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Immunogenicity of Self Tumor Associated Antigens Is Enhanced Through Protein Truncation

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We showed previously that expressing tumor-associated antigens (TAA) from Vesicular Stomatitis Virus eradicates established tumors. We show here that truncation of TAA expressed from VSV can occur to preserve the ability of the virus to replicate efficiently. We observed that truncation of VSV-expressed TAA affects the processing of the antigen, causing a bias towards an IL-17 anti-tumor response which was raised by cumulative signaling from different types of APC, each presenting specific, truncated antigens. Whereas processing of full length, self-TAA invoked an IFN-γ based, CD8+ dependent response, truncated versions of the same self-TAA (likely to be poorly and incompletely folded) were processed through a class II-dependent pathway, and invoked an IL-17 based response. Significantly, the IL-17-mediated anti tumor response was both more therapeutic, and durable, than the response against full length self-TAA. These data show that the type/potency of anti-tumor immune responses against self-TAA can be manipulated *in vivo* through the nature of the self protein (full length or truncated), inclusion of multiple TAA to recruit the optimal combination of APC, and the resultant skewing of the T cell response to either an IFN-γ or IL-17 producing phenotype. Therefore, in addition to generation of neoantigens through sequence mutation, immunological tolerance against self-TAA can be broken through manipulation of protein integrity, allowing for rational design of better self immunogens for cancer immunotherapy.