



Immunosuppressory activity of ubiquitin fragments containing retro-RGD sequence.

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Streszczenie

A peptide fragment corresponding to the ubiquitin(50-59) sequence (LEDGRTLSDY) (U50-59) possesses a very high immunosuppressory activity, comparable to that of cyclosporine, both in the cellular and humoral immune responses. We found that the pentapeptide DGRTL (U52-56) is the shortest, effective immunosuppressory fragment of ubiquitin, although its potency is weaker than that of U50-59. Replacement of each consecutive residue with alanine in U52-56 allowed identification of essential amino acids involved in the immunosuppression. We also evaluated the roles of its N- and C-terminal groups by their acetylation and/or amidation, respectively. The active sequence is located in the external loop of the molecule and therefore it may serve as an important functional epitope for intermolecular binding. Based on the crystal structure of ubiquitin molecule, we designed and synthesized the cyclic analogue with a restricted conformation, cyclo(Glt-Gln-Leu-Glu-Asp-Gly-Arg-Thr-Leu-Ser-Asp-Lys)-NH₂ (Glt = glutaryl) by reacting the C-terminal Lys side chain with the glutarilated N-terminus. The peptide was designed to mimic the ubiquitin(48-59) loop, in order to obtain the ligand that may interact with hypothetical receptors of the loop. The cyclization product selectively but strongly suppresses the cellular immune response. The results indicate that the 48-59 loop may serve as an important functional epitope in the ubiquitin molecule for intermolecular binding.

Adres publiczny

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