SUMMARY

The acyl-CoA binding protein (ACBP) is a small intracellular protein, which binds C14-C22 acyl-CoA esters with high affinity and specificity. ACBP is highly conserved through evolution and expressed in all eukaryotic species investigated. Moreover, ACBP is expressed in all mammalian tissues investigated. ACBP was discovered in 1987 and since then the protein has been thoroughly investigated. *In vitro* studies have indicated, that ACBP acts as an acyl-CoA pool former that can transport acyl-CoA esters between different enzymatic systems; however, the knowledge about *in vivo* functions of ACBP remain sparse. In an effort to elucidate the *in vivo* function of ACBP, mice with a target disruption of the *Acbp* gene (ACBP$^{-/-}$) were generated. ACBP$^{-/-}$ mice are born in a normal Mendelian ratio and they are viable and fertile. At birth ACBP$^{-/-}$ mice are indistinguishable from their ACBP$^{+/+}$ littermates; however, around 16-18 days of age ACBP$^{-/-}$ mice develop a greasy and tousled fur, which persists throughout their life. With age ACBP$^{-/-}$ mice display alopecia and scaling of the skin. Furthermore, the transepidermal water loss (TEWL) is elevated in ACBP$^{-/-}$ mice, demonstrating that the epidermal barrier function is defect.

Around the time of weaning ACBP$^{-/-}$ mice experience a delayed induction of the sterol regulatory element binding protein (SREBP)-driven lipogenic and cholesterogenic gene programs in the liver, which is likely to be caused by accumulation of triacylglycerol (TAG) and cholesterol ester (CE) in the liver. Surprisingly, mice with liver specific depletion of ACBP (Alb-ACBP$^{-/-}$) did not recapitulate this liver phenotype; however, the liver phenotype was recapitulated in mice with keratinocyte specific depletion of ACBP (K14-ACBP$^{-/-}$). Interestingly, this demonstrates that it is the depletion of ACBP in the keratinocytes rather that endogenous lack of ACBP in the liver, which causes the liver phenotype. Furthermore, the application of an artificial barrier on the skin of ACBP$^{-/-}$ mice rescued the liver phenotype, which indicates that it is the impaired epidermal barrier of ACBP$^{-/-}$ mice that causes the liver phenotype.

The work presented in this thesis aimed at elucidating the molecular and cellular mechanisms in the skin upon ACBP depletion. We showed that epidermal proliferation was increased upon ACBP depletion. Additionally, ACBP depletion decreased the level of protein bound [OS] ceramides in stratum corneum (SC). We also found the sebaceous gland to be enlarged in ACBP depleted mice, which was due to elevated differentiation of the sebaceous gland cells. Interestingly, the elevated differentiation of the sebaceous glands was accompanied by increased secretion of sebum lipids onto the fur of ACBP depleted mice.

Collectively, these results suggest that the reported impaired epidermal barrier in ACBP depleted mice is caused by reduced amounts of [OS] ceramides. Therefore, we hypothesize that the epidermal proliferation and differentiation are likely to be increased to compensate the epidermal barrier impairment upon ACBP depletion. Furthermore, the sebaceous gland hypertrophy indicates that ACBP is involved in regulation of sebaceous gland lipid synthesis and homeostasis.

Additionally, we have investigated the involvement of ACBP in the synthesis of ceramides. We found that ACBP is a very potent stimulator of CerS2 and CerS3 activity both *in vitro* and *in vivo*. Furthermore, we showed that ACBP interacts with CerS2-6. Taken together, these results indicate that ACBP is an important regulator of ceramide synthesis.