Nanochemistry and biotechnology

Synthesis of the conjugate of tricationic porphyrin telomerase inhibitor TMP3 with polymalic acid

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Telomerase, an enzyme performing telomeric DNA elongation, is a promising target for anticancer therapy. Tris(N-methylpyridiniumyl)porphyrin (TMP3) was shown to be efficient telomerase inhibitor with antiproliferative properties active *in vitro* at low micromolar concentrations [1]. To improve the cellular transport of TMP3 we have attached it to polymalic acid (PMLA), a natural polymer recently reported as highly efficient carrier for drug delivery into the tumor cells [2].

COOH groups of PMLA were activated to obtain amine-reactive polymeric N-hydroxysuccinimide ester. TMP3 derivative functionalized with aminoalkyl linker containing the biolabile S-S bond was synthesized. This reagent was conjugated to NHS-activated polymer under mild conditions (50 mM carbonate buffer, pH 7.5), and the product was purified by gel filtration on Sephadex G-25. TMP3 content in various samples of nanoconjugate was in the range 200-400 μmol/g.

S-S bond is easily cleaved in the cell by reducing agents like glutathione allowing the release of bioactive compound after the polymeric conjugate uptake. Indeed, the overnight treatment of TMP3-PMLA with dithiothreitol (50 mM, pH 7.5) resulted in almost quantitative cleavage of porphyrin telomerase inhibitor from the polymer carrier.

1. *Negrutska V.V., Dubey L.V., Ilchenko M.M., Dubey I.Ya*. Design and study of telomerase inhibitors based on G-quadruplex ligands // Biopolym. Cell.-2013.-**29**.-P. 169-176.
2. *Ding H., Portilla-Arias J., Patil R., Black K.L., Ljubimova J.Y.*, Holler E. The optimization of polymalic acid-peptide copolymers for endosomolytic drug delivery // Biomaterials.-2011.-**32**.-P. 5269-5278.