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Abstract

Antitumor Cytokine DR5-B-Conjugated Polymeric Poly(*N*-vinylpyrrolidone) Nanoparticles with Enhanced Cytotoxicity in Human Colon Carcinoma 3D Cell Spheroids †

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Abstract: Self-assembled nanoparticles based on amphiphilic poly(*N*-vinylpyrrolidone) (Amph-PVP) were proposed earlier as a new drug delivery system. In the current work, we study the antitumor activity of Amph-PVP-based self-assembled polymeric micelles covalently conjugated with the antitumor receptor-specific TRAIL variant DR5-B (P-DR5-B). The Amph-PVP polymer was synthesized by the earlier developed one-step technique (Kulikov et al., Polym. Sci. Ser. D, 2017). To stabilize Amph-PVP associates, the hydrophobic core was loaded with the model substance prothionamide. For the covalent conjugation with DR5-B, the hydrophilic ends of polymeric chains were modified with maleimide, and a DR5-B N-terminal amino acid residue valine was mutated to cysteine (DR5-B/V114C). DR5-B/V114C was conjugated to the surface of polymeric micelles by the selective covalent interaction of N-terminal cysteine residue with maleimide on Amph-PVP. The cytotoxicity of DR5-B-conjugated Amph-PVP polymeric nanoparticles was investigated in 3D multicellular tumor spheroids (MCTS) of human colon carcinoma HCT116 and HT29 cells, generated by the RGD-induced self-assembly technique (Akasov et al., Int. J. Pharm., 2016). In DR5-B-sensitive HCT116 MCTS, the P-DR5-B activity slightly increased compared to that of DR5-B. However, in DR5-B-resistant HT29 MCTS, P-DR5-B significantly surpassed DR5-B in the antitumor activity. Thus, the conjugation of DR5-B with the Amph-PVP nanoparticles enhanced its tumor-cell killing capacity. In the current study, we obtain a new nano-scaled delivery system based on Amph-PVP self-aggregates coated with covalently conjugated antitumor DR5-specific cytokine DR5-B. P-DR5-B overcomes DR5-B-resistance of the human colon carcinoma MCTS in vitro. This makes Amph-PVP polymeric nanoparticles a prospective and versatile nano-scaled delivery system for the targeted proteins.

Keywords: amphiphilic polymeric nanoparticles; poly(*N*-vinylpyrrolidone); antitumor therapy; colon carcinoma; receptor-specific TRAIL variant DR5-B

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