

## Preface

**Biologic Role of the Plasminogen–Plasmin System: Thrombolysis, Bleeding, and Beyond**Hau C. Kwaan, MD, FRCP<sup>1</sup> Andrew P. Mazar, PhD<sup>2,3</sup><sup>1</sup>Division of Hematology/Oncology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois<sup>2</sup>Chemistry of Life Processes Institute, Northwestern University, Evanston, Illinois<sup>3</sup>Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Evanston, Illinois

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*In many modes of destroying life the blood is deprived of its power of coagulation, as happens in sudden death produced by many kinds of fits, by anger, electricity or lightning; or by a blow on the stomach, etc. In these cases we find the blood, after death, not only as fluid a state as in the living vessels, but it does not even coagulate when taken out of them*

—John Hunter<sup>1</sup>

Since Morgagni<sup>2</sup> and John Hunter<sup>1</sup> observed postmortem fibrinolysis in the 18th century, our knowledge of fibrinolysis has evolved from viewing it as a means of dissolving fibrin clots to being an important component of many biologic processes. In the 1950s, *fibrinolysis* was recognized to be a system that regulates hemostasis. In the following decades, interests centered on the development of fibrinolytic compounds for use in thrombolytic therapy. Then, beginning in the early 1990s, components of the fibrinolytic system were found to be involved in both normal physiologic as well pathologic processes. This opened up new, previously unanticipated avenues of investigation in the biology of the fibrinolytic system. As such, the “fibrinolytic system” is now more commonly referred to as the “plasminogen–plasmin system” (P–P system). The P–P system, in addition to plasminogen, is composed of several plasminogen activators (urokinase plasminogen activator [uPA] and tissue plasminogen activator [tPA]), several plasminogen activator inhibitors (PAI-1 and PAI-2) and the inhibitor of plasmin ( $\alpha_2$ -antiplasmin). In 1991, an issue of *Seminars in Thrombosis & Hemostasis* was devoted to the “Cell Biology of Fibrinolysis.”<sup>3</sup> In the ensuing 20 years, the field has expanded greatly, and it is time for our readers to get an update, which is presented herein.

This issue begins with reviews on the major components of the P–P system. These include a review by Miles and Parmer on recently discovered plasminogen receptors,<sup>4</sup> an update on

a role for the canonical plasminogen receptor, annexin A2, in diseases,<sup>5</sup> followed by a molecular view of the uPA receptor (uPAR) by Ferraris and Sidenius.<sup>6</sup> Another member of the P–P system that has a versatile role in biology and the pathogenesis of many diseases is PAI-1 and its implication on various processes is expanding almost on a daily basis. A series of reviews on this emerging important therapeutic target follow. An update of our understanding of this molecule is given by Declerck and Gils.<sup>7</sup> This is followed by a description of the more recently discovered inhibitor of plasmin and plasminogen activator, the thrombin activatable fibrinolytic inhibitor, which is discussed by Vercauteren et al.<sup>8</sup>

As PAI-1 is now recognized to be of the key factors in pulmonary fibrosis, and so an account of this is provided by Tucker and Idell.<sup>9</sup>

Much recent work has been devoted to determine the importance of the P–P system in cancer. uPA, uPAR, and PAI-1 have all been implicated in tumor progression, and expression of these various components is associated with poor prognosis in various cancer types. In particular, the uPAR is a key member in the complex interactions of this system that drive tumor progression. This is reviewed by Kwaan et al.<sup>10</sup>

The role of the P–P system is also emerging in various other diseases. The remaining parts of this issue therefore focus on these emerging roles of the P–P system, beginning with an article by Gando,<sup>11</sup> which describes the role of fibrinolysis in patients with sepsis and trauma. A critical review of the tissue-plasminogen activator, tPA, for intraventricular hemorrhage is then presented by Wong and Bailes<sup>12</sup> and followed by a review from del Zoppo<sup>13</sup> on the state of thrombolytic therapy for treating stroke. In the next article, Violi and Ferro<sup>14</sup> review the role of increased fibrinolysis in the pathobiology of liver disease. Dhillon and Adams then discuss an important but often overlooked role for the fibrinolytic system in systemic lupus erythematosus.<sup>15</sup> This represents just one example of

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the potential role of the P–P system as well as dysregulated coagulation in autoimmune diseases and an area that probably deserves more attention from the translational community working in fibrinolysis and coagulation. Finally, this issue of *Seminars in Thrombosis & Hemostasis* concludes with a series of three reviews on “applied” thrombolysis, two on catheter-directed thrombolysis for arterial and venous thrombosis by Wicky et al<sup>16</sup> and Oklu and Wicky<sup>17</sup> and a discussion of thrombolytic therapy to treat pulmonary embolism by Tapson.<sup>18</sup> These three reviews provide some critical additional specific application narrative to the general conceptual review on novel and emerging therapies for thrombus-targeted fibrinolysis recently published in this journal.<sup>19</sup>

In total, the diversity of reviews presented in the current issue of *Seminars in Thrombosis & Hemostasis* reflects the growing understanding of the diversity of normal and pathological processes in which the P–P system plays a role. Given space limitations, certain aspects of the role of the P–P system in diseases have not been presented. For example, there is a growing body of evidence implicating dysregulation of the P–P system in various neurodegenerative diseases, including Alzheimer disease.<sup>20,21</sup> These other functions of the P–P system are also important, and we anticipate that the role of the P–P system in these diseases will continue to be elucidated. To summarize, much has changed in our understanding of the role of the P–P system in normal physiology and diseases since the *Seminars in Thrombosis & Hemostasis* issue titled “Cell Biology of Fibrinolysis” in 1991<sup>3</sup> and the field continues to evolve and expand. This should make the next 20 years of Fibrinolysis research and clinical application even more interesting to observe.

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