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Exploring differential regulation of blood clot degradation

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Blood clots are physiologically degraded via a biochemical cascade initiated by tissue plasminogen activator (tPA). tPA, which is also used clinically to treat stroke, creates plasmin, the main protein involved in degradation. We explore the effects of tPA unbinding and diffusion on clot degradation. We propose that plasmin can “force” tPA to unbind from the clot, which has significant implications for the resulting clot degradation. Using a 3-dimensional stochastic multiscale model, four different regulatory mechanisms are explored when tPA is forced to unbind: 1) tPA is immediately able to rebind to fibrin; 2) tPA is immediately removed from the system; 3) tPA is bound to a fibrin degradation product (FDP) that is small enough to diffuse through the clot, and after some time determined by the kinetic unbinding rate, the tPA unbinds from the FDP and is available for rebinding; 4) tPA is bound to an FDP that can only diffuse along or away from the clot (due to its size), and after some time determined by the kinetic unbinding rate, the tPA unbinds from the FDP and is available for rebinding. We discuss the contributions of each mechanism in clot degradation, the surprising role of plasmin, and the implications for stroke treatment.

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