A LYMPH NODE TARGETED AMP-PEPTIDE VACCINE GENERATES FUNCTIONAL T CELL IMMUNITY AGAINST MUTANT P53 AND BRAF

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Background p53 and BRAF are frequently mutated proteins that together contribute to a significant proportion of human solid cancers. While mutations in both proteins are known to be recognized by T cells in humans,1-4 therapies designed to promote these responses have led to limited clinical success.5-6 To improve the efficacy of anti-tumor immunotherapies, the Amphiphile (AMP) platform promotes the delivery of vaccine components to lymph nodes (LN) where immune responses are orchestrated. Here, conjugation to an albumin-binding lipid enables AMP-modified antigens and adjuvants to ‘hitch-hike’ on albumin into LNs where they elicit strong tumor-directed T cell responses. Application of this approach for cancer vaccine immunotherapy is known to improve LN delivery and promote activation of polyfunctional, cytotoxic T cells relative to unmodified comparators. Promising clinical safety, T cell activation, and anti-tumor biomarker responses have recently been observed for ELI-002, an mKRAS-targeting AMP therapeutic vaccine (AMPLIFY-201 NCT05726864). Application of this approach to mutant BRAF and p53 (mBRAF/mp53) offers the potential for improved immunotherapeutic activity in a setting of significant unmet need.

Methods C57BL/6J mice were immunized with three doses of AMP-modified or soluble comparator vaccines, comprised of mBRAF/mp53 peptides and CpG-adjuvant, which were subcutaneously injected in two-week intervals. Immunological readouts were performed 7 days post dosing. To assess antigen-specific T cell responses, ELISPot (IFNγ, Granzyme B), multiplexed proteomic, and flowcytometric analysis of effector cytokines (IFNγ, TNFα, IL-2) were performed following antigenic stimulation. Cytolytic capabilities of antigen-specific T cells were evaluated via in vivo killing assays, in which antigen-pulsed target cells were intravenously transferred to immunized recipient mice, recovered after 24 hours from spleens, and analyzed by flow cytometry.

Results AMP-immunization generated robust immune responses yielding strong T cell activation against both mp53 and mBRAF in vivo. Soluble comparators were inactive with no response above mock immunized animals. Responses were characterized by the generation of significantly increased frequency of polyfunctional T cells specific to mp53 (IFNγ: 122-fold) and mBRAF (IFNγ: 69-fold). T cells demonstrated significant levels of cytolytic activity including Granzyme B production and specific elimination of target cells in vivo.

Conclusions By providing efficient delivery of immunogens directly to the LNs, the AMP-platform is capable of enhancing the potency of peptide vaccines. For mp53 and mBRAF, substantially improved immune response represents a promising therapeutic opportunity for targeting these cancers in a large fraction of human tumors. Furthermore, this platform technology is simple, rapid and scalable for broad clinical application.

REFERENCES


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