegiance to Ludwig Wittgenstein teaches that language conditions perceptions. When we use the term 'cytotoxic T lymphocyte' or 'helper T cell' we tend to orientate our own thinking processes, and those of listeners or readers, down particular paths. Part of the problem is that we are often describing cell populations by functions that may either be a property of only a proportion of those that are being assayed, or are simply inferred from the expression of various cell-surface markers. The consequence can be a measure of confusion that might be avoided if we could communicate with greater clarity. Is it possible to achieve a better terminology that will be accepted generally? The following are some examples of why there may be some value in thinking about this.

Keywords: memory; helper T cell; cytotoxic T cell; terminology

1. CYTOTOXIC T LYMPHOCYTE

The term cytotoxic T lymphocyte (CTL) implies that the lymphocyte has the capacity to kill other cells. This has always been a source of considerable confusion. In the first place, even if we have a population that is highly active in the standard ^{51}Cr release assay, we have absolutely no idea what proportion of these cells are functional killers. The situation is even worse when we realize that many who work with (for example) human systems will write that 'CTL were recovered from the blood', when what they are actually saying is that lymphocytes that can be restimulated *in vitro* to mediate CTL activity are present in the circulation. There is a big difference between these two scenarios: the former implies continuous activation, while the latter is simply describing the presence of established memory.

The availability of tetrameric staining reagents of MHC class I glycoprotein + peptide (tet) has made the terminology problem more urgent. We may now describe tet^+CD8^+ cells as CTL effectors (eCTL) if they are isolated during the acute phase of the host response, or as memory CTL precursors (mCTL) if they are measured after we can no longer detect antigen. However, it is highly likely that many of the tet^+CD8^+ cells that are recovered when high levels of antigen are still present are not activated to mediate eCTL function but are on their way to becoming mCTL. Also, what proportion of the tet^+CD8^+ mCTL that we stain will later actually develop eCTL function *in vivo* following a re-encounter with the cognate antigen? How do we describe the tet^+CD8^+ cells that are around in the long term under conditions of persistent infection, the normal situation with Epstein–Barr virus (EBV) and other herpesviruses? Are these mCTL or eCTL? Calling them partially activated CTL (paCTL) would add a further level of silliness.

2. MEMORY

Nowhere has the problem of semantics led to more pointless debate and confusion than in the discussion of memory. The difficulty is that some consider 'memory' and 'protection' to be synonymous, while others argue that 'memory' simply implies evidence of a prior encounter with antigen. The former definition would seem to exclude people who work with proteins such as hen egg lysozyme from the memory field, which does not make much sense. Even so, our practical concern as immunologists is clearly to maximize protection. Memory is a perfectly respectable English word, but the dictionary definition addresses 'the (mental) faculty of retaining and recalling' and 'persistent modification of behaviour resulting from the organism's experience', so does not help us much with the current argument. We could, for example, talk about protective (pCTL) and mCTL, but 'p' is already widely used for 'precursor', which refers directly to the implied starting population measured by limiting dilution analysis (LDA).

3. HELPER (T_H) AND DELAYED TYPE HYPERSENSITIVITY (DTH) CELLS

The terminology for the $CD4^+$ subsets is little better than that applied to the $CD8^+$ T cells. We often talk about T_{H1} or T_{H2} cells in contexts that have little to do with providing 'help' for B lymphocytes but are focused instead on various effector functions operating, for example, during the course of an inflammatory process required to control some protozoan parasite. In the past, this would have been referred to as 'DTH' but, like cell-mediated immunity (CMI), the term 'DTH' has been tending to fall from use. Maybe that is not such a bad thing, as the definitions of 'hypersensitivity' are somewhat historical and also carry elements of confusion. Transferring the T_H

nomenclature to $CD8^+$ T cells that may be canalized to produce particular cytokines (T_{C1} and T_{C2}) has also added a new level of potential complexity, though some of what we discuss as CTL function may be more appropriately considered in the 'T_C' context.

The term 'T_H' has also been singularly unhelpful when we discuss the capacity of a concurrent $CD4^+$ T-cell response to promote the clonal expansion and differentiation of $CD8^+$ effector and memory cells. 'Help' for B cells implies a cognate interaction between the two lymphocytes, mediated via one cell recognizing MHC class II glycoprotein + peptide expressed on the other. What is the nature of 'help' for $CD8^+$ T cells, which are unlikely to process antigens through the exogenous pathway and, in any case, are MHC class II^- in the mouse? The two processes are clearly different. It would be useful if the terminology could reflect this.

4. WHAT SHOULD BE DONE?

The following suggestions are meant simply to stimulate discussion. The underlying idea is that we should be able to develop a better and more concise descriptive code. Maybe we could think about the following.

(i) Should we drop 'CD4' and 'CD8'? Though the use of the 'CD' nomenclature has generally been valuable, it would eliminate at least one letter from the code if we went to T8 and T4. Also, could we accept that T8 (or CD8) means $T8^+$ or $CD8^+$, unless we need to add the qualifier to identify (for example) thymocyte subpopulations or odd subsets in the periphery?

(ii) A useful convention is to put the term that provides a physical description in front. An example would be $CD44^{hi}$T8: might this be simplified '44^{hi}T8'?

(iii) Could we develop a set of universal qualifiers to define the stage of the host response rather than a particular function? These might be: N, naive; A, acute; M, memory; and P, situations where there is known antigen persistence. This would mean that the 'tet^+T8A' population would simply be the set of tet^+T8^+ cells detected by flow cytometry during the acute phase of the response. The comparable lymphocyte population from an individual with controlled EBV infection would be 'tet^+T8P'.

(iv) It would then be possible to add the definition functional characteristics for particular subpopulations as upper-case subscripts. If we used 'K' (killer) and 'C' (cytokine), this would give us 'tet^+T8A_K' or 'tet^+T8A_{Cl}'. These convey more accurate information than 'tet^+eCTL' or 'tet^+mCTL'.

(v) Any further descriptor could be added as a lower-case subscript, to be defined in the particular context. A cell recovered during the acute response that expresses perforin might then be 'tet^+T8A_{Kp}'.

(vi) The problem of terminology for the tetramers also needs to be tackled. One suggestion is to give the MHC allele, then the protein and the first position number for the sequence. An influenza nucleoprotein (NP)-specific $CD8^+$ memory T cell that stains with the tetramer of H-$2D^b$+$NP_{366–374}$ would then be described as 'D^bNP_{366}T8M'. The obvious problem is that this reads like a postcode. Given that the MHC allele has been defined as class I, is it sufficient to say 'D^bNP_{366}M'?

5. CONCLUSIONS

Having taken the time to set down some possible ways that we might modify the nomenclature for T lymphocytes, I am not sure that all (or any) of the above suggestions are useful. Some of these proposals look to be worse than the present situation. However, the intention has been to stimulate discussion. This will hopefully provide a starting point. Where, if anywhere, do we go from here?

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