Perfecting peptide priming

A single amino acid change in a tumor-derived peptide results in the priming of a bigger and better T cell response upon vaccination, according to a study by Chen et al. on page 1243. Thus, results obtained with the original peptide, which is in phase I clinical trials as an anticancer vaccine, may be further enhanced by using the modified peptide.

Single amino acid changes in peptides can either enhance or inhibit activation of the T cells whose T cell receptors (TCRs) bind the peptide–HLA complex. Structural alterations in the HLA–peptide–TCR complex are thought to cause these functional changes, although how structural changes modify the signaling events inside the T cell is not completely understood.

To address this question, Chen et al. crystallized peptide–HLA–TCR complexes using either a wild-type tumor peptide or a variant peptide containing a cysteine to valine mutation at the COOH-terminal residue—a mutation they had previously shown to enhance killing of peptide-coated target cells by cytotoxic T cells. The altered peptide bound to the HLA molecule more tightly and created a longer lasting, more snug fit between the peptide–HLA complex and the TCR.

This cozier interaction caused T cells to polarize their lytic granules toward target cells more rapidly and produce more cytokines upon target cell contact. The authors think that the tailored complex optimizes signaling events at the immunological synapse. Indeed, T cells stimulated with the altered peptide were less dependent on the CD8 coreceptor, which is necessary to stabilize some lower affinity TCR–HLA interactions.

Immunization of mice with the tighter fitting peptide primed more interferon-γ-producing T cells than were primed by the wild-type peptide, suggesting that vaccines that use the altered peptide vaccine may produce a superior T cell response.

Slight alterations in peptide sequence alter the peptide–HLA–TCR interaction and affect T cell priming.

Prostate cancer’s one–two punch

Tumors can avoid immune destruction despite being invaded by tumor-specific CD8+ T cells. On page 1257, Bronte et al. describe one way that prostate tumors subdue T cells—they make two enzymes that combine forces to cripple T cell signaling components.

Tumors use a variety of tactics to avoid attack by cytotoxic CD8+ T cells; one is to establish an inhospitable environment that inhibits T cell activation. In recent mouse studies, myeloid suppressor cells infiltrated tumors and set up an inhibitory environment, apparently by making two enzymes—arginase and nitric oxide synthase 2 (NOS2).

Both enzymes can inhibit T cell functions independently. But when expressed together, the enzyme duo triggers a cascade of reactions that culminates in the production of peroxynitrite—an oxidizing agent that nitrates tyrosine residues on proteins. Tyrosine nitration blocks the tyrosine phosphorylation events required for T cell activation and promotes apoptosis.

Increased expression of both arginase and NOS2 in human prostate tumors has been reported, but their affect on tumor-infiltrating T cells has never been directly studied. Bronte and colleagues now show that CD8+ T cells in human prostate tumors failed to up-regulate the activation markers CD25 and CD69 in response to mitogenic stimulation. Activation was restored when both arginase and NOS2 were inhibited. This occurred even without exogenous stimulation, suggesting that the reawakened T cells were responding to in situ–presented tumor antigens.

The need to inhibit both enzymes to reanimate the T cells, and the presence of nitrotyrosine-positive cells in the tumor tissue, pointed to tyrosine nitration as the key to the T cell inhibition in this model. The authors are now trying to understand what triggers the expression of these enzymes in tumors and whether the same mechanisms operate in other human tumors.
Healing with hyaluronan

Specialized T cells in the skin lay a sugary foundation for macrophage migration into wounds, according to a study on page 1269. Jameson and colleagues show that the absence of dendritic epidermal γδ T cells (DETCs) removes the impetus for skin cells to secrete hyaluronan, an extracellular glycan that is required for macrophage entry into wounds. Without macrophages, wounds can't heal.

Wound healing is initiated when DETCs recognize an unknown antigen on damaged skin cells. Neutrophils and, later, macrophages migrate to the wound site; both cell types are needed for complete healing. This group had previously shown that wound repair breaks down in the absence of DETCs due to a lack of keratinocyte growth factors FGF-7 and FGF-10, which are produced by DETCs in wounds and stimulate keratinocyte regeneration.

Jameson et al. noted that nonhealing wounds in DETC-deficient mice were less inflamed than normal wounds. They now show that, though neutrophils arrived at the wound on schedule, macrophages showed up late. The macrophage tardiness could be traced back to the lack of FGF-7. In normal wounds, FGF-7 was found to trigger the production of hyaluronan by neighboring keratinocytes and hyaluronan was needed to recruit macrophages. If hyaluronan (or FGF-7) was added back to the wounds, the macrophages returned and healing was restored.

Impaired wound healing is prevalent in patients with diabetes and rheumatoid arthritis. The authors hope to investigate whether impaired DETC function may be to blame in these human diseases. JEM

Neutrophil–DC close encounters

On page 1281, van Gisbergen and colleagues describe for the first time a direct interaction between neutrophils and dendritic cells (DCs). The event triggers DC activation, primes T helper 1 (Th1) cells, and may help explain why Th1 responses to some pathogens are impaired in the absence of neutrophils.

Neutrophils have been shown to influence the priming of Th1 responses indirectly: they secrete cytokines and chemokines that promote Th1 responses and recruit DCs into infected tissues. But van Gisbergen et al. now show that neutrophils don’t always keep their distance. They can interact with DCs directly through binding of the C-type lectin DC-SIGN on DCs to specific carbohydrate structures on the neutrophil integrin Mac-1. Neutrophil–DC binding triggered activation of the DCs as measured by DC up-regulation of CD86 and secretion of interleukin-12. But this only happened if the neutrophils were first activated, suggesting that DC activation only occurs in an inflammatory setting. Neutrophil-activated DCs went on to prime interferon-γ-producing Th1 cells.

One possible consequence of this interaction, the authors speculate, might be transfer of antigens from the neutrophils to the DCs, although this idea remains to be tested. Another open question is whether neutrophils receive signals as part of the relationship with DCs. JEM

Polymerase pinch hitters

On page 1191, Delbos and colleagues provide the first proof that the error-prone polymerase η (polη) is responsible for mutations at A-T base pairs during somatic hypermutation (SHM) of immunoglobulin (Ig) genes in mice. But when polη is removed from mice, another sloppy enzyme, not previously thought to contribute to SHM, can fill in as a pinch hitter.

SHM generates high affinity antibodies in response to antigenic challenge; it does so by introducing point mutations into the antigen-binding regions of B cell antibody genes. Mutations at C-G base pairs during SHM are the work of the enzyme AID (activation-induced cytidine deaminase), which turns cytosine into uracil. A-T mutations have been harder to explain. Error-prone polymerases are thought be the culprits behind A-T mutation, but specific roles for these enzymes have been difficult to assign, as mice lacking individual polymerases have thus far shown no defects in SHM.

Polη has been the primary suspect charged with mutating A-T base pairs, as the pattern of errors made by polη in vitro is reminiscent of that seen in mutated Ig loci. In addition, humans lacking polη have fewer A-T mutations in their Ig genes than normal. Delbos et al. now solidify the evidence by showing that elimination of polη in mice decreases Ig gene mutations at A-T base pairs.

The few A-T mutations that occurred in the absence of polη—to the authors’ surprise—bore the signature of another polymerase, polκ, which does not normally meddle in SHM. The authors suggest that the mismatch repair protein complex MSH2–MSH6, recently shown to recruit polη to AID-induced U-G mismatches, may in polη’s absence instead bind polκ. The polκ would then cause mutations at nearby A-T sites. JEM