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Strategies of antigen retargeting for improvement of DNA vaccine performance

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Antigens encoded by DNA vaccines are synthesized in the host cells, processed and presented by MHC molecules for cells of immune system. Natural processing of the antigen may not lead to an effective antigen presentation resulted in inefficient immune response. We applied retargeting of antigen processing to improve the performance of weak gene immunogens. A model weak gene immunogen was the reverse transcriptase of HIV-1 (RT). By attachment of different specialized signals, RT was retargeted for different pathways of intracellular degradation. Enhancing the proteasome degradation with subsequent generation of peptides for MHC class I binding was achieved by fusing RT to proteasome-targeting signal of ornithine decarboxylase, and to lysosomal degradation with subsequent generation of peptides for MHC class II binding, by fusing RT to lysosomal targeting signals of lysosome associated membrane protein I, Invariable chain, and Gly-Ala repeat of EBNA 1 of Epstein-Barr Virus. Finally, we tested targeting of RT for secretion by fusing it to the leader sequence of NS1 protein of Tick Borne Encephalitis virus. The latter led to 10-fold increase in antibody response to RT including the induction of systemic RT-specific IgA. Newly generated DNA constructs were tested for expression and stability/processing in cell culture and then used to immunize BALB/c mice. Immune responses evoked were characterized by T-cell tests (ELISpot, ICCS) in splenocytes and serology. All modifications led to expected changes of antigen processing as well as potentiated anti-RT immune responses. This confirms the validity of antigen retargeting strategies for potentiating the performance of DNA vaccines.

Biography

Elizaveta Starodubova has completed her PhD in 2006 in the Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, and continued her Postdoctoral studies at the Department of Microbiology, Tumor and Cell Biology (MTC), Karolinska Institutet, Stockholm. She performs her studies in the field of antigen processing and design of prototype DNA-vaccines against different viruses.

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