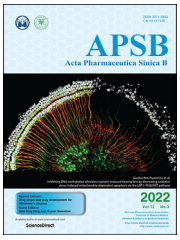
Acta Pharmaceutica Sinica B 2022;12(3):1534−1535

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



COMMENTARY

Using proteomimetics to switch angiogenic signaling

Peng Teng[a,*], **Jianfeng Cai**[b,*]

[a]*College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China*
[b]*Department of Chemistry, University of South Florida, Tampa, FL 33620, USA*

Received 9 January 2022; received in revised form 17 January 2022; accepted 19 January 2022

KEY WORDS

Proteomimetics;
AApeptides;
VEGF;
VEGFR

Angiogenesis is a vital process in the event of various healthy and diseased conditions especially in the tumor metastatic pathway, and it is one of the key hallmarks of cancer cells[1,2], therefore, angiogenesis inhibitors are potential anti-cancer agents. However, silenced angiogenesis on the other hand could result in stroke, heart attack, and other cardiovascular diseases[3]. Yet, the precise manipulation of contradictory pro-angiogenic and anti-angiogenic signaling remains extremely challenging in both molecular biology and therapeutics. In the recent issue of *J Am Chem Soc*, Abdulkadir et al.[4] have made progress to enable controlled inhibition or activation effects on angiogenic cellular responses using proteomimetics developed in the same research group.

The process of tumor vascular proliferation and metastasis is mainly modulated by various chemical signals especially a glycoprotein vascular endothelial growth factor (VEGF) in the body[5]. VEGF-A, the most predominant VEGF isoform, is a potent modulator of VEGF-specific receptor tyrosine kinases including both VEGFR-1 and VEGFR-2 overexpressed on cancer cells. Clinically available angiogenesis inhibitors targeting VEGF-A/VEGFRs have been exemplified by Bevacizumab, an US Food and Drug Administration (FDA)-approved monoclonal antibody to treat cancers and an eye disease[6]. Nevertheless, the success of antiangiogenic agents was not concomitant with the universal anticancer efficacy of VEGFR targeted agents as expected, highlighting the need for better understanding of the mechanism of angiogenesis[7]. A peptide QK derived from the helix region (17−25) of the VEGF binding interface from a previous report was shown to have good binding affinity to VEGF receptors but induced angiogenesis *in vitro*[8]. Whereas another peptide MA, which has differences of only two amino acids compared with QK, was able to inhibit angiogenesis[9]. However, the molecular mechanism behind the distinct responses of VERGR binders to modulate angiogenic signaling remains elusive, further biological application of the canonical peptides was also jeopardized by the poor stability toward proteolytic enzymes.

The sulfono-γ-AA peptide based peptidomimetics developed by Abdulkadir et al.[4] carries the potential to mimic the positioning and residues (Phe17, Met18, Tyr21, and Tyr25) of helical binding domain of VEGF-A: helix-α1 (16−25). Surface plasmon resonance (SPR) assays demonstrated remarkable selectivity for VEGFR1 and VEGFR2 with sulfono-γ-AA peptide **V2** and sulfono-γ-AA peptide **V3**, respectively. It is particularly intriguing that the only difference between **V2** and **V3** is one side chain to mimic Phe17. The peptidomimetic **V2** bearing phenyl residue was found to markedly increase the number of human umbilical endothelial cells (HUVECs) migrating, suggesting it is a potent activator of angiogenesis. However, an indole side chain at the same position in **V3** abolished

*Corresponding authors.
E-mail addresses: pengteng@zju.edu.cn (Peng Teng), jianfengcai@usf.edu (Jianfeng Cai).
Peer review under responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2022.01.016

the pro-angiogenic effect, inducing profound anti-angiogenic activities (Fig. 1). The authors speculated that an alternative mechanism of angiogenesis modulation would come from the selectivity for different VEGFR isoform, instead of the different receptor conformation upon binding[9]. In the subsequent western blot, immunofluorescence, computational modeling, and other studies, the researchers demonstrated the ability of proteomimetics to switch angiogenic signaling owing to the selective binding to either VEGFR1 or VEGFR2. Specific binding to VEGFR-1 results in amplified angiogenesis, whereas targeting VEGFR-2 specifically inhibits VEGF-A/VEGFR-2 protein−protein interaction (PPI) and consequently suppresses angiogenesis signaling pathway. Authors hypothesized that VEGFR-1 mainly functions as a decoy receptor with the major role of dampening VEGFR-2 mediated angiogenesis signaling. Selectively targeting VEGFR-1 thus could free VEGF and shift the balance for VEGF binding to VEGFR-2 over VEGFR-1 binding. A better understanding, probing, and controlling of the process of the angiogenic switch using proteomimetics would provide tremendous opportunities to intervene imbalances in angiogenesis, which are the main cause in several disease conditions especially solid tumors.

Peptidomimetic foldamers have exhibited exceptional prospects of mimicking protein domains essential for PPIs, due to the unique advantages of peptidomimetics with respect to known structure, stability, and bioavailability[10]. Sulfono-γ-AA peptides have displayed superior helical propensity to the α-helix and showcased therapeutical potential toward medicinally relevant PPIs[11]. The design by Abdulkadir et al.[12] was very effective, which was mainly attributed to the crystal structures of sulfono-γ-AA foldamers solved by the same research group. In this report, helical foldameric mimetics derived from sulfono-γ-AA peptide demonstrated another achievement considering the significance of angiogenetic modulation in solid tumors. Moreover, the reported lead mimics displayed remarkable stability in pronase, a mixture of proteolytic enzymes from the genus *Streptomyces griseus*, which used to be a great concern in conventional peptide based molecular probes or drug candidates. The results from the article implied the potential of sulfono-γ-AA peptides to interrogate a myriad of PPIs.

In summary, angiogenesis has received immense interest in anticancer drug development efforts. Inhibition of angiogenesis is particularly crucial to the treatment of cancer especially when metastasis occurs. On the other hand, the stimulation of angiogenesis plays a therapeutic role in ischemic heart disease, wound healing, and organ repair. Governing the double-edged sword of angiogenesis, in another word, pro-angiogenic *versus* anti-angiogenic signaling, is the "Patron" of the healthy vascular response. The significance of this study lies in that the helical foldameric mimetics of the key helix of VEGF-A at the PPI interface were successfully designed and proven to be either pro- or anti-angiogenic. In essence, probing and perturbing angiogenic imbalances using unnatural peptidomimetics add new members to the toolbox of chemical biology. The novelty of this paper can be summarized as follows: (1) It is the design and synthesis of the first example of unnatural peptidomimetics that mimic helix α1 of VEGF-A. (2) Through functional study, authors identified two sulfono-γ-AA peptide based helical mimetics **V2** and **V3**, which could either activate or inhibit angiogenesis, respectively. This is the first example of complete control of the angiogenesis through unnatural peptidomimetics, which provide us a key to switch the angiogenic signaling. This work demonstrated the versatility of employing helical sulfono-γ-AA peptides to develop new anticancer drugs toward medicinally relevant PPIs. For future applications, it would be interesting to find out whether this class of peptidomimetics have good cell permeability and are suitable for intracellular PPI targets. Backbone stapling may be a viable way to mitigate the issue of impermeability if identified. Also, it is intriguing to develop helical sulfono-γ-AA peptides to mimic more residues that are not necessarily on the same face of α-helix, which is the case indeed more universally identified in PPIs.

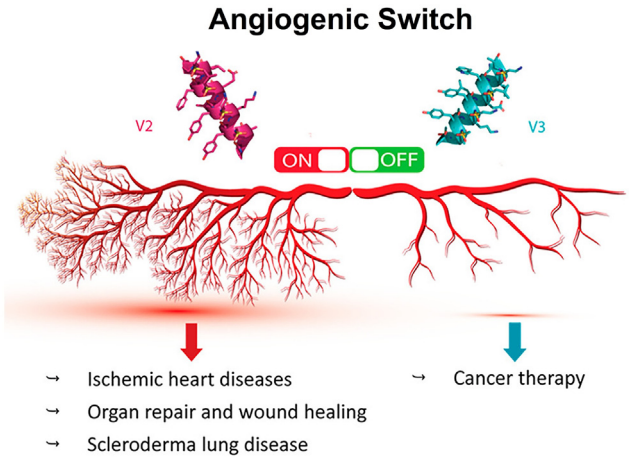


Figure 1 Modulation of the angiogenic switch signaling with sulfono-γ-AA proteomimetics (**V2** or **V3**) of VEGF-A. Reprinted with permission from Ref. 4. Copyright © 2022 American Chemical Society.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;**144**:646.
2. Fares J, Fares MY, Khachfe HH, Salhab HA, Fares Y. Molecular principles of metastasis: a hallmark of cancer revisited. *Signal Transduct Target Ther* 2020;**5**:28.
3. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. *Nature* 2000;**407**:249.
4. Abdulkadir S, Li C, Jiang W, Zhao X, Sang P, Wei L, et al. Modulating angiogenesis by proteomimetics of vascular endothelial growth factor. *J Am Chem Soc* 2022;**144**:270−81.
5. Loges S, Mazzone M, Hohensinner P, Carmeliet P. Silencing or fueling metastasis with VEGF inhibitors: antiangiogenesis revisited. *Cancer Cell* 2009;**15**:167.
6. Cook KM, Figg WD. Angiogenesis inhibitors: current strategies and future prospects. *CA Cancer J Clin* 2010;**60**:222.
7. Ronca R, Benkheil M, Mitola S, Struyf S, Liekens S. Tumor angiogenesis revisited: regulators and clinical implications. *Med Res Rev* 2017;**37**:1231.
8. D'Andrea LD, Iaccarino G, Fattorusso R, Sorriento D, Carannante C, Capasso D, et al. Targeting angiogenesis: structural characterization and biological properties of a *de novo* engineered VEGF mimicking peptide. *Proc Natl Acad Sci U S A* 2005;**102**:14215.
9. Basile A, Del Gatto A, Diana D, Di Stasi R, Falco A, Festa M, et al. Characterization of a designed vascular endothelial growth factor receptor antagonist helical peptide with antiangiogenic activity *in vivo*. *J Med Chem* 2011;**54**:1391.
10. Pelay-Gimeno M, Glas A, Koch O, Grossmann TN. Structure-based design of inhibitors of protein–protein interactions: mimicking peptide binding epitopes. *Angew Chem Int Ed* 2015;**54**:8896.
11. Sang P, Shi Y, Huang B, Xue S, Odom T, Cai J. Sulfono-γ-AApeptides as helical mimetics: crystal structures and applications. *Acc Chem Res* 2020;**53**:2425.
12. She F, Teng P, Peguero-Tejada A, Wang M, Ma N, Odom T, et al. *De novo* left-handed synthetic peptidomimetic foldamers. *Angew Chem Int Ed* 2018;**57**:9916.