What Is Wrong With the Allosteric Disulfide Bond Hypothesis?

Ronald R. Bach, Dougald Monroe

Initial models of coagulation postulated a strict separation of the initiator of coagulation, tissue factor (TF), from the coagulation factors in blood. More recent studies have shown low but detectable levels of TF in blood1 (reviewed in2). This suggests that TF activity is under some level of control beyond simple expression levels.

One mechanism of control is suggested by the observation from cell culture studies that TF activity on cells can be rapidly and substantially increased without significant changes in TF antigen.3 TF with reduced activity has been referred to as encrypted. The evidence supporting TF encryption and decryption has been dealt with in a previous review.2

It has been proposed that chemical reactions involving two half-cystines in the extracellular domain of tissue factor, cys186 and cys209, are the key events regulating TF procoagulant and signaling functions.4–8 According to the allosteric disulfide bond hypothesis, when the side chains are reduced TF is inactive/encrypted. When the sulfhydryls are oxidized, the resulting disulfide bond formation induces a conformational change that converts TF to a procoagulant/decrypted state. Some of the literature has proposed that protein disulfide isomerase (PDI) is responsible for the oxidation step.5

After three years there is still no direct quantitative evidence for free thiols in TF. In tissue culture studies, both oxidizing and reducing agents can promote TF decryption.9 Further, studies on PDI have suggested that lipid contamination of the protein might account for the TF decryption observed in some studies.10 More problematic is the issue of accessibility. Are the half-cystines available for the proposed redox reactions? This is a relevant question because the half-cystines are buried deep within complex when activated factor VII (FVIIa) binds to the extracellular domain of TF11 (see Figure).

Direct binding studies have established that encrypted TF and decrypted TF form stable high-affinity associations with FVII and FVIIa.12–14 All the observed dissociation constants are well below the plasma concentration of FVII. Also, there is sufficient extravascular FVII/FVIIa to saturate TF on perivascular cells even in the absence of injury.15 Finally, during the ionophore-induced conversion of encrypted TF-FVIIa to decrypted TF-FVIIa the enzyme remains bound to the cofactor.3 This body of evidence supports the conclusion that FVII/FVIIa is bound to essentially all the TF molecules on cells in blood and the surrounding vessel wall. Therefore, cys186 and cys209 are not available to interact with PDI or even participate in the proposed reactions.

Disclosures

None.

References


What Is Wrong With the Allosteric Disulfide Bond Hypothesis?
Ronald R. Bach and Dougald Monroe

doi: 10.1161/ATVBAHA.109.194985
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/29/12/1997

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/