Guest editors' introduction

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Accepted: 26 June 2021 / Published online: 15 July 2021

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Few medically important proteins match the longevity of coagulation Factor Xa for generating sustained interest in functional characterization, tinkering and targeting. In 1904 Paul Morawitz proposed that there might be an enzyme, thrombokinase, that converted prothrombin to thrombin. Several decades of increased understanding about the nature of enzymes and development of improved protein isolation procedures passed before J. Haskell Milstone isolated and characterized such an enzyme from plasma. Milstone and Morawitz both initially thought that the enzyme–substrate interaction would be straightforward with calcium acting as a co-factor. Early in the 1950s Milstone realized that activity of his enzyme was greatly enhanced by lipid and by a serum co-factor, and in 1964 concluded that the reaction catalyzed by the enzyme, thrombokinase, could only have physiologic significance in the presence of additional “accessory factors”. Analytical innovations in the 1970s, showing that thrombokinase was undeniably the same as Factor Xa which had been discovered and studied in the context of genetic bleeding disorders, opened the door to understanding the nature and complexity of interactions with lipid, Factor V in an activated form and other coagulation factors. In the 1990s Factor Xa became the target for intensive drug development resulting in novel, highly effective anticoagulants. More recently, identification of substrates for thrombokinase other than prothrombin has expanded its role into cell signaling and inflammation.

The papers to follow were derived from talks given at Yale University, where JH Milstone worked and a new research grant was recently established in his honor.

Originally scheduled as a live symposium, it was converted to a webinar in November, 2020. The goal was to capture the broad history of Factor X by learning from and honoring some those who made seminal contributions to understanding this important protein. They were asked to go beyond the facts which can be found in textbooks and scientific literature and to address conceptual, personal and technical challenges they faced and what role new technology and/or serendipity played in moving their work forward. This history of thrombokinase/Factor Xa demonstrates that the concepts and methods used to describe the chemical nature of thrombokinase, used to understand its activities, and used to target it to treat disease are a template for appreciating the evolution and history of discovery, analysis and manipulation of medically important proteins.

The Question and Answer sessions that followed each talk were edited from a transcript and approved by the participants.

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