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Nuclear export signal and immunodominant CD8+ T cell epitope in influenza A virus matrix protein 1

Masanori Terajima
University of Massachusetts Medical School

Et al.

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Shuai Cao et al. recently identified and characterized a nuclear export signal (NES) in influenza A virus matrix protein 1 (M1) (5). We noticed that the identified NES, ^{59}ILGFVFTLTV^{68}, almost completely overlaps the HLA-A2-restricted CD8$^+$ T cell epitope, ^{58}GILGFVFTL^{66} (6), which is considered immunodominant in individuals carrying the HLA-A2 allele (3, 15).

Colocalization of the NES and the immunodominant HLA-A2-restricted CD8$^+$ T cell epitope in M1 explains why escape mutation in this epitope was not found in nature. Escape mutation from CD8$^+$ T cell recognition are known for the nucleoprotein of influenza A virus in the context of HLA-B*08, -B*2705, and -B*3501 alleles (4, 11, 13). Considering that the HLA-A*0201 allele or alleles belonging to the HLA-A2 supertype are very common in the human population (more than 40%) (12), it is expected that escape mutation may emerge in the M1 CD8$^+$ T cell epitope. However, as Cao et al. pointed out in their paper, the NES in M1 is highly conserved among influenza A subtypes (5). Berkhoff et al. previously showed that mutation at the P2 anchor residue in the M1 epitope (the I residue at position 59) costs viral fitness (1, 2). Now we know that the fitness cost is due to the loss of functional NES in M1.

Another implication of the colocalization is that there may be more cases of HLA-A2-restricted CD8$^+$ T cell epitopes overlapping with the NES in viral or cellular proteins. Key residues in the NES (**I**LGF**V**FT**L**T**V**) are also anchor or auxiliary anchor residues (in bold type) in the HLA-A2 binding motif (G**I**LGF**V**FT**L**) (10) except for the V at position 68, which is outside of the CD8$^+$ T cell epitope. We searched for the HLA-A*0201 binding motif overlapping with the NES mentioned in the paper by Cao et al. (in Table 1 and the text of the article [5]) using the epitope prediction algorithms, HLA Peptide Binding Predictions at BIMAS (http://www-bimas.cit.nih.gov/molbio/hla_bind/) (8) and SYFPEITHI (http://www.syfpeithi.de/) (9). Among them two NESs were found to overlap with the HLA-A*0201 binding motifs. The NES in the receptor-interacting protein 3 (RIP3), ^{116}LLCRLLKEVVL^{126} (16) with ^{116}LLCRLLKEV^{124} (the BIMAS score is 271.948 and the SYFPEITHI score is 28, while the scores for ^{58}GILGFVFTL^{66} are 550.927 and 30, respectively), and the NES of Nipah virus matrix protein, ^{106}LLEELCSLKV^{115} (14), with ^{105}DLLEELCSL^{113} (the BIMAS score is 55.902, and the SYFPEITHI score is 29). Colocalization of the NES and the HLA-A*0201-restricted epitopes is consistent with recent bioinformatic analysis by Hertz et al. showing that human major histocompatibility complex (MHC) class I molecules tend to target conserved regions of human and viral proteins (7).

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Masanori Terajima
Francis A. Ennis
Center for Infectious Disease and Vaccine Research
Division of Infectious Diseases and Immunology
Department of Medicine
University of Massachusetts Medical School
Worcester, Massachusetts, USA

Address correspondence to Masanori Terajima, Masanori.Terajima@umassmed.edu.

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