Amino-terminal dimerization of peptides on the solid support. Synthesis and biological activity of the immunosuppressive HLA-DR fragments linked by poly(ethylene glycol)s.

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Streszczenie

The nonapeptide fragment of the HLA−DR molecule, located in the exposed loop of the β chain (164−172) and having the sequence VPRSGEVYT, suppresses the immune response. On the basis of the three-dimensional structure of the HLA−DR superdimer, we designed new dimeric analogs in which the VPRSGEVYT peptides are linked through their N-termini by poly(ethylene glycol) linkers of different lengths and are able to mimic the dimeric nature of the immunosuppressive fragments of HLA class II molecules. The analogs were synthesized using standard solid-phase peptide synthesis protocols. The dimerization was achieved by cross-linking the N-terminal positions of the peptides, attached to an MBHA resin, with α,ω-bis(acetic acid) poly(ethylene glycol), activated by esterification with pentafluorophenol. Our results demonstrate that the amino-terminal dimerization of the peptide results in enhanced immunosuppressive activity and that the potency of the conjugates depends on the length of the poly(ethylene glycol) linker. MS/MS analysis of the obtained dimeric peptides is also presented.