HLA-DQ7β_1 and β_2 derived peptides as immunomodulators.

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Rok wydania

2009

Czasopismo

Journal of Peptide Science

Numer woluminu

15

Strony

296-304

DOI

10.1002/psc.1115

Kolekcja

Naukowa

Język

Angielski

Typ publikacji

Artykuł

Streszczenie

Modulation of protein-protein interactions involved in the immune system by using small molecular mimics of the contact interfaces may lead to the blockage of the autoimmune response and the development of drugs for immunotherapy. The nonpolymorphic beta-regions, exposed to the microenvironment, of the modeled HLA-DQ7, which is genetically linked to autoimmune diseases, were determined. Peptides 132-141 and 58-67, located at the beta(1) and beta(2) domains of HLA-DQ7, respectively, were tested for their involvement in the interactions with CD4(+) T lymphocytes. Linear, cyclic, and dimeric analogs that mimic the exposed surfaces of HLA-DQ7 were designed and synthesized. Their immunosuppressory activities, found in the secondary, humoral immune response to sheep erythrocytes (SRBC) in mice in vitro, ranged from 11% to 53%. The significance of the total charge of the peptides, the pattern of the hydrogen bonding, and the presence of secondary structure were investigated in relation to the immunomodulatory effect of the peptides. Two dimeric analogs of the HLA-DQ7 58-67 fragment, consisting of the two monomers covalently linked by a polyethylene glycol (PEG) spacer, able to mimic the superdimers, were also synthesized and studied. As the 58-67 segment is located at the beta(1) region of HLA-DQ7, close to the major histocompatibility complex (MHC) groove, one may assume that the 58-67 peptide could accommodate the association between T-cell receptor (TCR) and human leukocyte antigen (HLA) by activating a co-stimulatory molecule of the TCR/HLA interaction. This hypothesis is supported by the confocal laser image of the fluorescein-labeled 58-67 peptide and by the fact that it is an immunostimulator at low concentration.