Abstract

The epidermal barrier provides a life-sustaining barrier, protecting the organism from external agents such as chemicals and pathogens. In addition, the skin plays a crucial role in preventing excessive water loss and regulating body temperature. The outermost layer of the skin, stratum corneum, contains a highly ordered layer of lipids and proteins, which together generates the barrier function. Alterations in this layer can potentially result in a disruption of the barrier function, eventually causing development of various skin diseases. Suffering from skin diseases can have enormous impact on life quality and can at worst be lethal. However, besides from dysfunction of the epidermal barrier, skin diseases are increasingly being associated with modulation of whole body metabolism including non-alcoholic fatty liver, diabetes and energy expenditure.

In this thesis the metabolic consequences of epidermal barrier dysfunction are studied in mice. In the first study we demonstrate that mice with targeted disruption of the *Acbp* gene (ACBP$^{-/-}$) display increased energy expenditure, elevated food intake and remodeling of the white adipose tissue, likely due to impaired barrier function. This hypothesis is further supported by the notion that skin specific ACBP depleted mice (K14-ACBP$^{-/-}$) also display increased energy expenditure, increased food intake and browning of the white adipose tissue. Interestingly, housing the mice at thermoneutrality abolishes these phenotypes. Taken together, this suggests that epidermal barrier dysfunction is caused by lack of ACBP specifically in the skin. We postulate that the mice have increased cold perception caused by a disrupted epidermal barrier, necessitating an increased requirement for energy in order to maintain normal body temperature. This perception is further reinforced by the observation that the increased food intake and increased browning of the white adipose tissue in ACBP$^{-/-}$ and K14-ACBP$^{-/-}$ mice are abolished by injection of the non-selective beta-blocker, propranolol.
In the second study, we show that *ma/ma Flg*$^{ft/ft}$ mice, a widely accepted model of skin dysfunction, also display increased food intake and browning of the white adipose tissue, suggesting that the metabolic phenotype observed in the mice used in this study is directly linked to the epidermal barrier dysfunction. Moreover, ACBP$^{-/-}$, K14-ACBP$^{-/-}$ and *ma/ma Flg*$^{ft/ft}$ mice are all protected from diet-induced obesity and subsequent hepatic steatosis, hepatic inflammation and overall glucose insensitivity, which are associated with a lipid-rich diet.
In total, these findings indicate that an impaired epidermal barrier can affect whole body metabolism, illustrating a novel role for skin function in relation to whole body energy metabolism.