“License to kill” reflects joint action of CD4 and CD8 T cells

Cornelis JM Melief

ISA pharmaceuticals, & Leiden University Medical Center, Leiden, The Netherlands, corresponding author, e-mail: Melief@isa-pharma.com

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Running title: “License to kill” revisited
Summary

The spontaneous T cell responses to the KIF20A cancer-associated antigen found by Tomita and colleagues among PBMC of cancer patients, but not healthy people, involve both CD4 and CD8 T cells. Synthetic long peptides of KIF20A stimulate synergy between these two T cell types to promote cancer cell killing.
In this issue of CLINICAL CANCER RESEARCH, Yusuke Tomita and colleagues (1) report exciting results showing that the simultaneous presence of a CD4 and a CD8 epitope in long peptides of the tumor-associated protein kinesin family member 20A (KIF20A) synergistically stimulates tumoricidal CD8+ CTL responses. KIF20A is over-expressed in a variety of cancers, including 55% of patients with H&N cancer. Therefore the identification of synthetic long peptides (SLP) that harbor epitopes presented by both HLA class I and HLA class II molecules, recognized by CD4+ and CD8+ T cells, respectively, expands the number of attractive target antigens for immunotherapy of cancer. The study once more strikingly illustrates the important role that CD4+ helper cells can exert in promoting the activity of cytotoxic T lymphocytes (CTL, “killer cells”). Traditionally, emphasis in cancer immunotherapy against specific target antigens has been focused on CD8+ CTL, recognizing processed peptides presented by HLA class I molecules. Undoubtedly the induction of such CTL, capable of direct killing of cancer cells through perforin, Granzyme B and Fas-dependent mechanisms, is of utmost importance. Nevertheless, the crucial role that CD4 helper cells play in enhancing CD8 effector cell function, in establishing CD8 memory (reviewed in 2) and in favorably influencing the cancer micro-environment (3), has been underestimated. Moreover, recent evidence shows that CD4+ effector cells can exert formidable tumoricidal activity in their own right by the interferon-γ induced expression of MHC class II on cancer cells followed by cancer cell demise through the same killing mechanisms as used by CD8+ T cells (4), can stimulate tumoricidal macrophages (5) or cause cancer cell senescence via the production of a combination of interferon-γ and TNF-α (6).

Arguably, the formidable power unleashed by CD4+ helper cells triggered by specific HLA-class II-bound peptides in enhancing DC activation through CD40Ligand (CD154) up-regulation on the CD4 T cell surface, followed by CD40 triggering of DC (the so-called “Licence to kill” signal, Fig. 1) is what matters most (reviewed in 2). The importance of a productive interaction between three major cell types, CD4+ T cells, DC and CD8+ T cells in establishing robust cell-mediated effector function of the CD4+ T cells themselves and of CD8+ T cells optimally “licensed to kill” by DC and to simultaneously establish CD4 and CD8 memory (Fig. 1), has been amply demonstrated in many infectious disease and cancer models (reviewed in 2). To some extent TLR Ligand triggering of DC can replace or synergize with CD40L triggering (7). Residual questions concern the efficiency of cross-presentation to CD8+ T cells of SLP by DC and the need for specific help versus non-specific help. Although SLP are more efficiently cross-presented by DC than proteins (8), SLP cross-presentation can be further enhanced by covalent coupling of TLR ligands to the SLP (8). This leads to simultaneous DC targeting and DC activation in vivo, allowing reduction of immunogen dose and increased efficacy of therapeutic vaccination. Not surprisingly, the use of tumor-specific help appears to be superior to the use of non-specific help, such as that provided by vaccination with Keyhole Limpet Hemocyanin (KLH).

How then can we use these insights for optimization of cancer vaccines? First, the report of Tomita et al. reinforces the notion that optimal cancer vaccines should contain both CD4+ and CD8+ epitopes of the intended target antigen(s). An efficient way to present these to the immune system is by SLP incorporating both types of epitopes. Second, these vaccines should be delivered together with powerful DC stimuli such as appropriate TLR ligands or other powerful ligands of molecular danger sensors. Although meaningful clinical results have been achieved by vaccination with short
exact HLA class I-binding peptides with appropriate adjuvants\textsuperscript{(9)}\textsuperscript{(10)}, in particular TLR9 Ligand CpG\textsuperscript{(10)}, vaccination with short peptides can sometimes lead to deletion of T cells \textsuperscript{(2)} and is in any case suboptimal, because it does not benefit from the opportunity provided by specific CD4+ help induction. Covalent linkage of TLR Ligands or other “danger” sensors and SLP enhances the efficacy \textsuperscript{(8)}. These same principles apply to DNA- or RNA-based cancer vaccines, that should and often do encode both helper epitopes and CTL epitopes next to danger signals. Viral vectors can also fulfill these requirements, but suffer from antigenic competition of tumor antigens encoded by the vector with viral vector sequences and from often complex immuno-modulatory effects mediated by the viral vector that may prove hard to harness. Finally, regardless of the potency of new generations of cancer vaccines, combination treatment with traditional therapies such as chemotherapy or radiation therapy or with recently developed therapeutic modalities such as checkpoint control antibodies\textsuperscript{(11)}\textsuperscript{(12)}, is likely essential for major therapeutic impact. Appropriate timing and dosing of traditional treatments and immunotherapy need to be carefully studied to achieve optimal results.

**References**


Legend to Figure 1

Licence to kill. Optimal induction of MHC class I-restricted cytotoxic T lymphocyte responses involves processing from long peptides of sequences presented by both MHC class I molecules and by MHC class II molecules of professional antigen presenting cells, Dendritic Cells (DC). CD4 T cells triggered by MHC class II presentation up-regulate CD40 ligand (CD40L, synonymous with CD154) . CD40 L will engage CD40 on DC to mature (activate) the DC, causing up-regulation of a variety of co-stimulatory molecules: CD80, CD86, CD70 and of MHC molecules themselves. Together this array of co-stimulatory molecules and optimal specific antigen presentation by MHC class I licenses the DC to induce optimal expansion and activation of CD8 killer cells (“licence to kill”). Simultaneous TLR Ligand triggering of the DC can synergize with CD40 triggering for optimal DC maturation.
Figure 1:

- T-helper
- T-killer
- iDC
- mDC
- IL-2
- CD40L
- CD40
- TLR ligands
- Activation
- Costimulation

Synthetic long peptides
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Cornelis JM Melief

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