

ENHANCING IMMUNOGENICITY BY LIMITING SUSCEPTIBILITY TO LYSOSOMAL PROTEOLYSIS

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In order to be recognized by T lymphocytes, protein antigens are converted into short peptides bound to major histocompatibility molecules (MHC) and displayed on the surface of antigen presenting cells (APCs). The ability of APCs to generate peptide-MHC complexes is therefore essential to the initiation of the immune response. However, the mechanism of peptide selection is incompletely understood, and consequently the differences in the immunogenicity of protein antigens remain unpredictable and difficult to manipulate. Recently, we found that professional APCs (dendritic cells, B lymphocytes) exhibit unexpectedly low capacities for lysosomal proteolysis, suggesting that their lysosomes are optimized for the production of antigenic peptides rather than for exhaustive proteolysis. Such findings predict an inverse relationship between the efficiency at which a given antigen is degraded and its ability to stimulate an immune response. We took a direct and physiological approach to investigating a possible relationship between antigen proteolysis and immunity in vivo. We compared the immunogenicity of proteins with the same sequence (same T cell epitopes) and structure (same B cell epitopes) but with different susceptibilities to lysosomal