Berberine Recognition of the dGMP-bound PDGFR-β Promoter G-quadruplex: Structural Insight into Specific Drug Targeting

Kai-Bo Wang, Jonathan Dickerhoff, Yichen Han[1], and Danzhou Yang[1,2,3,4]*

[1] Purdue University, College of Pharmacy, Medicinal Chemistry and Molecular Pharmacology, 575 W Stadium Ave, West Lafayette, IN 47907 USA

[2] Purdue Center for Cancer Research, 201 S University St, West Lafayette, IN 47906 USA

[3] Department of Chemistry, Purdue University, West Lafayette, IN 47907, USA

[4] Purdue Institute for Drug Discovery, 720 Clinic Dr, West Lafayette, IN 47907, USA

* To whom correspondence should be addressed. Tel: (765) 494-8148; Fax: (765) 494-8352; Email: yangdz@purdue.edu

Abstract

PDGFR-β (Platelet-Derived Growth Factor Receptor beta) is a receptor tyrosine kinase whose overexpression drives the progression and metastasis of many cancers. It is an established anticancer target and PDGFR-β inhibition via kinase inhibitors has been actively sought-after. However, PDGFR-β kinase inhibitors often lack specificity. The PDGFR-β gene promoter forms DNA G-quadruplexes that are transcription silencer whose stabilization by small molecules represses PDGFR-β expression. Therefore, targeting PDGFR-β promoter G-quadruplexes for transcriptional silencing is a promising alternative strategy for cancer therapy. G-quadruplex is an exciting family of non-canonical DNA secondary structures. DNA G-quadruplex within the PDGFR-β gene promoter forms novel vacancy pockets (vG4) that can be filled-in by guanine metabolites such as dGMP and cGMP. This presents an attractive target for small molecule targeting. Herein, we present the binding of the natural product berberine with the unique PDGFR-β dGMP-vG4 binary complex to form a novel ternary complex, the first case observed in DNA G-quadruplexes. Using circular dichroism, fluorescence, and nuclear magnetic resonance (NMR) spectroscopy, we demonstrated that berberine binds with high affinity and strongly stabilizes the dGMP-fill-in PDGFR-β vG4. Our determined high-resolution NMR structure of this ternary complex in K^+-containing solution reveals a 2:1 binding stoichiometry of berberine to the dGMP-fill-in PDGFR-β vG4. Significantly, one berberine directly stacks upon and extensively covers the dGMP. This direct binding mode provides structural basis for targeting the unique PDGFR-β promoter G-quadruplex by small molecules and suggests an intriguing strategy of designing drug-like, guanine-conjugated molecules to selectively silence the PDGFR-β gene. Because vG4 formation and dGMP fill-in is a unique property of the PDGFR-β promoter G-quadruplex, our study provides a structural basis for rationally designing small molecule drugs to specifically target the PDGFR-β promoter G-quadruplex to inhibit oncogenic PDGFR-β for cancer therapeutics.