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Project Title: Novel mechanism for regulation of cutaneous wound healing by caveolins,
Year Awarded: 2015

What do you hope to learn through this research? The goal of this project is to identify a specific mechanism by which caveolins (CAVs) and membranous fraction of the glucocorticoid receptor (mbGR) regulate keratinocyte migration and wound closure along with the role they play in diabetic foot ulcers (DFUs). Because DFUs are arguably the most debilitating complication of diabetes mellitus, affecting 6.5 million patients annually and often leading to lower limb amputations, understanding mechanisms that participate in inhibition of healing in DFUs will provide new treatment approaches and novel targets for intervention. We hypothesize that CAV is a novel regulator of wound healing through orchestration of nongenomic mbGR signaling. Thus, CAV-mbGR is a potential mechanism that inhibits keratinocyte migration and wound closure and contributes to pathology of DFUs. I hope that outcomes of this project will provide fundamental insights into the molecular mechanisms of non-genomic glucocorticoid signaling and introduce CAV as a novel target in regulation of cutaneous wound healing, both of which will have an important clinical and translational impact and significance on skin biology and wound healing.

What can you tell us about the progress made in this area since you first began your research? Caveolin is the principal structural component of caveolae, which are specialized flask-shaped cytoplasmic leaflets of plasma membrane microdomains highly enriched in cholesterol and sphingolipids, which are implicated in numerous cellular processes including cell growth, signal transduction and solute transport. CAV-1 has been shown to interact with different signal transduction molecules that contain a CAV binding domain and is thought to sequester and compartmentalize these signal transduction molecules, affording orchestration of transmembrane signaling events and allowing cross-talk between various downstream effectors. Due to its promiscuous relationship with numerous signaling molecules, there has been growing attention focused on the mechanisms by which CAVs serve to either sequester or compartmentalize various signaling molecules and hence affect numerous biological processes. Recently, it has been shown that aged skin exhibits upregulation of CAV-1 (that is negatively correlated to expression of collagen-1) and interestingly that perturbance of caveolae by cholesterol depleting agents (such as Methyl-β-cyclodextrin), can downregulate CAV-1 and subsequently upregulate collagen-1 in chronologically aged mouse and human skin, thereby suggesting a potential role for CAV-1 as an anti-aging target.

How can this research help patients, clinicians and/or scientists? To the best of our knowledge, the role of CAV and mbGR signaling in regulation of keratinocyte migration and the wound healing process has never been studied. Understanding the mechanisms through which CAVs and glucocorticoids (GCs) participate in epidermal response to injury will provide a data-driven rational basis for prevention and targeted therapeutic approaches. Our findings will also provide new insights into mechanisms of action of CAV, membranous glucocorticoid receptor (mbGR), revealing the basis of their tissue specificity in epidermis/skin. In addition, approach to utilize human skin *ex vivo* model as well as primary cells generated from patients suffering from DFUs to elucidate these mechanisms will provide unique insights that will have significant impact not only to skin biology and clinical dermatology, but also provide new treatment avenues for wound healing disorders, including DFUs.

Has your work thus far yielded any surprises? The discovery of epidermis as a source of extra-adrenal cortisol synthesis in response to injury is paradigm-changing. In addition, membranous localization of glucocorticoid receptor and its non-genomic signaling from plasma-membrane is surprising in the context of its anti-inflammatory effects in various skin disorders including inhibition of healing.

How did this award help your career? The WHF-3M Fellowship Award will fund my research for the next year and provide me the opportunity to obtain the answers to fundamental questions that I outlined in the proposal. This award will provide support at the very important point in my career development towards becoming an independent scientist as I plan to pursue an academic career.

How did you get interested in wound healing and this area in particular? I am a molecular and cell biologist by training. Because my PhD dissertation dealt primarily with *in vitro* models, focusing on endomembrane trafficking, more specifically transport from the plasma membrane to the early endosome, I was looking forward to integrate my skills with a clinically relevant research questions during my post-doctoral training. Given that CAVs participate in regulating signaling, which plays important role in regulation and coordination of the wound healing process, cutaneous wound healing seemed to me as an ideal research field to expand my research to study mechanisms that regulate it.

What are your future plans for your work in wound healing? Wound healing is an exciting field of research with many open questions that provide great opportunities. CAVs can orchestrate compartmentalization of numerous signaling cascades, it will also be interesting to delineate which other signal transduction cascades may be affected and how therapeutically targeting CAVs may indirectly affect them as well.

Who do you consider your mentors and your close associates in this project? How did you start working with them? I consider Dr. Marjana Tomic-Canic to be my closest mentor who provides superb guidance and support and helped me mature as a scientist and a teacher. Our research group is a dynamic, robust and, most importantly, fun research “playground” that facilitates discussions and exchange of ideas in a very supportive environment and I am very fortunate to interact closely with Dr. Irena Pastar and Dr. Olivera Stojadinovic, as well as my post-doctoral colleagues Dr. Liang Liang, Dr. Rivka Stone and graduate/medical students

(Horacio Ramirez, Andrew Sawaya Ashley Rosa and Joshua Fox). In addition, I am surrounded by scientists and clinicians that are advancing the field of wound healing, including Dr. Robert Kirsner and his entire Clinical Research Team, Dr. Evangelos Badiavas, Prof. Stephen Davis and many others who continue to inspire me and provide guidance and support. I started working with them when I joined Tomic-Canic Lab and I am very fortunate to be working in such extraordinary wound healing research environment.

Tell us about your life away from the lab? When I am away from the lab I like to pursue my other love, teaching, where I instruct an upper level undergraduate cell biology class at Nova Southeastern University. I believe that communicating science to students and exposing them to breakthrough and innovative research that is currently taking place is a great way to both educate the populace on basic science as well as raise awareness to the current research opportunities. Along with my wife, I also volunteer at the local animal shelter and we foster dogs until they are ready for adoption. Lastly, I am an avid fan of soccer and hence in my spare time I like to play in local Sunday leagues.