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Presentation of an immunodominant epitope in a given protein antigen is not always intrinsic: Implication in peptide vaccine design

Syamal Roy
Indian Institute of Chemical Biology, India

We investigated how the processing of a given antigen by antigen presenting cells (APC) governs the immunodominance of a known epitope when placed in the different sites of a given carrier protein. Here, a known immunodominant sequence of bacteriophage lambda repressor N-terminal sequence 12-26 [λR(12-26)] was engineered at the N and C termini of a heterologous leishmanial protein, Kinetoplastid membrane protein-11 (KMP-11); the resulting proteins were defined as N-KMP-11 and C-KMP-11 respectively. The presence of λR-12-26 in N-KMP-11 and C-KMP-11 was established by western blot analysis with antibody to λR-12-26 peptide. N-KMP-11 but not C-KMP-11 could stimulate the anti λR-12-26 T-cell clonal population very efficiently in the presence of appropriate MHC restricted APCs. Priming of BALB/c mice with N-KMP-11 or C-KMP-11 generated similar levels of anti-KMP-11 IgG, but anti λR-12-26 specific IgG was observed only upon priming with N-KMP-11. Interestingly, uptake of both N-KMP-11 and C-KMP-11 by APCs was similar but catabolism of N-KMP-11 but not C-KMP-11 was biphasic and fast at the initial time point. Kratky plots of small angle X-ray scattering showed that while N-KMP-11 adopts flexible Gaussian type of topology; C-KMP-11 prefers Globular nature. To show that KMP-11 is not unique as a carrier protein, an epitope (SPITBTNLBTMBK) of Plasmodium yoelii (PY) apical membrane protein 1[AMA-1 (136-148)], is placed at the C and N terminals of a dominant T-cell epitope of ovalbumin protein OVA (323-339) and the resulting peptides are defined as PY-OVA and OVA-PY respectively. Interestingly, only OVA-PY could stimulate anti-OVA T-cells and produce IgG response upon priming of BALB/c mice with it. Thus for rational design of peptide vaccine it is important to place the dominant epitope appropriately in the context of the carrier protein.

sroy@iicb.res.in