Researcher (s):	Dr Yanling Liao (Primary Investigator -PI) Prof Mitchell Cairo (Co-Researcher)
Research Institution:	New York Medical College, USA
Project Title:	Identifying innate and adaptive immune mechanisms associated with fibrosis in animal models of RDEB
Research Area (s):	Wound Healing
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Lay Summary

Inflammation is the body's natural defense system against infection and/or injury. However, many studies demonstrate that cutaneous squamous cell carcinomas in patients with RDEB arise at sites of persistent chronic inflammation. The skin of patients with RDEB is associated with trauma-induced lesions as well as microbial colonization. How the inflammatory responses evolve into an unwanted chronic condition in patients with RDEB is not clearly elucidated. In our preliminary analysis in a mouse model of RDEB (lacking COL7A1), we demonstrated that the immune cells in the skin of one and two- week old mice have distinct organization patterns, with the prior distributed in the dermis and the latter clustered around hair follicles. We hypothesize that this represents a critical transition of RDEB immunity against unsuccessful wound healing concomitant with the appearance of microbial colonization. In this study, we propose to define main immune cell types in the skin from developmental stages of fetus into infant (3 weeks of age) and identify key regulatory factors that trigger the temporal immune responses and/or fibrosis. The results from this study will likely lead to identification of therapeutic targets for prevention and/or treatment of chronic inflammation and fibrosis in patients with RDEB.

Project Abstract

Continuous and unremitting wounds lead to chronic inflammation and fibrosis, which in turn create a microenvironment permissive for cutaneous squamous cell carcinoma (cSCCs) transformation. A known key pathway in fibrosis formation and cSCC transformation in recessive dystrophic form of EB (RDEB) is TGFβ signaling. Our recent studies demonstrated a significant enhancement of TGFβ signaling in RDEB (col7a1-/-) mice beginning in the interdigital folds of the paws as early as a week after birth and progressing into overall periphery of the skin at two weeks and beyond. Moreover, our preliminary gene expression analysis demonstrated that factors

involved in Wnt/β-catenin signaling, Egfr and integrin signaling, in addition to TGFβ signaling were also dysregulated in the one week- col7a1-/- skin, suggesting possible contribution of other signaling pathways to the pathophysiology of RDEB.
Our preliminary studies also revealed a dynamic immune response in postnatal col7a1-/- murine skin. In the newborn and one week old col7a1-/- skin, an abundant number of immune cells was noted infiltrating in the dermis at or toward the edge of separated dermal-epidermal junction (DEJ). Strikingly, in two weeks, the immune cells were mostly clustered around hair follicles. Similar aggregation of T cells together with antigen presenting cells has been associated with different pathological conditions after microbial infection or contact sensitization.
We hypothesize that in col7a1-/- mice, separation of DEJ results in release of extracellular matrix components and complement proteins, which trigger sterile inflammation resulting in immune cell infiltration in neonates.
Upon unremitting wound healing and/or commensal colonization, the innate immune response transitions in adaptive immune cell activation, resulting in clustering of immune cells around hair follicles.
The proposed study will focus on early pathophysiology in col7a1-/- mouse model, to identify candidate therapeutic targets for the prevention and/or treatment of chronic inflammation and fibrosis in RDEB. We propose to profile temporal changes of RDEB cellular immunity and elucidate key genes and/or signalling axes that result in the development of fibrosis and immune responses. We will further investigate the function of the
peri-follicular clustered T cells and their responses to external mechanical and bacterial component challenges.

Blog post written about project for website

https://debraireland.org/eb-news/understanding-immunity-and-fibrosis-in-recessive-dystrophic-eb/

Quotes we have from researchers

“It has been well recognized that chronic inflammation and fibrosis contribute to squamous cell carcinoma development in patients with RDEB. The inflammatory response, which is a natural defense system in our body, is supposed to be resolved after defending infection and/or injury, yet it is not resolved in patients with RDEB. Instead, it evolves into an unwanted chronic condition in these patients. As such, our investigations will help us identify how immune cells in the skin change with time in response to changes within the dermal microenvironment. This research will help us understand the mechanism of chronic inflammation and identify novel targets for the treatment or prevention of chronic inflammation and fibrosis in patients with RDEB.” Dr Yanling Liao

Researcher (s) Bio

Dr. Yanling Liao obtained her Bachelor of Science in Biology at Xiamen University, P.R. China and her PhD from the Department of Biochemistry at Albert Einstein College of Medicine, New York, investigating the mechanism of RNA transcriptional regulation. She did her postdoctoral training in Dr. Helen Blau's laboratory at the Department of Immunology & Microbiology at Stanford University School of Medicine, California, and later joined Dr. Mitchell Cairo's laboratory in the Department of Pediatrics, Columbia University Medical Center, New York. Dr. Liao became a Research Assistant Professor of Pediatrics in 2011 and an Assistant Professor of Pediatrics in 2014 at New York Medical College, where her main research has been focused on preclinical development of stem cell and protein therapies for RDEB.

Professor Mitchell Cairo is currently the Associate Chairman and Professor (with tenure) in the Department of Pediatrics at New York Medical College (NYMC). His additional current leadership positions include being the Chief of the Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, Program Director of the Adult & Pediatric BMT Program, Director of the Childhood and Adolescent Cancer and Blood Disease Center, Medical and Scientific Director of the GMP Cellular and Tissue Engineering Laboratory at Westchester Medical Center (WMC), Medical Director of the WMC Hematotherapy Program and Chair of the WMC Adult and Pediatric Cancer Program. Dr. Cairo's additional academic appointments include being a Professor of Medicine, Pathology, Microbiology and Immunology and Cell Biology and Anatomy and Public Health at NYMC.