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PII: S0304-4165(17)30127-7
DOI: doi:10.1016/j.bbagen.2017.04.002
Reference: BBAGEN 28817

To appear in: *BBA - General Subjects*

Received date: 3 January 2017
Revised date: 14 March 2017
Accepted date: 2 April 2017

Please cite this article as: Xiantao Yang, Yuejie Zhu, Chao Wang, Zhu Guan, Lihe Zhang, Zhenjun Yang, Alkylation of phosphorothioated thrombin binding aptamers improves the selectivity of inhibition of tumor cell proliferation upon anticoagulation, *BBA - General Subjects* (2017), doi:10.1016/j.bbagen.2017.04.002

Alkylation of phosphorothioated thrombin binding aptamers improves the selectivity of inhibition of tumor cell proliferation upon anticoagulation

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Abstract

Background: Recently, aptamers have been extensively researched for therapy and diagnostic applications. Thrombin-binding aptamer is a 15 nt deoxyribonucleic acid screened by SELEX, it can specifically binds to thrombin and inhibits blood coagulation. Since it is also endowed with excellent antitumor activity, the intrinsic anticoagulation advantage converted to a main potential side effect for its further application in antiproliferative therapy.

Methods: Site-specific alkylation was conducted through nucleophilic reaction of phosphorothioated TBAs using bromide reagents. Circular dichroism (CD) spectroscopy and surface plasmon resonance (SPR) measurements were used to evaluate anticoagulation activity, and a CCK-8 assay was used to determine cell proliferation activity.

Results: The CD spectra of the modified TBAs were weakened, and their affinity for thrombin were dramatically reduced, as reflected by the K_D values. On the other hand, their inhibition of A549 cells was retained.

Conclusions: Incorporation of different alkyls apparently disrupted the binding of TBA to thrombin while maintaining the antitumor activity.

General Significance: A new modification strategy was established for the use of TBA as a more selective antitumor agent.

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