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Nanodynamics of MHC/Peptide complexes and its dependence on MHC polymorphism

Initiative: Konformationelle Kontrolle biomolekularer Funktionen (beendet)

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The causative role of the human major histocompatibility gene HLA-B27 in spondyloarthropathies, a common group of chronic inflammatory rheu- matic diseases, is not understood, but the HLA-B27 molecule itself appears as the strongest predisposing factor for pathogenesis. The B*2709 subtype exhibits limited association to ankylosing spondylitis (AS)and differs only at one position in the peptide binding groove from the common, AS-associated subtype B*2705. It is proposed to in- vestigate the peptide dynamics and conformational changes in a com- parative study with these two differentially disease-associated HLA- B27 subtypes, complexed with two self-peptides and a sequence-related foreign peptide of viral origin. Advantage will be taken of different new developments in molecular dynamics simulations and peptide synthe- sis, and these techniques will be combined with real-time fluorescence depolarization measurements to address the main questions: (1) Is there a correlation between peptide dynamics and HLA-B27 polymorphism? (2) Can differential peptide dynamics be linked to the biological re- sponse in terms of T cell activity? Photocontrol of differential pep- tide dynamics by means of photoswitchable peptide analogs will provide additional insight into the peptide dynamics of HLA/peptide complexes and its dependence on HLA polymorphism.

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