Dimeric analogs of immunosuppressive decapeptide fragment of ubiquitin.

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Streszczenie

Our previous studies revealed that ubiquitin and its decapeptide fragment with the LEDGRTLSDY sequence, located on the exposed molecule loop, strongly suppressed the immune response. This suggested that the loop may serve as a functional epitope of ubiquitin molecule and that a possible mechanism of biological action of the synthesized peptides is associated with interfering in interactions of ubiquitin with other molecules. Ubiquitin is known to exist in oligomeric forms, which can interact with various oligomeric receptors. We designed and synthesized new dimeric analogs of the ubiquitin fragment, to probe whether dimeric peptides may have higher affinity towards the ubiquitin receptors responsible for immunosuppression, which are believed to form oligomeric structures. Three dimerization strategies, N-terminus to N-terminus, C-terminus to C-terminus, and N-terminus to C-terminus (head-to-tail) via PEG derivatives were used to synthesize the dimeric peptides on solid support. In the course of our research, we developed a new and straightforward procedure of dimerization where α-amino groups of the C-terminal lysine residues of two peptide fragments were linked by PEG spacer directly on solid support. The effect of dimeric analogs on the immunological response was tested in the AFC in vitro experiment. The immunological tests showed that the head-to-tail dimerization caused a more profound increase in the biological activity than other tested dimerization methods. Our results suggest that such orientation of peptide components may correspond to orientation of the hypothetic ubiquitin receptors responsible for the immunomodulatory activity.

Słowa kluczowe

dimerization strategies, dimerization on solid sypport, PEG linker, linker length, ubiquitin fragmetnts