Conjugation of cRGD Peptide to Chlorophyll a Based Photosensitizer (HPPH) Alters Its Pharmacokinetics with Enhanced Tumor-Imaging and Photosensitizing (PDT) Efficacy

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Abstract

ABSTRACT: The $\alpha_v\beta_3$ integrin receptor plays an important role in human metastasis and tumor-induced angiogenesis. Cyclic Arg-Gly-Asp (cRGD) peptide represents a selective $\alpha_v\beta_3$ integrin ligand that has been extensively used for research, therapy, and diagnosis of neoangiogenesis. For developing photosensitizers with enhanced PDT efficacy, we here report the synthesis of a series of bifunctional agents in which the 3-(1′-hexyloxyethyl)-3-devinylpyropheophorbide *a* (HPPH), a chlorophyll-based photosensitizer, was conjugated to cRGD and the related analogues. The cell uptake and *in vitro* PDT efficacy of the conjugates were studied in $\alpha_v\beta_3$ integrin overexpressing U87 and 4T1 cell lines whereas the *in vivo* PDT efficacy and fluorescence-imaging potential of the conjugates were compared with the corresponding nonconjugated photosensitizer HPPH in 4T1 tumors. Compared to HPPH, the HPPH−cRGD conjugate in which the arginine and aspartic acid moieties were available for binding to two subunits of $\alpha_v\beta_3$ integrin showed faster clearance, enhanced tumor imaging and enhanced PDT efficacy at 2−4 h postinjection. Molecular modeling studies also confirmed that the presence of the HPPH moiety in HPPH−cRGD conjugate does not interfere with specific recognition of cRGD by $\alpha_v\beta_3$ integrin. Compared to U87 and 4T1 cells the HPPH−cRGD showed significantly low photosensitizing efficacy in A431 ($\alpha_v\beta_3$ negative) tumor cells, suggesting possible target specificity of the conjugate.