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Epitope-optimization creates highly immunogenic alpha fetoprotein antigen to break immune tolerance and potently activates CD8 T cells to prevents autochthonous hepatocellular carcinoma

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In this study, we investigated whether mouse alpha fetoprotein (mAFP), the shared self/tumor antigen of hepatocellular carcinoma (HCC), could be rationally engineered to create effective vaccine to break tolerance and potently activate CD8 T cells to prevent clinically-relevant carcinogen-induced autochthonous HCC. We found that the computer-guided epitope-optimization created optimized opt-mAFP and that immunization with lentivector (lv) expressing opt-mAFP, but not wt-mAFP, potently activated CD8 cells specific for three novel H-2b restricted CD8 epitopes, which cross-recognized wt-mAFP epitopes naturally processed and presented by wt-mAFP+ tumor cells. Immunization with opt-mAFP-lv, but not wt-mAFP-lv, completely protected mice from wt-mAFP+ tumor challenge and effectively prevented carcinogen-induced autochthonous HCC. Prime-boost with opt-mAFP-lv and vaccinia vector opt-mAFP-vv significantly increased the wt-mAFP-specific CD8 T cells that were highly responsive to emerging HCC tumor cells in the liver, enhancing prevention of autochthonous HCC. Our data demonstrate that epitope-optimization creates immunogenic opt-mAFP that is able to break tolerance and activate potent CD8 responses, which can cross-recognize wt-mAFP peptides, but also recognize and kill mAFP+ tumor cells. Our study provides a practical roadmap to develop effective human vaccines that should have a better chance of success than the current human HCC vaccines based on native wt-AFP.

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