

Breaking the kinetic window of T-cell activation

T cells recognize peptide antigens associated with MHC molecules on the surface of target cells. The antigen specificity of T cells is conferred by the T-cell receptor (TCR). During the development of T cells, those expressing a TCR that recognizes a self-peptide–MHC weakly are selected for and those that bind to such a complex with high avidity are selected against. These positive and negative selection processes produce a peripheral T-cell repertoire that is MHC-restricted but not self-reactive. The ability of a peptide–MHC complex (pMHC) to trigger T-cell activation does not relate necessarily to the equilibrium binding affinity of the TCR–pMHC complex, but correlates better with the off-rate of the interaction. Small changes in the sequence of an antigenic peptide can lead to slightly faster off-rates; relatively small changes in the off-rate, and hence the half-life of the TCR–pMHC interaction, can affect greatly the ability of a ligand to trigger T cells. A single agonist pMHC has been shown to engage and down-regulate >100 TCR molecules from the T-cell surface. This process of ‘serial triggering’ is believed to be necessary for

optimal T-cell signaling and activation. Further extrapolation has predicted that agonist TCR–pMHC interactions fall within a ‘kinetic window’, representing a compromise between sufficient time to allow all of the molecular steps required to trigger the TCR and a rapid enough dissociation from the triggered TCR to make it available for further cycles of binding and triggering. An ‘affinity ceiling’, beyond which there is no advantage to T-cell activation, is implicit in such models.

Until recently, TCRs with sufficiently high affinities with which to test this hypothesis had not been isolated. However, Kranz and colleagues have engineered high-affinity mutants of MHC-class-I-restricted TCRs by a process of directed evolution. Their most recent study examines the ‘affinity ceiling’ for T-cell activation [1]. Their results challenge the current ‘kinetic window’ models of T-cell activation by showing that cells expressing a TCR with a 300-fold higher affinity and 45-fold longer off-rate (at 25°C) compared with the wild-type TCR, produce IL-2 in response to peptide at significantly lower peptide concentrations than T cells expressing wild-type TCR. Work in progress

indicates that this is true of other high-affinity TCRs and the findings also hold true in the presence of the CD8 coreceptor. It remains to be determined if such findings are relevant for other readouts of T-cell activation and for MHC-class-II-restricted T cells.

The authors believe that their findings are inconsistent with the notion that serial triggering is required for T-cell signaling and suggest that current models of T-cell activation need to be revisited. Increasing evidence suggests that negative selection might prevent the development of high-affinity TCRs *in vivo*. However, this study indicates that such TCRs could be more efficient at antigen recognition and further highlights the potential use of *in vitro* engineering of high-affinity TCRs to increase the activity of specific T cells in adoptive T-cell therapies.

1 Holler, P.D. *et al.* (2001) CD8⁺ T-cell transfectants that express a high-affinity T-cell receptor exhibit enhanced peptide-dependent activation. *J. Exp. Med.* 194, 1043–1052

Andrew K. Sewell

andy.sewell@ndm.ox.ac.uk

In Brief

Eating broccoli could prevent cancer



Previous research has suggested that selenium can protect humans against prostate and other cancers, and reduce the number of deaths from cancer. New research on laboratory rats shows that a diet containing selenium-enriched broccoli sprouts and florets might protect against breast and colon cancer. The broccoli used in the study was specially grown to contain larger amounts of selenium than in commercial products. Rats fed

high-selenium broccoli had a lower incidence of mammary tumors and fewer tumors overall at the end of the study period than rats fed low-selenium broccoli or selenium alone. The investigators found that high-selenium broccoli sprouts and florets were equally effective in protecting against colon cancer, and both were more effective than diets containing selenium in the form of selenite, the ordinary form of the mineral. So, to protect against colon cancer, one must take into consideration not only the total intake of selenium but also, the form in which selenium is supplied in a particular food or supplement. *J. Agric. Food Chem.* (2001) 49, 2679–2683 SW

Nanoscale silver bullets?

Alpha particles mediate effective radiotherapy by killing cells directly. However, delivering these particles to the target tissue often causes substantial collateral damage. Using actinium-225 coupled to a chelator molecule, in turn

bound to an internalizing monoclonal antibody, it is possible to give localized radiotherapy in murine models of solid and disseminated cancers. The molecular smart bomb is internalized efficiently, where it delivers four alpha particles to surrounding cells, resulting in their death. The construct has proved more effective than less potent short-lived bismuth isotopes, which deliver only a single alpha particle during their decay. The 10-day half-life of actinium-225 makes it a practical clinical source for tumor therapies. *Science* (2001) 294, 1537–1540 CM

A new gene family linked to asthma susceptibility



The identification of genes that predispose individuals to asthma has proven difficult. However, scientists led by Rosemarie DeKruyff