Multiscale Modeling of Wound Healing

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Abstract

Chronic wounds are a major threat to public health and the economy and present as a comorbid complication with major diseases with humans. Although the proper healing of cutaneous wounds requires collective and coordinated behaviors of multiple cell types, the rate-determining step is the recruitment and function of dermal fibroblasts, which are directed to invade the wound by a gradient in the concentration of platelet-derived growth factor (PDGF).

A great deal is known about the signal transduction pathways activated by PDGF receptors and other receptor tyrosine kinases; yet mechanistic insights about how those pathways are spatially organized to bias the dynamics of the actin cytoskeleton and the directionality of cell migration are still emerging. Furthermore, a larger fundamental gap lies in the integration of molecular, supramolecular, cellular, and tissue-level dynamics of wound healing, which then spans disparate time (seconds to weeks) and spatial (nm to cm) scales.

To advance this field, novel approaches are needed to fuse experimental and observational scales that are relatively data-rich (signaling, cytoskeletal dynamics) and data-poor (in vivo dynamics). To that end, we propose to develop a predictive, multiscale model of the proliferative phase of wound healing incorporating 1) receptor-mediated signal transduction (molecular scale), 2) self-assembly of contractile actomyosin (supramolecular scale), 3) morphodynamics and statistics of cell migration (cellular scale) and 4) collective cell behavior in vivo (tissue scale). By combining our expertise in experimental cell biology and biophysical modeling, the proposed model development will be guided by new quantitative measurements at every scale of biological abstraction.

Aim 1 (molecular scale): reaction-diffusion model to characterize amplification mechanisms in PDGF gradient sensing

PLC/PKC pathway: Activated PDGF receptors engage PLC, which hydrolyzes PIP2 to DAG and inositol triphosphate (IP3). PKC is activated by binding to DAG at the membrane, and active PKC regulates non-muscle myosin II contractility by phosphorylating the regulatory light chain (RLC).

MARCKS: Myristoylated alanine-rich C kinase substrate (MARCKS) binds to the plasma membrane by the hydrophobic insertion of myristate into the inner leaflet, and the electrostatic interactions of its effector region with acidic phospholipids. MARCKS synergizes with PKC feedback to:

- One MARCKS sequesters up to three PIP2 molecules.
- MARCKS phosphorylation by PKC liberates PIP2.
- Thus, the pool of free PIP2 available for hydrolysis is controlled.

MARCKS dynamics are sufficient to amplify the PLC/PKC pathway

Simulated time courses of the active PKC concentrations show amplification of the PLC/PKC pathway across a cell following stimulation by a gradient of PDGF at 1200s.

FrontBack ratio of active PKC

Without MARCKS

With MARCKS

Future Work

- Assess robustness of PKC amplification with varying PDGF gradient conditions.
- Characterize the mechanism by which MARCKS amplifies the PLC/PKC pathway.
- Assess the effect of boundary conditions on actomyosin structures.
- Parametric analysis of myosin II activation and inactivation rates.
- Couple the molecular and supramolecular scales and relate to cell motility/migration bias.

References


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