**Multiscale Modeling of Wound Healing**

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Fibroblast invasion of a clotted wound is directed by gradients of chemoattractants and matrix properties. In the chemotactic response to platelet-derived growth factor (PDGF), signaling through the phospholipase C (PLC)/protein kinase C (PKC) pathway has been proven necessary. We have developed and analyzed multiple mechanistic, reaction-diffusion models of this gradient sensing circuit, including the major proteins (PDGF receptor, PLC, and PKC) and lipids (PIP2 and DAG) in the canonical pathway, as well as other signaling molecules that we implicate in various positive feedback loops. Model simulations suggest that the synergy of at least two of the putative feedback loops is needed to drive order-of-magnitude enrichment in a shallow PDGF gradient, as observed in experiments. To link the molecular-scale signaling pattern to supra-molecular structures and mechanics, we have completed stochastic particle-based computer simulations of the actomyosin cytoskeleton, revealing the spontaneous formation of actin asters. A systematic parametric analysis identified biochemical steps in myosin activity that are good candidates for regulatory control. Finally, we investigated the effects of gradients of signaling activity by allowing key model parameters to vary in space. Interestingly, spatial regulation of motor stiffness led to time-dependent behavior of the actomyosin network, in which actin asters formed in regions of low stiffness, migrated up-gradient and then disassembled. These computational investigations at the molecular and supra-molecular scales have generated testable hypotheses that guide our ongoing experiments.