Studies in History and Philosophy of Biological and Biomedical Sciences xxx (2014) 1–12

Contents lists available at ScienceDirect

Studies in History and Philosophy of Biological and Biomedical Sciences

journal homepage: www.elsevier.com/locate/shpsc

Anticoagulant factor V: Factors affecting the integration of novel scientific discoveries into the broader framework

Michelle L. LaBonte

Department of Biological Sciences, Wellesley College, 106 Central Street, Wellesley, MA 02481, USA

ARTICLE INFO

Article history:
Received 15 October 2013
Received in revised form
21 March 2014
Available online xxx

Keywords:
Factor V
Factor V Leiden
Thrombophilia
Coagulation cascade
Anticoagulant

ABSTRACT

Since its initial discovery in the 1940s, factor V has long been viewed as an important procoagulant protein in the coagulation cascade. However, in the later part of the 20th century, two different scientists proposed novel anticoagulant roles for factor V. Philip Majerus proposed the first anticoagulant function for factor V in 1983, yet ultimately it was not widely accepted by the broader scientific community. In contrast, Björn Dahlbäck proposed a different anticoagulant role for factor V in 1994. While this role was initially contested, it was ultimately accepted and integrated into the scientific framework. In this paper, I present a detailed historical account of these two anticoagulant discoveries and propose three key reasons why Dahlbäck's anticoagulant role for factor V was accepted whereas Majerus' proposed role was largely overlooked. Perhaps most importantly, Dahlbäck's proposed anticoagulant role was of great clinical interest because the discovery involved the study of an important subset of patients with thrombophilia. Soon after Dahlbäck's 1994 work, this patient population was shown to possess the factor V Leiden mutation. Also key in the ultimate acceptance of the second proposed anticoagulant role was the persistence of the scientist who made the discovery and the interest in and ability of others to replicate and reinforce this work. This analysis of two different yet similar discoveries sheds light on factors that play an important role in how new discoveries are incorporated into the existing scientific framework.

1. Introduction

Factor V is a key component of the coagulation cascade, and it has long been established as an important protein in clot formation. However, first in 1983 and then again in 1994, two different anticoagulant (clot inhibiting) roles for factor V were proposed. The first proposed anticoagulant role was acknowledged briefly by biochemists but then it was largely forgotten, whereas the second proposed anticoagulant role was rejected initially but then eventually it was largely accepted (Fig. 1). In this paper, I explore these two related factor V cases, each in which an "unprecedented event" occurred. In Rheinberger's words, "Unprecedented events are about things and concatenations not sought for. They come as a surprise but nevertheless do not just so happen. … And yet they may commit experimenters to completely changing the direction of their research activities." (Rheinberger, 1997) (p134). While the factors and conditions that lead to unprecedented events are critical in the process of scientific understanding, perhaps equally important is what happens after novel discoveries are made. Given that the unprecedented event from 1994 did lead to a change in the path of future research and the 1983 discovery did not, these two cases serve as a means to explore the issue of how a relevant scientific community responds to reports of novelty and achieves consensus about whether and to what extent new findings should be incorporated into the existing framework.

There are many examples of unexpected findings being rejected or overlooked by the scientific community. When Francois Jacob first reported on his discovery of messenger RNA (which he termed component X at the time), scientists did not readily accept his findings. In fact, "No one reacted. No one batted an eyelash. No one asked a question. Jim [Watson] continued to read his

E-mail address: mlabonte@post.harvard.edu.

http://dx.doi.org/10.1016/j.shpsc.2014.03.007

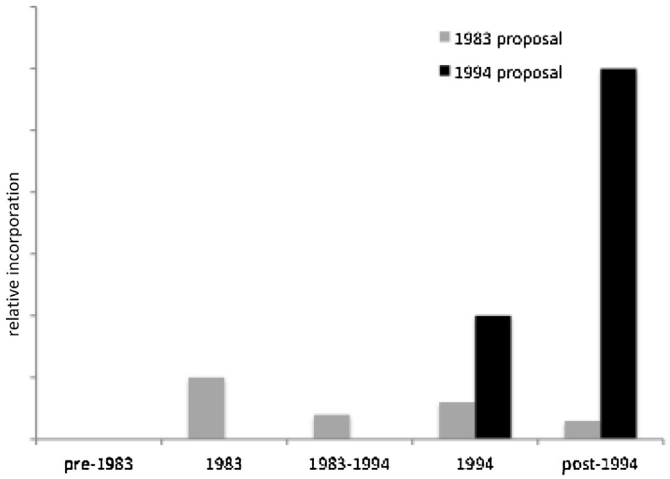

Fig. 1. The relative incorporation of the proposed factor V anticoagulant roles into the existing scientific framework over time. The 1983 proposal refers to Majerus' proposed anticoagulant role for factor V. The 1994 proposal refers to Dahlback's proposed anticoagulant role for factor V. Image is not to scale.

newspaper."(Rheinberger, 1997)[1] (p205) Various ideas have been put forth by scholars to explain why some discoveries are overlooked whereas others are more readily accepted by the scientific community. One argument is that discoveries are more likely to be overlooked if they do not clearly fit in with the existing scientific knowledge (Brannigan, 1981; Hook, 2002b; Stent, 1972). Other factors proposed to influence the reception of a discovery have included the status of the scientist, the relevance of the finding, to what extent the discovery is noticed, and whether the finding can be replicated (Brannigan, 1981; Gillies, 2005; Hook, 2002b; Latour & Woolgar, 1986).[2] To further explore potential determinants of how discoveries are received, the two factor V anticoagulant cases presented in this paper offer an important comparison because two similar discoveries followed two very different trajectories.

By looking at these two cases of proposed anticoagulant roles for factor V in parallel,[3] I hope to demonstrate the key factors that determined why only one of the two proposed anticoagulant roles for factor V became a matter of concern[4] (Latour, 2004, 2005). Perhaps most significant is the perceived clinical relevance of the factor V anticoagulant function discovered in 1994. In fact, the 1994 discovery was based on analysis of a population of patients with thrombophilia who would not long after be shown to possess the factor V Leiden mutation. In addition, Björn Dahlbäck, who made the 1994 discovery, was extremely persistent in the promotion of his hypothesis. Dahlbäck's persistence, coupled with the clinical significance of his discovery, resulted in replication and extension of the work and ultimate widespread acceptance of the 1994 factor V anticoagulant role. To fully appreciate these cases, I begin with a scientific overview of factor V.

[1] Quoted from Jacob (1988), p311.

[2] The reasons that potentially influence the acceptance of scientific findings are expanded upon in the discussion section.

[3] The historical analysis relies on published work and one interview. Björn Dahlbäck, the discoverer of the second proposed anticoagulant role of factor V, was interviewed by ML in 2013. The interview protocol was approved by the Wellesley College IRB. Philip Majerus and colleagues did not respond to interview requests. One of Majerus' coauthors on the 1983 article wrote ML, "I am not the best person for you to be talking to. Highly suggest Björn Dahlbäck." Björn Dahlbäck and Philip Majerus' papers are in their possession.

[4] Latour proposes that scientific information becomes a "matter of concern" when a finding becomes relevant. The second proposed anticoagulant role for factor V became relevant, or a matter of concern, due in large part to the clinical significance of the finding (Latour, 2004; Latour, 2005).

2. Procoagulant factor V

In 1943, a young woman named Mary came to a hospital in Norway because of a bleeding episode (Stormorken, 2003). Mary had been healthy for the first few years of her life, but she had suffered a severe bleeding episode at the age of three that left her blind, initially in both eyes. She had many bleeding episodes in the subsequent years, but menstrual bleeding proved to be the most problematic for Mary. It was for this reason that she came to the hospital at the age of 29. Paul Owren, an assistant professor at the hospital, was responsible for her care, and after laborious effort, it was he who discovered that she had a deficiency in a clotting factor. At that time, the theory of blood coagulation included just four clotting factors, so Owren named Mary's missing protein factor V, setting the precedent for the use of roman numerals in naming the blood coagulation factors (Giangrande, 2003; Stormorken, 2003). He published his work in Norway in 1944, but his results were not widely known until after the war, when he was able to publish in *The Lancet* (Owren, 1947).

Owren's findings "spurred an unprecedented activity in the field"(Stormorken, 2003), and factor V has since been known to play a key role as a procoagulant protein in the coagulation cascade. By the early 1980s, there was a consensus model for how the clotting cascade worked. The activated form of factor V, termed factor Va, was known to play an important role in the coagulation cascade because it serves as a cofactor in the conversion of prothrombin to thrombin. The enzyme thrombin cleaves fibrinogen into fibrin, which binds to and crosslinks platelets, resulting in a platelet plug and clot formation. Patients who are missing factor V have serious bleeding disorders because they are unable to generate factor Va. To properly regulate the coagulation cascade so that clotting doesn't continue out of control, factor Va can be inhibited by activated protein C (APC), thereby shutting down the cascade (Fig. 2).

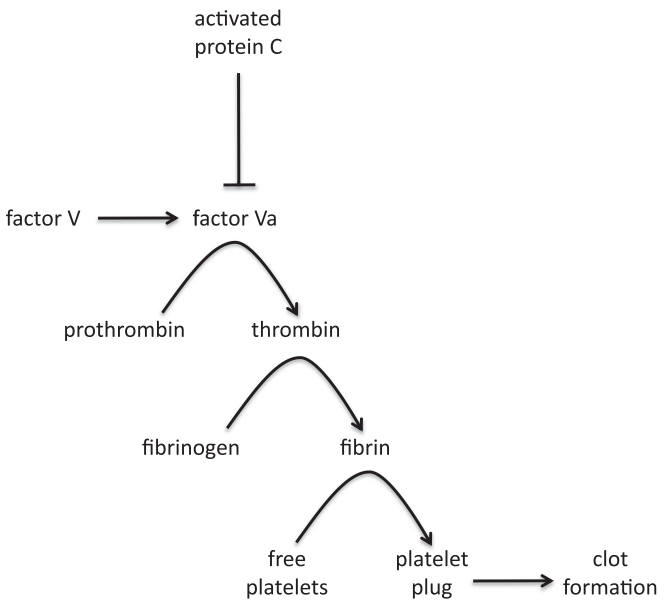

Fig. 2. Summary of some key components of the coagulation cascade as of the early 1980s. Factor V is converted to the procoagulant factor Va. Factor Va is instrumental in the conversion of prothrombin to thrombin. A cascade continues in which fibrinogen is converted to fibrin, free platelets are converted to a platelet plug, and clot formation occurs. Activated protein C serves as an anticoagulant protein by inactivating factor Va. Some details are omitted for clarity.

Please cite this article in press as: LaBonte, M. L., Anticoagulant factor V: Factors affecting the integration of novel scientific discoveries into the broader framework, Studies in History and Philosophy of Biological and Biomedical Sciences (2014), http://dx.doi.org/10.1016/j.shpsc.2014.03.007