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West nile virus highly conserved, HLA-restricted class I and II T-cell epitope peptides have wide distribution and variant representation in other flaviviruses

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Background: West Nile virus (WNV) is a member of the genus *Flavivirus*, an important group of human viral pathogens that includes at least 64 species, with global distribution,including dengue, yellow fever, and several that cause encephalitis. The proteins of flaviviruses are genetically related and contain many regions of the sequences that differ by one or more amino acids. A greater understanding of the evolutionary conservation and variability of the viral proteomes is important to studies of the immune responses in the event of multiple *Flavivirus* infection, in particular those that co-circulate. This study was directed at the identification and characterization of HLArestricted T-cell epitope peptides of the WNV proteome, with a focus on analysis of their specificity,conservation, and variability in reported sequences of WNV and to other flaviviruses.

Methodology/Principal Findings: WN V HLA-restricted epitope peptides were identified by use of H-2 deficient transgenic mice, each expressing one of the six predominant HLA class I or II alleles, and immunized with 452 overlapping peptides spanning the entire WNV proteome. ELISpot assays revealed 137 peptides that elicited a peptide-specific T-cell response with an average frequency of about 7% of the peptides analyzed per allele. The evolutionary conservation and diversity of the 137 peptides relative to all reported WNV sequences in public databases were studied by use of Shannon's entropy. Majority (~72%) of the epitope peptides were from highly conserved regions of the proteome (entropies < 0.7), and present in 88% or more of all recorded WNV sequences. The remaining ~12% contained minor intraspecies variants of the epitope, with each present in less than 1% of recorded WNVs. However, a principle finding of this study was that many of the conserved WNV epitope peptide sequences are highly shared with other flaviviruses, including those that are major human pathogens. Only 51 of the 137 sequences identified epitope peptides were WNV specific, while the majority (86) were shared with 64 other flaviviruses, either as full-length or partial identical (_ 9 amino acids) sequences. Majority of these were present in a large fraction (_ 90%) of the recorded sequences of flaviviruses with sufficient data. The remaining 10% or less contained sequences highly similar to the epitope peptides with one or more amino acid differences. Sequences of the flaviviruses that are fulllength/ partial identical or highly similar to the WNV epitope peptides are potential inter-species variants of the epitope, due to amino acid mismatches, either at the matching site or adjacent to it.

Conclusions/Significance: This study demonstrates the extensive presence in the WNV proteome of sequences that function in HLA binding and T-cell receptor (TCR) ligation and activation, and the widespread occurrence of variant sequences to these epitopes in a large number of other flaviviruses. The finding that only 51 of the identified 137 HLA-restricted WNV T-cell epitope peptides were specific to WNV and that all of the remainder were shared with many other flaviviruses highlights the possible risk of exposure toT-cell receptor altered peptide ligands for subjects exposed to multiple flaviviruses by infection or immunization, including the use of *Flavivirus* vector chimeras for delivery of DNA vaccines. The results suggest the use of pathogen-specific sequences rather than those based solely on evolutionary conservation in the design of newgeneration vaccines.