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Wound repair constitutes an essential component of every surgical subspecialty. The health care system spends millions of dollars annually to apply the latest “*go du jour*” onto wounds. But in spite of all we know about response to injury, we still do not offer good solutions to patients with chronic non-healing wounds or with hypertrophic scars and keloids. Our collective efforts have been focused on understanding the response to cutaneous injury for wounds with either insufficient or exuberant responses.

Burn Wound Repair

With increased patient survival following burn injuries, rehabilitation and problems associated with scarring, such as hypertrophy and itching, become important. Since early civilization, we have been adapting topical treatments for wounds. While the growth factors that we apply to wounds today are more sophisticated than the honey, wine, oil or resins that were used in ancient medical practices, we still do not know what the growth factors do or when they should be applied.

Valuable studies over the past 30 years have augmented our understanding of the progression of repair from an acute injury through coagulation, inflammation, blood vessel formation, fibrogenesis and epithelialization, and finally to remodeling. Nevertheless, we still do not fully understand normal wound repair and thus how to therapeutically modulate repair in compromised wounds.

We designed our basic science efforts to define cellular and extracellular inflammatory processes in normal burns. Our aim has been to better understand what deviations result in non-healing wounds or in abnormal scars in order to know when to perturb the healing process with a repair accelerant.

Collectively, our data support the theory that the skin itself is a component of the immune system and that non-inflammatory cells may contribute to the initiation and maintenance of the inflammation at the wound site. Furthermore, these studies have accentuated the notion that inflammatory mediators at the wound site are present at specific phases in the repair process, and that interventions with exogenous mediators must be timely.

Inflammatory Responses to Thermal Injury

With introduction of early excision and grafting and improved critical care, mortality following burn injury has dramatically decreased over the past 30 years; future improvements in survival will require innovative pharmaceutical and wound coverage interventions. For the past five years we have collaborated in a multicenter, multispecialty effort to understand host responses to injury. After five years and a renewal in 2006, we are positioned to correlate clinical data with corresponding genomic and proteomic analyses from patients with severe burn injuries. Ability to predict patients who are likely to develop multi-organ failure or die after a severe injury is the first step in understanding potential targets for therapeutic intervention.

Neuroinflammatory Responses to Wound Repair

Our lab has been dedicated to defining neuroinflammatory responses to wound repair. The sensory nerves in skin regulate pain transmission, but also a local inflammatory response within the wound bed. We have identified normal temporal and spatial distribution of pain fibers in human burn wounds.

We have demonstrated that patients with sensory deficits due to both spinal cord injury and diabetes mellitus have a dramatic reduction in cutaneous sensory nerves, especially in the wound beds. We have also determined that activity

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levels of neutral endopeptidase, a membrane bound enzyme that degrades substance P, are elevated in the wounds and skin of patients and mice with diabetes. Therefore, it was not a surprise to us that exogenous substance P shortens time to healing in a model of delayed wound repair in diabetic mice. We have also observed increased levels of the enzyme neutral endopeptidase in skin and wounds from diabetic mice. We have shown that increased glucose and fatty acids increase neutral endopeptidase levels in cultured endothelial cells. Most interestingly, this increase can be inhibited with antioxidant treatment.

Following injury, sensory nerves are absent within the injury site. With time there appears to be a transient abnormal increase in neuroinflammatory mediator within the wound that eventually approaches normal. These findings are important because itching, which is mediated by neuropeptides, is a major complaint of patients with thermal injuries. Hypertrophic scars have elevated levels of substance P and decreased neutral endopeptidase activity compared to uninjured skin and normal scars.

Our lab is focused on determining endothelial cell derived signals that govern nerve cell differentiation. Sensory nerve-derived neuropeptides stimulate endothelial cells following injury to round up, proliferate and synthesize adhesion molecules and cytokines. These studies are currently focused on intracellular signaling pathways that mediate substance P-mediated changes to the endothelial cell. Activated endothelial cells stimulate reinnervation of the injury site. We have defined this process to be a neuro-endothelial axis and believe that it may contribute to the pathophysiology of hypertrophic scar formation.

Response to Burn Injury: Role of Melanocortin 1 Receptor in Wound Healing.

One novel direction in our laboratory is to demonstrate a role for the melanocortin 1 receptor in hypertrophic scar formation using both genetic and cell biological approaches. The infrastructure for this project involves

creating a unique repository of DNA samples from affected individuals linked to a database of detailed phenotypic (i.e., clinical) information from the same individuals. The resulting DNA bank will also be available for future genomic study. We will evaluate the DNA for polymorphisms in the MC1R gene and correlate that with tendency for scarring. As a mechanistic corollary we will use RNAi technology to test our hypothesis at the cellular level by investigating the role of the melanocortin 1 receptor in fibroblast responses implicated in hypertrophic scar formation.

Surgical Wound Repair: Effect of Metabolic Memory on Neuro-Endothelial Responses

Type 2 diabetes mellitus, with characteristic hyperlipidemia and hyperglycemia, is common in overweight Americans and is a major risk factor for neurovascular complications. Multiple analyses from the Diabetes Control and Complications Trial demonstrate that patients treated with standard insulin therapy exhibit sustained inflammatory responses and develop vascular complications in spite of subsequent intensive insulin intervention. These findings have generated the widely accepted 'metabolic memory' theory that transient hyperglycemia involves epigenetic modifications that alter gene expression. Epigenetic modifications have been increasingly correlated with human diseases, and such associations are essential for understanding the pathophysiology of chronic diabetic wounds. Our hypothesis for this new project is that: 1) elevated levels of glucose and fatty acids, even transiently, alter paracrine interactions between dermal microvascular endothelial cells and neural progenitor cells in a sustained manner; and 2) antioxidants abrogate the dysfunctional responses to glucose and fatty acids. We have collaborated with Dr. Oleg Denisenko in the Department of Medicine to utilize chromatin immunoprecipitation to identify evidence of DNA or chromatin modulation – evidence that short term hyperglycemia and hyperlipidemia cause epigenetic changes in endothelial cell responses to injury.

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