Immunology

Cytolytic T-cell melodrama

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How can some T cells lyse other cells *in vitro*? The currently most popular view is that of a murder, the cytolytic T cells somehow sending pore-forming molecules to target cells which die as a direct consequence. The challenging opinion sees the cytolytic T cells as inducing the target cells to commit suicide. This opinion receives strong support from a report by David S. Ucker on page 62 of this issue[1] showing that a mutable element within the target cells governs their lysability by T cells or by glucocorticoids. Which precise mechanism is at work may well be of great practical importance, as lysis by T cells *in vitro* probably mimics the disposal by T cells *in vivo* of virus-infected cells and possibly of tumour cells.

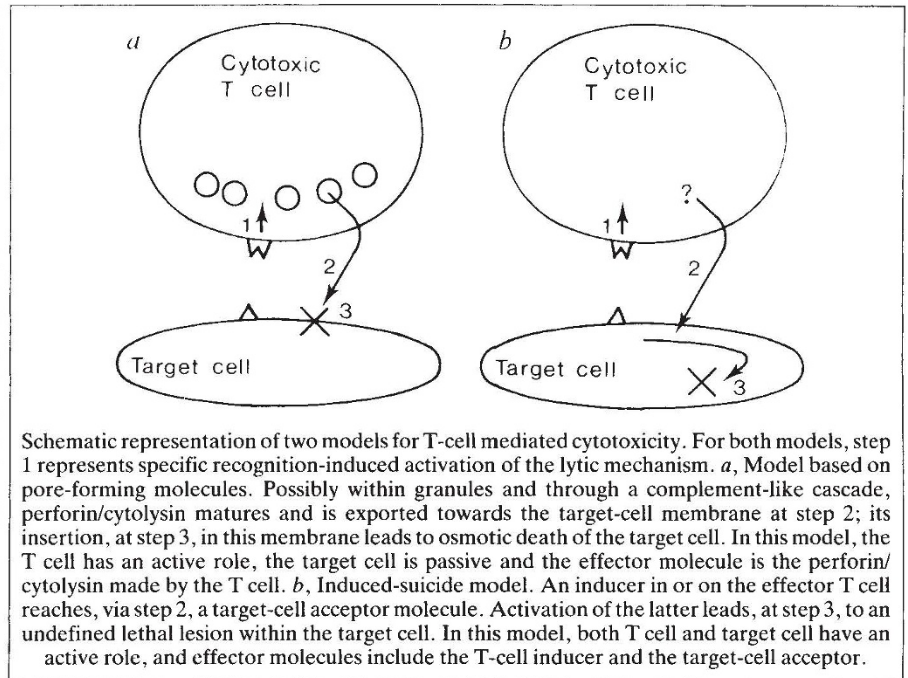
The current quasi-dogma, based on pore-forming molecules (*a* in the figure), stems from striking apparent analogies between lysis by T cells and lysis by soluble factors of the complement system. First, fractionation experiments[2,3] led to the discovery in cytolytic T and natural killer (NK) cells of pore-forming, lytic molecules called perforin or cytolysin, with similarity[4-6] to the lytic pore-forming C9 component of the complement system. Second, the presence of several serine esterases, identified either at the protein[7] or at the nucleic-acid level, mostly (but not only) in cytotoxic T and NK cells, is very reminiscent of the presence of other serine esterases at several steps of the complement maturation cascade. These results made a pore-forming, complement-like mechanism of T-cell killing a reasonable bet.

A few disquieting observations or questions have emerged, however. First, antibodies that inhibit perforin-mediated lysis do not inhibit T-cell mediated (as opposed to NK-cell mediated) lysis. Second, what protects the cytolytic T cell itself from being lysed by the pore-forming protein it produces? Third, no perforin activity was detected[8] in highly cytotoxic, sensitized T cells from the peritoneal exudate. Fourth, and relevant to what follows, when target cells are subjected to cytolytic T cells, it is their nuclear, not cytoplasmic, membrane that is altered first[9], with rapid DNA fragmentation[10]. Interestingly, corticosteroids induce similar phenomena in thymocytes[11]. How can the first detectable effect of an external toxic agent be the lysis of an internal membrane?

The alternative, then, was to postulate[9-11] that an internal auto-destructive mechanism is triggered (*b* in the figure). In line with this concept, Ucker in this issue[1] now shows that, although a given thymoma cell clone is sensitive to both corticosteroids and T-cell mediated cytotoxicity, a variant clone derived therefrom is resistant to both (but not, significantly, to complement-mediated lysis). He checked resistance by cloning efficiency, ^{51}Cr release and DNA fragmentation assays. The striking difference between parent and variant is not accounted for by any detectable difference in recognition pathways (that is in the amounts of glucocorticoid receptors on one hand or antigen-specific binding on the other — and the fact that lectin bypass of T-cell recognition still leads to no lysis of the variant cell). Moreover, a rare spontaneous revertant cell could be isolated, through its sensitivity to glucocorticoids, which is also sensitive to T-cell mediated cytotoxicity. Thus, a parent cell is sensitive to both corticosteroids and T-cell mediated cytotoxicity, a variant cell is resistant to both, and a rare revertant is sensitive to both.

A minimal conclusion from these results is that a mutable target-cell molecule, at a stage apparently distinct from recognition by corticosteroids or T cells, controls target-cell lysability by either. This molecule would not be required for cell life (because a variant cell where it is mutated can still multiply) but would be required for certain varieties of cell death (as the same variant cell cannot be lysed any more by certain otherwise lethal agents). This putative molecule may have a more general function related to the ability of the cell to die, perhaps relevant to the programmed death postulated in the thymus and in some forms of cell senescence.

The increased possibility of an induced suicide mechanism may call for a modification of fractionation strategies (see figure legend). It may be necessary to look, not or not only for a cytolytic molecule in the effector cell, but for inducer molecule(s) in the effector cell and an 'acceptor' molecule (as inferred from Ucker's work) in target cells. Another implication comes from previous observations that cytolytic T cells can themselves serve as targets; their postulated inducer and acceptor molecules might have to reside in different cellular compartments if these cells are to live at all. Finally, which role would then remain for the T/NK cell pore-forming proteins — a decoy masking the induced suicide mechanism, or perhaps an alternative killing system operating as a function of the particular effector and/or target cells at play? □



Schematic representation of two models for T-cell mediated cytotoxicity. For both models, step 1 represents specific recognition-induced activation of the lytic mechanism. *a*, Model based on pore-forming molecules. Possibly within granules and through a complement-like cascade, perforin/cytolysin matures and is exported towards the target-cell membrane at step 2; its insertion, at step 3, in this membrane leads to osmotic death of the target cell. In this model, the T cell has an active role, the target cell is passive and the effector molecule is the perforin/cytolysin made by the T cell. *b*, Induced-suicide model. An inducer in or on the effector T cell reaches, via step 2, a target-cell acceptor molecule. Activation of the latter leads, at step 3, to an undefined lethal lesion within the target cell. In this model, both T cell and target cell have an active role, and effector molecules include the T-cell inducer and the target-cell acceptor.

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