A computational model of a positive loop feedback in endothelial cells sprouting to explain the effect of fibrinogen variants

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A computational model was developed to describe the angiogenesis-like invasion of endothelial cells (sprouting) into fibrin matrices. Using an *in vitro* assay of sprouting in fibrin matrices, Weijers *et al.* [1] showed that the composition of fibrin changes the sprouting progress: there was more ingrowth on high molecular weight (HMW) than on low molecular weight (LMW) fibrin. As it is not yet clear which mechanisms regulate this process, the processes that drive the reduced ingrowth in LMW as compared to HMW fibrin were studied using a hybrid computational model, cell-based and continuum, that describes the experimental tests. From the results obtained in this simulation, it is proposed that it is present a local positive feedback mechanism between urokinase receptor (uPAR), plasmin and Transforming Growth Factor $\beta 1$ (TGF$\beta 1$). This, due to stochastic fluctuations in the different concentrations, leads to some cells in the monolayer to invade the matrix and to produce sprouts. Plasmin-mediated fibrin degradation by invading cells releases TGF$\beta 1$ from the matrix which locally stimulates cells to increase fibrin degradation, leading to a positive feedback loop. Including the experimental observation that LMW binds less TGF$\beta 1$ than HMW fibrin, the model predicts reduced sprouting in LMW as compared to HMW [2].

Keywords: biological modeling; endothelial cells sprouting

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[2] Sonja E.M. Boas, João C.L. Carvalho, Marloes van den Broek, Ester M. Weijers, Marie-José Goumans, Pieter Koolwijk, Roeland M.H. Merks, A Local uPAR-plasmin-TGF$\beta 1$ Positive Feedback Loop in a Computational Model of Angiogenic Sprouting Explains the In Vitro Effect of Fibrinogen Variants, to be submitted.