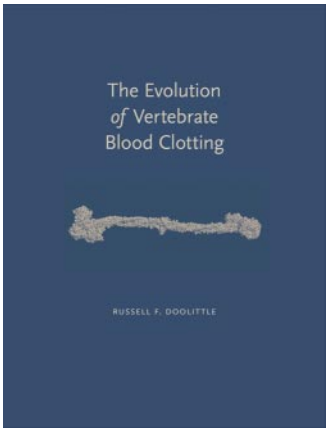

Stanching the Flow:
The Evolution of Vertebrate Blood Clotting
by Russell F. Doolittle (2012)

Joseph Loscalzo[1]

Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Hemostasis is an essential physiological response to acute injury in organisms with a circulatory system. In the Darwinian struggle that drove early natural selection, only creatures that were capable of limiting blood loss could survive wounds or injuries that breeched a vessel. Vertebrates, from hagfish to primates, suffer acute injuries that would lead to exsanguination were adequate hemostasis not in place. The clotting of blood in response to injury is a primordial\ but highly efficient and complex affair, the analysis of which remains a challenge.

A molecular ballet

In this marvelous book, the biochemist and evolutionary biologist Russell Doolittle addresses in exquisite detail the complexity of the blood-clotting system of vertebrates and its evolution. Lucidly written, this treatise presents the relevant aspects of all of the basic enzymology, structural biology, molecular biology, and phylogenetics to derive key principles that govern hemostatic mechanisms across various chordates. The author nicely embellishes this straightforward scientific presentation with relevant historical detail, such as the heritability of hemophilia among the British monarchy and the identification of dicoumarol in fungus-infected sweet clover as a cause of bleeding in cattle in the Midwest. The book is written at a level for graduate students of modern biology, with sufficient digressions into the necessary background to understand protein conformational determinants, gene duplications, and evolutionary dynamics of the genome. As such, it is a marvelous compendium of the key elements of hemostasis, presented with sufficient detail to bring readers of a wide range of scientific backgrounds up to an adequate level of knowledge to appreciate the more nuanced discussion of the molecular evolution of the clotting system.

The hemostatic system is a key element of the *milieu interieur*, whose evolved purpose is to limit the loss of that extracellular bathing fluid to the environment. To do so, it stanches the flow of blood quickly from breaches in the integrity of the skin or outermost tissue layer. The essential properties of the hemostatic system, which are presented in the first half of the book, include its amplifying features, a consequence of sequential, coupled enzymatic reactions that use substrates of increasing concentrations as the pathway progresses to the ultimate formation of fibrin from fibrinogen; multiple parallel and overlapping mechanisms to arrest blood flow, broadly defined as primary hemostasis, coagulation, and fibrinolysis; and exquisite regulation that incorporates antithrombotic, antifibrinolytic, prothrombotic, and profibrinolytic regulatory molecules. This latter battery of regulatory molecules is designed to ensure that once hemostasis begins, its effects can be contained to the site of injury, limiting its unbridled expansion throughout the circulatory system. This beautifully choreographed molecular ballet achieves its express purpose effectively under conditions of high and low blood flow in the venous and arterial circulations and through the actions of the fibrinolytic system, ultimately lyses the clot-restoring vessel patency and blood flow.

Fine-tuning the system

A detailed exposition on the evolution of the clotting system is provided in the second half of the book. Some interesting observations presented here include the facts that: bony fish lack three key contact-activated proteases important for the intrinsic coagulation pathway but have an enhanced extrinsic system with two factor VIIs; lampreys lack factors VIII and IX, which are the result of duplications of the genes for factors V and

[1] Correspondence: Brigham and Women's Hospital, Harvard Medical School, Dept. of Medicine, 75 Francis St., Boston, MA 02115-2394, USA. E-mail: jloscalzo@partners.org

Image courtesy of University Science Books, Mill Valley, California, USA.

doi: 10.1096/fj.14-0502ufm

X, respectively, seen in higher vertebrates but do not bleed, because their complement of factors V and X are sufficient to ensure adequate hemostasis; the tissue factor—the key initiator of hemostasis—is derived from a structurally similar cytokine receptor, present in the common ancestor of sea squirts and vertebrates; and the recombination events that led to the fusion of a γ-carboxyglutamic acid (GLA)-containing domain with an epidermal growth factor domain, in combination with a suitable protease(s), was a major evolutionary innovation that was selected for owing to the ability of the resulting clotting factor to bind to membrane phospholipids via calcium and GLA residues, where it could react with tissue factor and cleave target proteins to initiate and amplify coagulation.

From a basic evolutionary perspective, the vertebrate-clotting system is, to be sure, a consequence of the natural tendency of DNA to duplicate and mutate. Complementary mutations between duplicated genes led to selective interactions among clotting proteins (proteases and their protein substrates) that facilitated pathway divergence and functional redundancy. Fine-tuning of the system evolved as a consequence to ensure optimal hemostasis under a variety of environmental circumstances.

One can quibble about areas that might have been more fully developed in the book, such as the role of platelets and von Willebrand factor and their evolution; kinetic differences among coagulation enzymes from different species; and potential disadvantages of this evolutionary scheme in the development of thrombotic disorders in longer-lived, higher vertebrates. Yet, this marvelous book is a superb exposition on a complicated, essential defense mechanism in vertebrates that is well worth reading for general students of the biology and of life-long students of the field of hemostasis alike. FJ

Doolittle RF (2012) Stanching the flow: The evolution of vertebrate blood clotting. University Science Books, Mill Valley, CaliforniaGoogle Scholar. Fiusa MM, Carvalho-Filho MA, Annichino-Bizzacchi JM, De Paula EV (2015) Causes and consequences of coagulation activation in sepsis: an evolutionary medicine perspective. BMC Med 13: 105â€“0327CrossRefGoogle Scholar. Gualtierotti R, Ingegnoli F, Griffini S, Grovetti E, Meroni PL, Cugno M (2016) Prothrombotic biomarkers in patients with rheumatoid arthritis: the beneficial effect of IL-6 receptor blockade. Clin Exp Rheumatol 34: 451â€“8Google Scholar. Micropirin Stop blood from clotting, blocking blood flow. C $21.22. Buy It Now. Free Shipping. From Israel. Micropirin Stop blood from clotting, blocking blood flow. C $25.19. Buy It Now. +C $9.28 shipping. From Israel. The Evolution of Vertebrate Blood Clotting by Russell F. Doolittle. C $77.48. Buy It Now.Â The Evolution of Vertebrate Blood Clotting, , Russell F. Doolittle, Good, 2012-0. C $66.10. Buy It Now. Russell F. Doolittle, The Evolution of Vertebrate Blood Clotting (University Science Books, August 2012). ISBN 978-1-891389-81-8. John N. Abelson, Melvin I. Simon, and Russell F. Doolittle, Molecular Evolution: Computer Analysis of Protein and Nucleic Acid Sequences, Volume 183: Volume 183: Molecular Evolution (Methods in Enzymology) (Academic Press, Feb 28, 1990). ISBN 0-12-182084-X. Mosesson, Michael W. and Doolittle, Russell F. Molecular biology of fibrinogen and fibrin (Annals of the New York Academy of Sciences) (New York Academy of Sciences, 1983). ISBN 0-89766-209-1. References[edit]. ^