Dendritic cell vaccination and other strategies to tip the balance of the immune system

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Due to an oversight, two summaries of presentations held at this meeting were not integrated into the text. We apologize to the speakers for this mistake. The summary of the presentation of Pierre Coulie should have been in the section “Cancer vaccination in general”, and the summary of the presentation of Ugur Sahin should have been in “RNA electroporation”. These are presented here:

(addition to “Cancer vaccination in general”)

Pierre Coulie (Université catholique de Louvain, Belgium) introduced data from vaccination trials with a MAGE-A3 peptide or with ALVAC-MAGE (a canarypox virus containing MAGE-A3 and -A1 minigenes) about the numbers of anti-vaccine T cells. Frequencies of anti-MAGE-A3 CD8⁺ T cells in blood were low (around 10^{-5}), but higher in regressors than in progressors, indicating a correlation between clinical outcome and anti-vaccine T-cell responses [1]. Vaccination with eight peptides plus CpG did not lead to better responses in most patients. Two peptides (derived from NY-ESO-1 and NA-17) seemed more immunogenic or boosted pre-existing responses. The immunogenicity of DC-presented peptides was clearly better, shown by a comparison with data from a trial with NY-ESO-1 and MAGE-A10 peptide-loaded DC. To analyze

the anti-vaccine T cells, CTL clones from patients vaccinated with peptide (or ALVAC) or with peptide-pulsed DC were compared. The affinity and lytic capacity of the clones were similar, but clones from DC-vaccinated patients produced more IL-10 and less granzyme K and H. Notably, all patients had a pre-existing, tumor-specific T-cell response with frequencies up to 10^{-3} [2]. Coulie introduced a model explaining the observations made in tumor vaccination. Some tumor-specific T cells can be present in the tumor before vaccination, but are either anergic and suppressed, or recognize antigens that are lost or down-regulated. When new, vaccine-specific clones are induced by the therapy, they “spark” an immune reaction in the tumor. This happens either by breaking a local suppressive environment, or by increasing antigen presentation through IFN γ , or by inducing the priming of new CTL clones, specific for previously untouched tumor antigens. Clinical trials combining vaccines and local immunomodulation may promote these mechanisms, leading to increased clinical efficacy.

(addition to “RNA electroporation”)

Ugur Sahin (Johannes Gutenberg University Mainz, Germany) investigated decay kinetics of protein and epitopes after RNA transfection in immature and mature DC using two model RNAs (i.e., EGFP- or OVA_{aa256–267}-encoding RNA). By genetically modifying the RNA-production vector, they found that the best RNA, considering stability, translation and processing efficiency, is produced with a vector that has a long (120 bases) polyA tail, which was digested by an enzyme creating a clean A-nucleotide overhang, and has two 3' β -globin UTRs [3]. Stimulation with DC electroporated with OVA_{aa256–267}-encoding RNA generated with this vector led to higher antigen-specific CD8⁺ T-cell numbers with improved effector functions, compared to wild-type RNA.

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To increase the CD4⁺ T-cell response (i.e., to retarget the antigen into the MHC-cl. II pathway), an MHC-cl. I trafficking domain (MITD) [4–6], was introduced into the RNA production vector. CMVpp65 and NY-ESO-1 RNA with MITD electroporated into DC to stimulate CD4⁺ T cells resulted in a better proliferation and an increased cytokine production of these cells. These T cells were further characterized by selecting single tetramer-positive and cytokine-producing cells. Via a single cell PCR, the TCR α/β variable regions were cloned and transferred by RNA electroporation into T cells. By using K562 cells, transfected with each HLA-subtype, and pp65 peptide pools, the HLA-restriction and epitope specificity of these TCR were determined. Furthermore, the mode of RNA transfection into DC was investigated. Adoptive transfer of RNA-electroporated DC may be bypassed if the pharmacologically improved RNA could be used for in vivo passive pulsing. Intranodal (i.n.) immunization with naked RNA in mice was tried, resulting in an efficient uptake of RNA by CD11⁺ DC in the LN. Immunization of naïve mice with OVA_{aa256–267}-encoding RNA resulted in strong expansion of CD8⁺ T effectors, and adoptive transfer of OT-I SIINFEKL-specific memory cells followed by RNA immunization resulted in expansion of memory CD8⁺ T cells. This suggests that in vivo passive pulsing is possible with the optimized RNA.

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