NIH Award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases

Principal investigator: Kathleen Janee Green, pathology
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- Project: Function of Desmoglein 1/Pemphigus Foliaceus Antigen
- Start Date: September 24, 2009
- Total Award Amount: $464,286

How the results of this project will benefit society:
Desmogleins are “sticky” molecules found on the surface of many cells in the human body. Functional ablation of the desmogleins found in human skin cells results in severe skin disease. The studies in this application will provide funds to support personnel, supplies and equipment to explore a novel pathway through which desmogleins regulate cell behaviors that supersede their known roles in sticking cells together, including regulation of cell motility during skin wound healing.

The problem the project is trying to solve:
Desmogleins (Dsgs) are Ca2+-dependent adhesion molecules that partner with desmocollins to make up the adhesive core of intercellular junctions called desmosomes. This competing revision supplement proposes to expand the scope of our parent grant, a major goal of which was to elucidate the function of desmoglein 1, which is first expressed as cells begin to differentiate and becomes concentrated in the superficial layers of the epidermis. During the course of these studies, the armadillo protein plakoglobin (PG) has emerged as an important Dsg1-associated molecule capable of orchestrating its adhesion-dependent and -independent activities. Proteomics analysis of cell-substrate contact material derived from PG-null cells revealed dramatic alterations in integrin and matrix profiles, which could explain previously observed alterations in motility of single PG-deficient cells. Cell-cell and cell-substrate adhesion is carefully coordinated during normal tissue morphogenesis as well as during epithelial remodeling that occurs in wound healing.

How the project will work:
We propose that Dsg1 plays a central role in this coordination through its partner PG, strengthening cell-cell adhesion in intact tissues, and regulating motility in remodeling epithelial cells with limited intercellular contact. To test this idea, we propose: (1) To determine whether Dsg1 acts as a “rheostat” to regulate ECM deposition, integrin-mediated keratinocyte cell-substrate interactions and cell motility in a PG-dependent manner, and (2) To test the hypothesis that PG inhibits keratinocyte motility by regulating cytoskeletal and ECM remodeling through Src. Taken together, this work will help to better understand a novel aspect of desmosomal cadherin biology—their functional cross-talk with cell-ECM junctional molecules. Integrated with advances from the parent grant, these studies will provide insight into normal and pathological processes in epidermis involving this novel signaling axis. The requested funds will provide an extension of employment for a postdoctoral fellow during the hiatus between NRSA funding and securing independent funding. In addition the funds will support hiring a new technician and small equipment to help accelerate the pace of the proposed studies.

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