

More on the Source of D-Dimer in COVID-19

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The most remarkable biomarker in COVID-19 is a high plasma D-dimer level.^{1–3} This had been shown to be predictive for the severity of the disease^{4,5} and for thrombotic events.^{1,4,6} D-dimer is the product of plasmin degradation of cross-linked fibrinogen monomer.⁷ Thus, its production requires the obligatory activity of plasmin. With the fibrinolytic shutdown in COVID-19, mostly due to elevated plasminogen activator inhibitor 1 (PAI-1) levels in plasma,⁸ the activation of systemic plasmin is effectively blocked. Thus, the origin of D-dimer becomes somewhat of an enigma.⁹ D-dimer is generally believed to arise from fibrin deposition in pulmonary lesions that occur in severe COVID-19 respiratory distress. As there is a hypercoagulable state in COVID-19, associated with a high fibrinogen level, tissue factor released by injured lung epithelial cells results in activation of

coagulation providing ample amounts of fibrin monomers for the formation of D-dimer. Hunt and Levi point out that the source of plasmin is the pulmonary lesion,¹⁰ where urokinase plasminogen activator (uPA) as the activator of plasminogen can generate plasmin. In addition, the increased macrophages in these lesions may also provide metalloproteinases for the proteolysis of fibrin monomers.¹⁰ uPA have been observed in the bronchial lavage fluids, bronchus, pleural, and alveoli. We are providing additional information that multiple forms of uPA exists at these sites.¹¹ Each has a different proclivity of generating plasmin (►Fig. 1). In kidney and other cells, uPA is released as single-chained uPA (scuPA) and quickly converted to two-chained uPA (tcuPA) by plasmin. tcuPA then readily binds to its receptor (uPAR) which is anchored to the cell surface by a

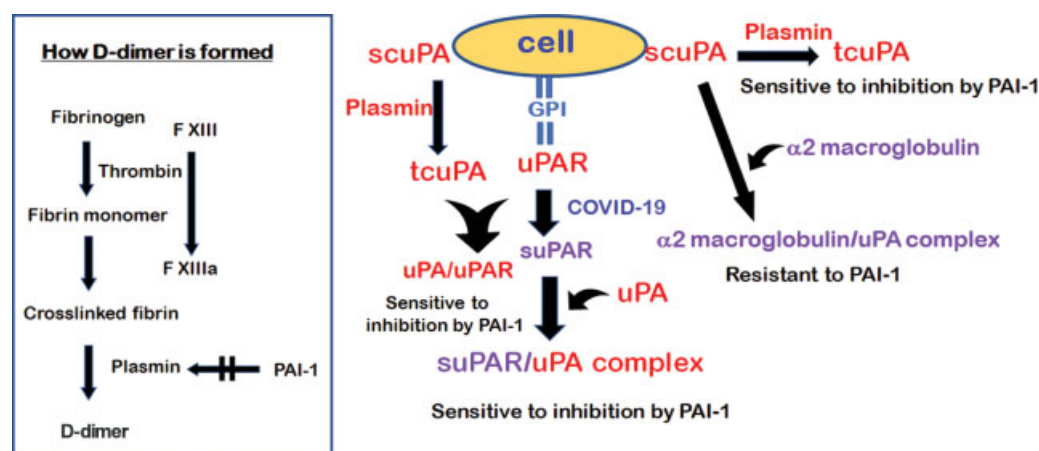


Fig. 1 The steps in the formation of D-dimer is shown in the box on the left, showing that plasminogen activator inhibitor 1 (PAI-1) inhibits (—|—) this process. On the right, different forms of uPA including single-chain uPA (scuPA), two-chain uPA (tcuPA), uPA/uPAR complex, and scuPA/uPA complex are able to convert plasminogen to plasmin but can be sensitive to inhibition by PAI-1. The exception is when scuPA is bound to α2-macroglobulin forming α2-macroglobulin/uPA complex. This complex is resistant to PAI-1.

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glycosyl-phosphatidyl-inositol (GPI) anchor. Proteolysis of the GPI anchor will free uPAR from the cell surface forming soluble uPAR (suPAR). Plasma suPAR is high in COVID-19 and is predictive for severity of disease and for extent of organ injury.¹² With its ligand (uPA), it can also generate plasmin from plasminogen.

In the case of formation of D-dimer in COVID-19, the issue is how much plasmin generating potential does each form of uPA has in the affected organs. This obviously depends on their respective sensitivity to the inhibitory action of PAI-1. PAI-1 level is high in COVID-19.⁸

On the cell surface, tcuPA forms a complex with its receptor uPAR. The uPA/uPAR complex is active in generating plasmin, but its action is effectively inhibited by PAI-1 in the vicinity. On the other hand, the single chain zymogen form of uPA (scuPA) is less sensitive to PAI-1 inhibition by virtue of its' forming a complex with α 2-macroglobulin. This complex is resistant to the inhibition by PAI-1 and thus presents an alternative pathway for plasminogen activation.¹³ scuPA injected into the injured pleural cavity has been found to be a source for a slow-release form of fibrinolytic activity.¹³ On the other hand, plasmin and other proteases convert scuPA to two chain uPA (tcuPA), which is readily inhibited by PAI-1. Thus, it can be seen that during the course of COVID-19, these components of the fibrinolytic system, namely, uPA in its various forms and PAI-1, will influence the amount of plasmin generation and the ensuing D-dimer formation.

A full understanding of the complex interactions of active PAI-1, scuPA, tcuPA, uPAR, and suPAR in the generation of active plasmin in involved organs in COVID-19 may explain the utility of D-dimer level as a biomarker in assessing the severity of the disease. How D-dimer values may assist in the management of anticoagulation in COVID-19 remains to be explored.

Conflict of Interest
None declared.

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