Fusing Antigens and Adjuvants into Traceless Nanogels

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Antigens and adjuvants were fused into "traceless" nanogels in order to produce an enhanced personalized cancer vaccine.

The development of potent cancer vaccines that mount robust tumor-specific immunity and could suppress metastatic growth is one of the current holy grails in cancer (immuno)therapy. For this approach to be effective, antigens that are either overexpressed by tumors (so-called self-antigens) or uniquely expressed due to somatic mutations (so-called neoantigens) need to be delivered to a subset of immune cells, called antigen presenting cells. To promote antigen presentation to T cells and initiate the development of T cell responses that can recognize and eliminate the cancer expressing neoantigen, codelivery of immunostimulatory drug molecules to the same antigen presenting cell is an attractive strategy. In this issue of ACS Central Science, Tang and co-workers have developed a very elegant strategy\(^1\) that addresses several of the hurdles in cancer neoantigen vaccine development.

Their approach is based on extending the amino acid sequence of the peptide epitope with five lysine motifs. These lysine molecules serve a dual purpose. First, they increase the hydrophilicity of the peptide, thereby tackling an important drawback of peptides vaccines for neoantigen vaccination. Indeed, neoantigens can show large variations in hydrophilicity, and hydrophobic amino acid sequences often impair the solubility of the resulting peptide and thus pose challenges for pharmaceutical formulation. Such challenges are detrimental in the context of personalized vaccination against neoantigens. Upon identification of patient-specific neoantigens by whole exosome sequencing and processing of candidate antigens, the formulation of the lead peptide antigen(s) into a pharmaceutical dosage form that can administered to individual cancer patients must be completed within a very short time frame. Hence, the strategy reported by Tang et al. holds high potential as increasing the aqueous solubility of potentially hydrophobic amino acid sequences is a crucial step in the development of a generic strategy for personalized cancer vaccines based on peptide antigens. The second purpose of extending the peptide epitope with five lysine motifs is to introduce a sufficient number of primary amines that are subsequently used for chemical conjugation using a traceless amine reactive cross-linker. The latter is known from the literature to temporarily cross-link soluble proteins, while they can resolubilize through cleavage of a disulfide bond in the cross-linker followed by a cyclization–elimination reaction that liberates primary amines in their native form.\(^2\) This chemistry was also elegantly applied previously by Tang and Irvine to condensate immunomodulatory cytokines into nanogels that could be backpacked onto tumor homing T cells.\(^3\) The use of a so-called “traceless” cross-linker is crucial in this approach as lysine residues can also occur within the minimal epitope sequence of the peptide antigen.

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itself. Therefore, transient conjugation of these peptides is needed to retain the capacity of the peptides to be loaded on the surface of antigen presenting cells and be recognized by T cells through their T cell receptor.

Tang et al. took further advantage of their lysine-reactive cross-linking strategy for coencapsulation of the immunostimulatory drug Pam3CSK4, an agonist of Toll-like receptors 1 and 2. Owing to the presence of four lysine residues in Pam3CSK4, this molecule can become transiently conjugated using exactly the same chemistry as used for peptide cross-linking. Using this approach, the authors demonstrate that through controlling the reaction conditions, nanogels with sub-100 nm dimensions can be obtained, a size range that endows nanoparticles with high tissue mobility and a strong tendency to reach lymphatic tissue.4−6 In a variety of immunobiological assays, Tang et al. demonstrate a high potential of their approach, showing robust antigen-specific immune responses in vivo in mouse models and the induction of antitumor immunity.

The lack of macro- or supramolecular nanoparticle forming excipients such as lipids or polymers is a genuine advantage that reduces the complexity of the formulation and holds potential to rapidly translate peptide neoantigen identification into a pharmaceutical formulation for rapid administration. However, to fully support this hypothesis, further investigation is needed, testing a broad range of peptides with varying physicochemical properties. Moreover, mounting T cell responses solves only one piece of the very complex puzzle that needs to be resolved to successfully treat cancer. T cell activity is more often damped over, mounting T cell responses solves only one piece of the puzzle.

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