

Abstract

Type 2 diabetes mellitus (T2DM) is increasingly prevalent in the western population and is associated with a plethora of skin diseases, such as impaired wound healing, dry and itchy skin (Pruritus and Psoriasis). Yet, it remains unresolved whether diabetic skin complications are a direct consequence of impaired insulin/IGF-1 signaling (IIS) in the skin or occurs secondarily in response to metabolic alterations. The skin epidermis provides a structural and innate immune barrier that protects the organism from outside challenges as well as water loss. Previously, the lab identified a crucial role for epidermal IIS in epidermal morphogenesis and stratification. Initial data also suggested that epidermal IIS controls the formation of a functional barrier. The overall aim of this thesis was to define the contribution of cell autonomous IIS in the epidermis to skin barrier function and in diabetes-associated skin complications. First, we addressed whether epidermal IIS signaling controls the formation of a functional barrier. Using a combination of functional assays, RNA and protein expression, and immunohistochemical analysis revealed that loss of epidermal IIS altered terminal differentiation and impaired skin barrier function. We then asked whether dietary conditions that promote obesity or T2DM mimic epidermal IIS loss. Mice on a high fat diet already presented with insulin resistance in the skin after six weeks. In addition, these mice, as well as a genetical mouse model for T2DM, exhibited barrier dysfunction, epidermal atrophy and alterations in p63, thus linking impaired cell autonomous IIS in the epidermis to diabetic associated skin complications. Our results also show that even though loss of IIS resulted in a severe barrier defect during embryonic development, barrier function improved at later stages, suggesting activation of a compensatory repair response. On the molecular level, loss of IIS induced p38 α Map kinase (MAPK) stress response at E16.5, the onset of barrier function. Combined epidermal loss of IIS and p38 α , but not p38 α alone, resulted in severe barrier defects, thus showing that increased p38 signaling upon IIS loss activated a compensatory repair response. Spike-in SILAC, followed by mass spectrometry identified Epidermal Differentiation Complex (EDC) components as key downstream targets of p38 α and IIS. Finally, we asked whether epidermal IIS controls regeneration of the barrier as well as UV-B-induced skin carcinogenesis, using a DNA repair-deficient model (epidermal ERCC1-deficient mice). Whereas reduced IGF-1 signaling did not reduce UV-B-induced tumor growth, its loss restored barrier dysfunction, induced by chronic UV-B in ERCC1 deficient mice, suggesting that reduced IIS, as seen in aging, is beneficial for barrier regeneration. Taken together, this thesis identifies a key role for epidermal IIS in skin barrier formation and regeneration and may be responsible for early skin barrier dysfunction in obesity and T2DM that likely may contribute to late-onset diabetes-associated skin complications.