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Vaccination with HLA class-I presented viral epitopes

William Hildebrand
The University of Oklahoma Health Sciences Center School of Medicine and Pure Protein LLC, USA

Intracellular viral infections cannot be directly accessed by adaptive immune mechanisms. Rather, T lymphocytes are able to discern the infected status of a cell through class I Human Leukocyte Antigens (HLA). Here, HLA molecules were gathered from WNV infected and uninfected cells. Peptides presented by HLA molecules were comparatively analyzed by mass spectroscopy to identify HLA/peptide complexes distinct to WNV infected cells. The immunogenicity of these peptides was tested with both ELISPOT and ICS assays. Monoclonal antibodies called T cell receptor mimics (TCRm) were developed to confirm the timing and levels of antigen presentation. Immune assays demonstrate that 3 HLA/WNV peptide complexes are highly immunogenic, and TCRm mAb show that these 3 HLA/WNV peptide complexes are presented at different times and levels on the infected cell. The most immuogenic HLA/WNV complex was incorporated into a DNA vaccine encoding HLA single chain trimers (SCT). This SCT vaccine directed T cells to HLA/WNV complexes in HLA transgenic mice challenged with a lethal dose of WNV, providing both short-term and long-term protection from a lethal WNV challenge. In summary, high value, well-validated cell surface targets are a prerequisite for developing new T lymphocyte driven vaccines. Here, the HLA of the infected cell indicated what represents a distinct cell surface antigen. These HLA/WNV antigens were validated and the immunodominant antigen was incorporated into a T lymphocyte eliciting SCT DNA vaccine that protected HLA transgenic mice from a lethal virus challenge. We therefore describe a circuit of viral HLA antigen discovery, validation, and therapeutic targeting.

Biography

William Hildebrand applied biochemical and molecular techniques to characterize mouse major histocompatibility complex molecules for his MS and PhD at Southern Illinois University. He then applied these skills to the human leukocyte antigens as a Postdoctoral Scholar at Stanford University. He started his own laboratory at the University of Oklahoma Health Sciences Center in 1993 where he is now a Professor of Microbiology and Immunology. In 1999 he founded the biotech company Pure Protein to provide a commercial outlet for his HLA proteins and epitopes.

william-hildebrand@ouhsc.edu