Precision guiding of cytolytic T-lymphocyte responses in cancer immunotherapy

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Molecular triggers of dendritic cell (DC) activation sufficient for induction of CD8+ cytotoxic T lymphocyte (CTL) responses include agonistic CD40 antibody or ligands of Toll like receptors such as LPS (TLR4 ligand) or CpG (TLR9 ligand). In natural immune responses specific CD4 cells, reactive with peptide antigens presented by MHC class II molecules on DC, can also drive maturation of DC that is required for CD8+ CTL response induction. CD4+ T helper cells to a large extent operate through upregulation of CD40L which then interacts with CD40 on DC to cause the required DC activation. Important cognate interactions for full CD8+ CTL induction by activated DC are CD80/CD86 on the DC, costimulating CD28 on the CD8 cells. For maintenance and full expansion of CD8+ T cells, interaction of 4-1 BBL [another member of the TNF(R) family] on DC with 4-1 BB on CD8+ CTL is also important. In the absence of CD80/CD86 costimulation, the 4-1 BBL > 4-1 BB interaction appears to be inactive. Thus proper induction, expansion and maintenance of CD8+ CTL responses involve delicate interactions between CD4+ T-cells, DC and CD8+ T-cells involving several members of the TNF(R) family, including as signal transduction molecules CD40 on DC and 4-1 BB as well as CD27 on CD8+ CTL precursors. Recently we obtained conclusive evidence that immature DC loaded with antigen cause T-cell division but not T-cell effector cell induction, nor T-cell survival in appreciable numbers. LPS stimulated DC, in contrast, stimulated vigorous CD8+ CTL responses *in vivo*. Such CD8+ effector cells showed loss of CD62L and CCR7 lymphoid homing receptors, compatible with their migration into blood and parenchymal tissue in large numbers.

We recently investigated the conditions for optimal therapeutic CD8+ CTL induction by long peptide vaccins against human papilloma virus induced mouse tumours. The 32–35 amino acid long peptides were given subcutaneous (SC) in IFA or in CpG 1826 adjuvant. Powerful therapeutic CTL induction by single peptide vaccination crucially depends on coinjection at the same site of CpG adjuvant and this response was MHC class II independent. In prime-boost regimes a second mechanism started contributing to CTL induction, namely CD4+ T helper cell mediated CD40L dependent activation of DC. Toll like receptor triggering is therefore very useful in CD8+ CTL priming, while CD40L activation starts operating in boosting.

In addition, quite apart from their activation of CD4+ helper cells, long peptides are superior to exact MHC class I binding peptides. It appears that the exact MHCI binding peptides indiscriminately bind to all MHCI positive cells, including B-cells and T-cells. The latter cell types loaded with exact MHC binding peptides, recirculate and tolerize the immune system. Long peptides, in contrast, need to be processed by professional antigen-presenting cells (APC). As a result only professional APC present MHC I and II epitopes processed from long peptides *in vivo*.

The combined data show that a new powerful generation of therapeutic anti-cancer vaccines consists of completely synthetic compounds: specific long synthetic peptides with or without molecularly defined adjuvants.