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EPITHELIAL IMMUNE CROSSTALK IN DEVELOPMENT AND DISEASE

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In our lab we study the mammalian skin to elucidate the complex interactions between the epithelial cells and macrophages, both in the context of the developing skin and in inflammatory skin disorders. Embryonic macrophages derived from the yolk sac and foetal liver, enter the skin at E12.5 and contribute to both homeostasis and inflammation, rather than serving as bystander cells. We have been particularly focused on the metabolic crosstalk between epithelial cells and macrophages. The insights gained from these studies will pave the way for research focused on interrogating epithelial-immune metabolic crosstalk in cancer.

A major question in the field of inflammation is how you initiate an immune response and terminate it after a defined period. Compromising either the start or end of an inflammatory response can lead to debilitating states such as infection and sepsis or, at the other extreme, chronic inflammatory diseases. Both subtle and dramatic alterations in the sheet of epithelial cells that comprise the barrier of various organs in the body are known to elicit an inflammatory response. Though this phenomenon is well-documented, a mechanistic understanding of how epithelial homeostasis governs an inflammatory reaction is still far from reach. Over the past several years, we have attempted to address this using our integrin beta1 knockout mouse model. Of relevance is a strong inflammatory and wound response that is elicited in the integrin KO mice. A differentiating feature of this mouse model is the fact that immune/wound-healing response is elicited during embryonic development, at a time when there are no extrinsic wounds and no skin microbiome that may facilitate this process. The integrin KO mouse thus offers an excellent model system to understand the epithelial-immune crosstalk that contributes to excessive ECM remodeling.

Epithelial-immune metabolic crosstalk

In our recent study (Ayyangar *et al.*, 2024, *EMBO J*), using the epidermal integrin b1 conditional KO mice, we report that the epidermis and macrophages augment unique yet complimentary metabolic programs where the epidermis augments glucose uptake and glycolysis and the macrophages augment TCA cycle. This metabolic program is initiated by an early increase in reactive oxygen species (ROS) that aids in enhanced stabilization of glycolysis regulator, HIF1a (Hypoxia Inducible factor), in the epidermal compartment. Enhanced glycolysis in the epidermis leads to increased generation of glycolysis-end-product lactate that is subsequently exported and utilized by macrophages in the dermal compartment to augment a pro-remodeling fate that is characterized by increased MMP9 generation. Notably, inhibition of glycolysis and its regulators in the epidermis, TCA cycle in macrophages, and lactate-mediated crosstalk between the two compartments using metabolic drugs led to a remarkable reduction in the pro-remodeling fate acquisition in macrophages and in turn, skin inflammation. Mechanistically, we show that lactate augments the TCA cycle and MMP9 generation, in part, through NF-kB activation. **Impact:** this work provides us a pathway to understand the metabolic underpinnings of inflammatory skin diseases such as psoriasis, as well as the future development of metabolic drugs to treat skin inflammatory disease, such as atopic dermatitis and psoriasis.

Understanding the Metabolic Underpinnings of Inflammatory Skin Disorders

Psoriasis is a chronic hyper-proliferative inflammatory skin disorder that affects up to 2 percent of the world's population and the incidence seems to be increasing over time. Notably, some individuals suffering from psoriasis are at higher risk of developing other diseases, including arthritis and cardiovascular dysfunction, a phenomenon termed as psoriatic march. The current line of treatment for psoriasis primarily involves the use of strategies that control inflammation or inhibit the adaptive immune response. Interestingly, there is increasing evidence of the association between psoriasis and metabolic syndrome which encompasses abdominal obesity, glucose intolerance, diabetes, dyslipidaemia, and high blood pressure, suggesting that psoriatic skin disease is driven by metabolic remodeling of the skin. However, the upstream regulators and downstream effects of the metabolic remodeling in the skin in inflammatory skin diseases like psoriasis remains poorly understood. To understand this better, we have generated an IMQ-induced mouse model of psoriasis-like dermatitis. Interestingly, preliminary analysis of IMQ-induced mouse models suggests that the early stages of psoriasis induction is associated with augmentation of glycolysis and increased expression of lactate transporters MCT1/4 (Monocarboxylic acid transporters) in the epidermal compartment of the skin. Notably, inhibition of lactate-mediated crosstalk using MCT1/4 inhibitor, Syrosingopine (Syro) and inhibition of ROS using ROS scavengers led to a significant reduction in psoriatic phenotypes. **Impact:** these results potentially open a new paradigm and lay the foundation for treating psoriasis in human patients with inhibitors against ROS-HIF1a-glycolysis-lactate axis that target innate immunity in the skin, which can be used in conjunction with the existing treatment methods or as a replacement for better therapeutic outcomes. We are currently testing the ability of metabolic drugs to attenuate the psoriatic phenotypes and have filed a patent encompassing this work.

Publications listed on page 125

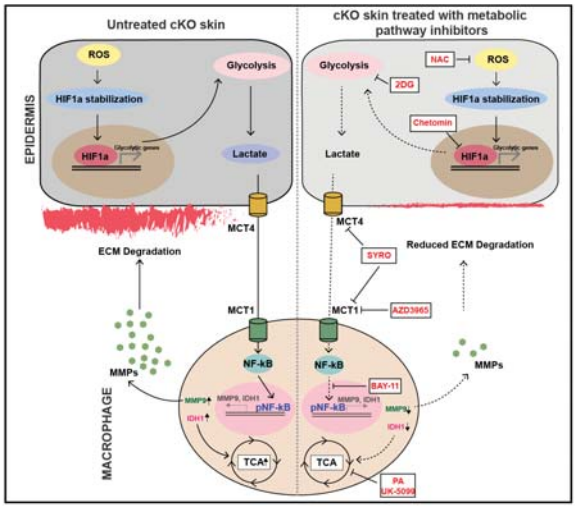

Figure 1. Under sterile inflammatory conditions in skin, early augmentation of ROS-HIF1a axis leads to enhanced glycolysis and lactate generation in the epidermal compartment. Consistently, inhibition of lactate transporters, epidermal-macrophage intrinsic metabolism and upstream glycolysis regulators in the epidermal compartment using small molecule inhibitors lead to inhibition of pro-remodelling fate and hence inflammation in the cKO skin.

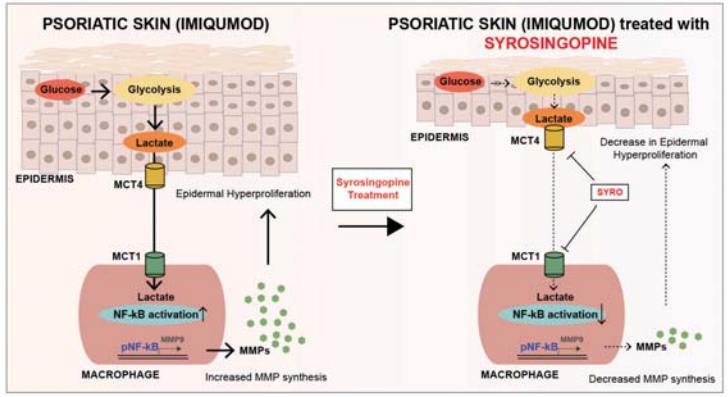

Figure 2. Schematic showing that epidermally derived lactate drives psoriasis through enhanced NF-kB activation in the macrophages that, in turn, leads to enhanced generation of MMP9. Inhibition of lactate mediated crosstalk between epidermis and macrophages using Syrosingopine attenuates psoriatic burden in imiquimod treated mice.