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Polymer cancerostatics with a coiled coil motif targeted against murine leukemia

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Coiled coil is a common structural motif in many natural proteins. It can be also utilized in design and preparation of the drug delivery systems for non-covalent connection of two macromolecules. In this work, two different pairs of peptides forming coiled coil heterodimers were designed, synthesized and characterized. While the peptide sequences (VAALEKE)4 (peptide EKE) and (VAALKEK)4 (peptide KEK) form a coiled coil heterodimer with random orientation of the peptide chains, (IAALESE)2-IAALESKIAALESE (peptide ESE) and IAALKSKIAALKSE-(IAALKSK)2 (peptide KSK) tend to adopt an anti-parallel orientation of the chains. The orientation of the peptide chains in the coiled coil heterodimers was determined using fluorescence spectroscopy with fluorescence resonance energy transfer labels attached to the ends of the peptides. Both coiled coil heterodimers were used for attachment of a recombinant targeting protein – a single-chain antibody fragment of B1 antibody – to a polymer drug conjugate based on *N*-(2-hydroxypropyl)-methacrylamide bearing an anti-cancer drug pirarubicin (THP). Both targeted polymer conjugates exhibited a markedly increased cytotoxic activity *in vitro* against BCL1 leukemia cells expressing the corresponding antigen compared to the non-targeted polymer drug conjugate. The targeted conjugate containing KSK/ESE coiled coil heterodimer (with the anti-parallel orientation) showed about 2-times higher cytotoxic activity and approximately 4-times higher cell-binding activity (as determined by flow cytometry) than the targeted conjugate with KEK/EKE anchor. *In vivo* therapeutic activity of the actively targeted polymer-THP conjugate (with KSK/ESE heterodimer) in mice bearing BCL1 leukemia was significantly higher (in terms of the survival time) compared with both the non-targeted polymer-pirarubicin conjugate and the parent drug. It was clearly demonstrated that the coiled coil heterodimers can be utilized for non-covalent attachment of recombinant targeting proteins to polymer-drug conjugates thus enabling preparation of a new generation of actively targeted macromolecular cancerostatics.

Biography

Michal Pechar, is a Senior Researcher in the Department of Biomedical Polymers, Institute of Macromolecular Chemistry of the Czech Academy of Sciences. He is the Head of a research group investigating both actively and passively targeted macromolecular therapeutics and diagnostics. His main research interests involve polymer and peptide synthesis, design and preparation of new polymer drug delivery systems based on copolymers of *N*-(2-hydroxypropyl)methacrylamide and poly(ethylene glycol) and targeting with synthetic peptides or recombinant proteins. He is co-author of 50 research articles in impacted journals and one patent with more than 1000 citations and H-index 19.

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