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Project Title: "The Role of Exosomes in the Pathogenesis of Cutaneous Scarring and Fibrosis"
Year Awarded: 2018 WHF-3M Award

What do you hope to learn through this research?

The physiologic response to cutaneous injury results in fibrosis or scar formation, which is intriguingly different in every individual and results in a "spectrum of scarring" phenotypes ranging from low to high. Irrespective of the heterogeneity of individual scar phenotypes that originate from seemingly similar injuries, a persistent finding is that once formed, the scars are permanent. This is a striking phenomenon given the continuous turnover of the skin. The focus of my research is to understand why we scar differently and why scars persist, which could provide relevant clues to develop new and effective anti-fibrotic therapies.

My scientific career evolved in the pursuit to know how fibroblasts, the preeminent arbiters of fibrosis, respond to injury, interact with the wound microenvironment, and govern scar formation. We showed that the fibroblast functional properties operate differently depending on the gestational stage and lead to distinct wound healing outcomes. I then sought to understand how inflammatory cytokines regulate fibroblast function and interaction with the inflammatory milieu and extracellular matrix (ECM) to drive dermal scarring. As I could grasp from my bioengineering acumen that tension influence cellular morphology, biochemistry, and function, and equally importantly, it regulates clinical scarring outcome, my research was further geared to investigate how biomechanical forces shape fibroblast phenotype and contribution to fibrosis. As such, my team identified that the fibroblast phenotype is highly responsive to local biomechanical, inflammatory and ECM signals, and can be altered to influence wound repair and fibrosis. However, despite our contributions and the progressive advances in scar research, the specific intercellular mediators that transduce scar signaling remain undetermined.

Thus, we sought to investigate the nature of pro-fibrotic intercellular events and noted that extracellular vesicles or exosomes can commute cell-to-cell communications under homeostatic and pathologic conditions. Secreted exosomes carrying lipids, proteins, nucleic acids are being increasingly recognized as central paracrine mediators of crosstalk among normal or pathogenic cells in the regulation of disease progression in cancer and pro-fibrotic diseases. Because the pathophysiology of exosomes in normal skin repair and fibrosis is still not known, my long-term goal is to study the role of exosomes in the mechanisms that control fibroblast interactions to contribute to scar heterogeneity and perpetuation.

What can you tell us about the progress made in this area since you first began your research?

The WHF-3M award provided us the support to develop a physiologically relevant biobank that would enable us to study patient responses to scarring and fibrosis. Accordingly, we are currently probing the biobank to investigate the role of exosomes in dermal scarring and have accrued significant preliminary data, which suggest that fibroblasts obtained from high and low scarring patient samples secrete exosomes with notably different content profiles and have uniquely distinct phenotypes. Moreover, when exosomes are transferred from one fibroblast phenotype to another, a switch in dermal fibroblast function and fibrotic phenotype can be observed. Fibroblast-derived exosomes from either low or high scarrers influence wound healing patterns and transduce the original scar phenotype (the propensity of the patient scarring from where they were isolated) in murine wounds suggesting they may perpetuate the scar phenotype. These findings strongly indicate that exosomes are perhaps key intercellular mediators which determine how individual people scar. To complement these data, we will also determine how different patient derived cells respond to mechanical stimulation and determine the role for exosomes in their characteristic fibrotic responses.

How can this research help patients, clinicians and/or scientists?

The relevance of this proposal stems from clinical observation of significant heterogeneity in patient scarring outcomes from which further stemmed our plan to address gaps of knowledge on mechanisms that regulate exosome-driven signal transduction, which could explain the heterogeneity of human scarring and why scars persist. The molecular content of fibroblast secreted exosomes could reveal unique biomarker signatures within the wound microenvironment which could become the basis to design target-guided precision anti-fibrotic therapies.

How did this award help your career?

I believe that the impact of the WHF-3M funding on my career is multifold: 1) provide my lab with a means to advance the field by pushing forward an exosome-centered paradigm of scar biology; 2) establish strong scientific premise and generate rigorous preliminary data to apply for federal funding; 3) develop my budding collaborative network of investigators to endeavor studying the role of exosomes in dermal scarring; 4) provide networking opportunity with eminent scholars in the field including basic science researchers, clinicians and industry members through the foundation luncheon and dedicated scientific sessions, which helped me establish key collaborative and mentorship connections; 5) the WHF-3M award has historically been considered the highest honor for junior faculty and fellows at the annual wound meeting as they embark on an independent career in wound sciences. As such it puts the name of the recipient on the map as a gatekeeper of that new line of wound research, with the expectation that the recipient will become a successful independent faculty, secure extramural funding and be an integral part of the wound healing society/foundation and a life-long proponent of its mission; 6) perhaps most importantly, I believe it serves as an endorsement of my new and exciting line of research, which keeps me motivated and solidify my department's resolve in providing much needed start up support to my lab.

How did you get interested in wound healing and this area in particular?

I grew up in an industrial colony in South India, where my parents use to work in heavy electrical and huge boiler building plants. Every time a boiler would be assembled and ready for export, the whole community would come together to celebrate and my parents would rave about the global impact their work has on improving human life, whether it be in mining, electrical power generation and/or transportation. So naturally, I studied mechanical engineering for my undergraduate and master's training and took up what I thought was my dream job in Caterpillar subsidiary where I was mostly doing small iterative changes to the engine design. I distinctly remember a senior colleague jokingly said, they revolutionized the engine design field 30 yrs ago and we get to enjoy it, which struck a chord with me. I was naively fixated on the word 'revolutionize', and it made me look back on my childhood and realize that my parents were so passionate about their jobs because they believed that they were revolutionizing the industrial era of newly independent India.

I started my research career in wound healing in 2005. When I look back to that time, I think our quest was to make human lives better with biomedicine, which was the next revolution. I left so energized and invigorated after my first conversation with my PhD mentor Dr. Narmoneva, where we talked about tissue engineering ideas, wherein I can combine the principles of engineering, biochemistry and biology to create novel therapeutics that can have a huge impact on human health, which I believe marks the beginning of my career in Bioengineering. I got accepted into PhD program and embarked on this journey. We first started studying how we can use tissue engineering approaches to improve neovascularization in cardiac fibrous tissue after myocardial infarction. But the fundamental biology and molecular mechanisms of post-injury tissue repair quickly because my main focus. As researchers we always look for ideal models to study the process of repair and fibrosis after injury. Human skin, remarkably has the potential to heal regeneratively while in mid-gestational fetal stage in utero, and yet as we mature, we default to scarring and fibrosis. This whole process was so fascinating to me and there is so much more to learn and discover. As such, my current research focuses on understanding the sequelae of fibrosis in response to dermal injuries in postnatal patients, with a particular emphasis on understanding the heterogeneity in scarring propensities of different postnatal patients and why scars persist once formed. We then comparatively assess the scarless wound healing mechanisms of the fetal regenerative responses, to ultimately recapitulate the scarless phenotype in adult healing and impact clinical patient care.

Tell us about some of the outcomes of your research you are most proud of and what it means for patients, clinicians and/or scientists.

My clinical surgical collaborators always mention that the standard of care in their practice is to individualize the repair and tissue reconstructive process using up-to-date techniques to help patients feel physically and emotionally complete. In spite of which, they routinely observe that there are dramatic differences in scarring phenotypes between individuals, even within a homogenous patient population treated using standardized surgical techniques and best practice post-operative management. This heterogeneity in scarring is difficult to predict and results in significant functional and psychological morbidity in the patients.

I am very excited that our proposal aims to understand the biological basis for these heterogeneous outcomes. In particular, I think it will be groundbreaking to elucidate how scarring and fibrosis is influenced via fibroblast-derived exosomes and the role of biomechanical forces on this process, as they might serve as biomarkers to predict patients' propensity to scar. I firmly believe this research program holds great promise and significant clinical impact, both in pre-operative planning and counseling patients as to their scarring outcome, and in the development of post-operative anti-fibrotic therapeutics.

Approximately how many publications have you published since becoming a Fellow? Of these, how many relate to your Fellow research?

Since becoming a WHF-3M fellow, I have published one article underscoring a sexual dimorphic role for fibroblast fibrotic phenotype when challenged with stressors such as hyperoxia. This study directly impacts what we study as part of the WHF-3M funded work. Importantly, I am mentoring undergraduate students and a postdoctoral fellow on this project. We have submitted our preliminary findings from this study as abstracts to the American Surgical Congress meeting. We anticipate to publish 2 basic science articles in the next semester from the results generated from this study.

What are your future plans for your work in wound healing?

My long-term career goal has always been to be a professor in a setting where I can participate in interdisciplinary wound healing surgical and bioengineering research and contribute to undergraduate/graduate/postdoctoral education and mentoring. I firmly believe that the concept that exosomes can transduce scarring tendencies in a high turnover environment such as the skin will bring new insights into the biology of fibrosis beyond the skin.

Who do you consider your mentors and your close associates in this project? How did you start working with them?

The achievements I have attained over the years stem from being a part of world-renowned and active Bioengineering and fetal surgery centers with top-tier research training curricula. I was privileged to work under Daria Narmoneva, PhD and Tim Crombleholme, MD for my graduate training. My PhD in Biomedical Engineering was in the area of diabetic wound healing and myocardial and diabetic cardio myopathy-associated fibrosis. We have shown that tissue repair with mechanically stable tissue engineered provisional matrices reverses the impaired cell phenotype due to 'glycemic memory' in endothelial cells and fibroblasts to promote wound healing. This work also demonstrated that the extracellular environment is not a passive player, but rather actively regulates wound healing outcomes. We published 5 high impact manuscripts and my work received the highest honor of Anita Roberts Award from the Wound Healing society.

To then learn fetal regenerative wound healing concepts I started working with Sundeep Keswani, MD and Tim Crombleholme, MD. I have studied the role of hyaluronan in tissue repair for my post-doctoral work and engineered transgenic mice strains to investigate the effects of interleukin-10 (IL-10), a pleiotropic immunomodulatory cytokine, on fibroblast-mediated synthesis of hyaluronan-rich wound matrix. Notably, we were the first to demonstrate the unique capacity of IL-10 to regulate extra cellular matrix organization in wound healing. In addition, I investigated the emerging function of IL-10 in wound neovascularization using the above cited transgenic mouse models, with notable impact to promote diabetic wound healing. This work, conducted through a long-standing collaboration with Dr. Sundeep Keswani resulted in high impact original research publications, review articles and book chapters, which underscored the seminal work and contributions of our team to the better understanding of IL-10 functions. Moreover, our collective studies further translated into a patent application on a hyaluronan-based hydrogel for sustained delivery of IL-10 to wounds, which foresees high-impact clinical applications. Our collective data provide a thought-provoking view of fetal regenerative a phenotype, which is characterized by reduced inflammation, unique hyaluronan-rich extracellular matrix (ECM) and fibroblasts with enhanced functions, such as migration and reduced production of pro-inflammatory cytokines, and decreased pro-fibrotic ECM, as compared to adults. This exceptional and productive venture empowered me to embark on an independent career in biomedicine.

We recently identified a link at the regulatory core of ECM-driven fibrosis between biomechanical tension/wound stiffness and fibroblast phenotype, in which fibroblasts transduce these different signals into wound fibrosis. While it is known that inflammatory factors and fibroblasts "crosstalk" it remains to be determined how tissue mechanics regulate inter-cellular communications, specifically among fibroblasts, to further propagate fibrosis. One of our goals in the proposed studies is to elucidate the fibroblast signaling mechanisms that communicate and regulate the fibrogenic phenotype, which could be mediated via the secretion of extracellular vesicles also known as exosomes. Moreover, we also intend to know whether exosomes play a key role as mediators of fibroblast crosstalk, which could render these unique microvesicles as diagnostic biomarkers for potential therapeutics. As I began to formulate new directions to study these mechanisms, I was fortunate to have the opportunity to discuss my work with Drs. Chandan Sen, Jane Grande-Allen, Gail Besner and Kenneth Liechty. Their commitment to our quest to attenuate fibrosis and the collective experiences in mechanobiology, miRNA and epigenetics, exosome biology and regenerative healing will provide invaluable insights into this project, which is clearly at the interface of engineering and fundamental biology. As an Assistant Professor in the Division of Surgery, I have the unique opportunity to study patient scarring outcomes at the bedside in collaboration with Dr. Shayan Izaddoost, and have direct access to patient derive samples, to then elucidate the mechanisms of scarring in my lab, which can lead to the development of novel therapeutics to help patients. Bioinformatics analysis of the exosome cargo to understand the underlying biology forms the cornerstone of the proposed work. I have established an ongoing and productive collaboration with Drs. Cristian Coarfa and Matthew Robertson which will enable a thorough characterization of the exosomes and uncover novel fibrosis biology.

Tell us about your life away from the lab?

I live in Houston, Texas. I am a mom of 2 very active boys who are 9 and 4y old. We enjoy riding bikes to the local nature discovery center and explore the plants, insects, birds and animals. I also coach the 9y old Odyssey of the mind team, which I thoroughly enjoy as I get multiple opportunities to brag about STEM and women in engineering and even simple incidents as paper cut can turn into a wound healing discussion.

The Wound Healing Foundation is a 501(c)3 organization.