Chapter 7

Discussion and Future Prospects

Discussion and Future Prospects

The studies described in this thesis were aimed to increase insight in the catalytic versatility and potential functions of glucocerebrosidase, inside and beyond the lysosome. The specific goals of investigations are formulated in the introductory chapter. General background on glycosphingolipids and their metabolizing enzymes is provided in **chapter 2**. Special attention is focused to the acid β-glucosidase aka glucocerebrosidase (GCase; GBA), the main object of the conducted investigations. Historically, the function of GCase inside lysosomes has received considerable interest. For half a century it is known that deficiency of the enzyme causes Gaucher disease, a relatively common lysosomal storage disorder characterized by accumulation of glucosylceramide (GlcCer) laden macrophages in tissues [1]. The relatively recent recognition that carriers of a mutant *GBA* allele have a markedly increased risk for developing α-synucleinopathies (Parkinson's disease and Lewy-body dementia) has further boosted interest in the function of the enzyme [2]. Complete GCase deficiency proves to be incompatible with terrestrial life due to disturbed skin barrier function [3, 4]. This finding has raised interest in the role of GCase beyond the lysosome.

Beyond the lysosome: the stratum corneum of the skin

The first section of this thesis concerns the role of GCase in the human skin. **Chapter 3** describes the use of fluorescent activity-based probes (ABP) to visualize active GCase molecules *in situ* in the skin. This method is more robust and sensitive than zymography using either substrate 4-methylumbelliferyl-β-D-glucopyranoside or resorufin-β-D-glucopyranoside as substrate rendering diffusing products, the blue fluorophore, 4-methylumbelliferone and the red fluorescent resorufin, respectively. Active GCase was found to be primarily located in the extracellular lipid matrix of the most outer part of the skin, the

stratum corneum (SC). This location of active GCase molecules is consistent with literature reports on the enzyme's role in generating ceramides in the SC [5-7]. The lipid rich environment and low pH (ranging from 4.5–5.3 on the outside, to 6.8 on the inside) of the SC likely contributes to the local stability of GCase [8, 9].

In recent times 3D cultured skin models mimic the properties of native human skin, called full thickness models (FTMs), have been successfully developed (as reviewed in [10]). ABPs targeting GCase can be used to visualize active enzyme molecules in these models. Moreover, the ABPs and their cyclophellitol-epoxide scaffold are potent suicide inhibitors of GCase and could therefore be used to generate on demand an enzyme deficiency in a FTM. The importance of GCase in features of skin could thus be studied in unprecedented manner. Also a superior, entirely GCase-specific suicide inhibitor, a cyclophellitol tagged at C8 with a hydrophobic bulky adamantyl, has recently been developed [11, 12].

Meanwhile, multiple ABPs reacting with various retaining glycosidases have been designed [13-18]. Active enzyme molecules visualized with these ABPs are lysosomal exo-glycosidases (galactocerebrosidase, α-galactosidases A and B, acid α-mannosidases, acid α-glucosidase, α-fucosidase, α-iduronidase, acid β-galactosidase, β-mannosidase and β-glucuronidase). Available are also ABPs labeling other non-lysosomal human β-glucosidases (GBA2 and GBA3) and the intestinal lactase-phlorizin hydrolase that also shows β-glucosidase activity [19-21]. With all these ABPs in place, the presence of active glycosidase molecules can now be rigorously studied in samples of normal and diseased human skin as well as in FTMs. The presence of lysosomal enzymes in the SC is still poorly documented and little is known about the possible presence of enzymes like GBA2 and GBA3 in the epidermis.

Two other hydrolases are also of specific interest in relation to the SC: acid sphingomyelinase (ASM) and acid ceramidase (AC). ASM crucially converts sphingomyelin (SM) molecules to their ceramide backbones in the SC. AC is able to fragment ceramides to sphingosine and free fatty acid (FFA) moieties. Both ceramide and FFA are crucial components of intercellular lipid lamellae in the SC constituting the skin barrier [22]. At the moment the only way to visualize the activity of ASM is zymography using 6-hexadecanoyl-4-methylumbelliferyl-phosphorylcholine (6-HMU-PC) as substrate [23, 24]. It is appealing to consider the use of ABPs to render more detailed information on ASM and AC in the skin. Arenz and co-workers have designed fluorescent phosphosphingolipids capable of Förster resonance energy transfer [25]. The compound is a structure mimic of SM in terms of its polarity, conformation, and steric bulk and can be used to determine ASM activity by fluorescence

spectroscopy. Recently, Fabrias and coworkers have designed very specific ABPs for AC, based on analogues of the AC inhibitor SABRAC [26]. It will be valuable to establish with the ABPs the precise location of ASM and AC in the human skin and to determine the ratios between active GCase, active ASM and AC molecules in normal and diseased tissue.

The lipid composition of the SC is crucial for a proper barrier feature of the skin that is determined by a delicate balance between ceramide, fatty acid and cholesterol in lipid lamellae [22]. **Chapter 4** illustrates the great value of ABPs in determining the location of active enzyme molecules. Described is the altered localization of active GCase and ASM in the epidermis of atopic dermatitis (AD) patients that is related to abnormal barrier function and SC lipid changes, particularly at lesional skin sites.

Altered localization of ASM relates to increased ceramide subclasses [AS] and [NS] in AD SC, lipids known to be crucial for proper SC lipid lamellae and barrier function [27-30]. In the study described in **chapter 4**, the altered location of active GCase molecules in the epidermis was found to correlate with reduction of total SC ceramides, particularly the subclasses [NP], [NH] and EO ceramides that are not derived from the catabolism of SM by ASM. At the moment it can't be distinguished whether the observed changes in SC lipid organization (partially) originate from altered active enzyme distribution or that the disturbed barrier causes the changed location of enzymes. It is conceivable that abnormal enzyme location and changed SC lipid composition enforce each other. It will be informative to test how fast acute inactivation of GCase with suicide inhibitors causes a disturbed barrier over time. Moreover, it could be analyzed whether the location of ASM is influenced by such imposed change in SC lipid lamellae. Likewise, it could be studied with FTMs whether available inhibitors of glucosylceramide synthase (GCS; Miglustat and Eliglustat) [31, 32] can balance a deficiency in active GCase with respect to desired barrier features. If so, topical administration of GCS inhibitors could be developed as therapeutic avenue.

The occurrence of glucosylated cholesterol (GlcChol) in human cells and tissues has recently been documented [33-35]. It has become apparent that GlcCer is the biosynthetic precursor of GlcChol. The cytosol-faced GBA2 normally generates GlcChol using GlcCer as sugar donor and cholesterol as acceptor via transglucosylation [33]. During extreme lysosomal accumulation of cholesterol (as occurs in Niemann Pick type C disease), GlcChol can be also formed by GCase via transglucosylation, however under normal conditions GCase catalyzes the cleavage of GlcChol to free glucose and sterol [33].

Chapter 5 demonstrates the existence of GlcChol in the SC. Local formation of GlcChol in the SC by GCase via a transglucosylation reaction seems the plausible biosynthetic pathway: active GCase molecules are present in the SC (**chapter 3**) and GlcCer and cholesterol are abundant local lipids.

At present the physiological function of GlcChol in the SC is unclear. It can be speculated that GlcChol has a role in natural desquamation (shedding of the outermost layer of the skin), similar to that postulated for cholesterol sulfate [36]. An additional and/or alternative function of SC GlcChol might involve barrier features. To investigate this, the TEWL (Trans Epidermal Water Loss) in a SC substitute model (porous substrate covered with synthetic SC lipids) with and without GlcChol could be measured [37]. It could be also experimentally investigated whether GlcChol content of skin samples (or cultured 3D skin) can be increased by exposure to exogenous glucosylated sterol and if so whether this impacts the barrier function.

Formation of GlcChol in the SC seems dependent on GCase. Therefore, the SC content on GlcChol could in theory offer a readout for presence of active GCase in the SC of individuals with lesions. Such hypothetical diagnostic application for SC GlcChol warrants further investigation. It can be confirmed with FTM that pharmacological inactivation of GCase prohibits formation of GlcChol and reduces the levels of the glucosylated sterol. Of note, GlcChol and GlcCer were measured in SC sheets obtained from patients suffering from Netherton syndrome (NTS) with severely impaired skin barrier (**chapter 5**). The ratio GlcChol/GlcCer in the patient samples was found to be quite normal. In samples of some patients supra-high levels of both GlcChol and GlcCer were observed, but inter-subject differences were very high, as earlier reported for lipid abnormalities in skin of NTS patients [38].

Lamellar bodies

To conclude the thesis section dealing with skin, a more in-depth discussion of lamellar bodies (LBs) is of interest. LBs play a key role in the delivery of lipids into the SC [39-41]. They are specialized intracellular organelles packed with lipids, including GlcCer and SM [22]. In upwards migrating keratinocytes of the stratum spinosum the formation of LBs is initiated. The organelles have a surrounding membrane and contain internal lipid membrane structures. The membrane protein ATP-binding cassette sub-family A member 12 (ABCA12) is responsible for the transport of GlcCer's into the LBs [42-44]. Moreover, the LBs contain enzymes such as GCase and ASM. Following extrusion of LBs at the interface between the stratum granulosum and the SC, the enzymes GCase

and ASM metabolize their lipid substrates to ceramides, essential steps for proper SC lipid lamellae [40, 41]. LBs are lysosome related organelles (LROs), sometimes referred to as secretory lysosomes [45]. They share features of late endosomes and lysosomes. The latter are cytoplasmic organelles that serve as a major degradative compartment in eukaryotic cells, carried out by more than 50 acid-dependent hydrolases [46].

As discussed in **chapter 2**, newly formed and correctly folded GCase molecules bind in the ER to LIMP2 (lysosomal integrated membrane protein 2), which is essential for proper transport of GCase to lysosomes [47, 48]. At first glance it therefore seems likely that LIMP2 also mediates the transport of GCase to LBs, and thus could co-determine skin features. However, acute myoclonic renal failures syndrome (AMRF) patients with a defective LIMP2 develop no overt skin problems, despite reduced GCase in most cell types [48]. Since GCase in LIMP2 deficient cells is secreted by default, it might be that the SC of AMRF patients contains sufficient, directly secreted, enzyme to allow local degradation of GlcCer. It is unlikely that some other β-glucosidase compensates for GCase in the SC since such compensation does not occur in

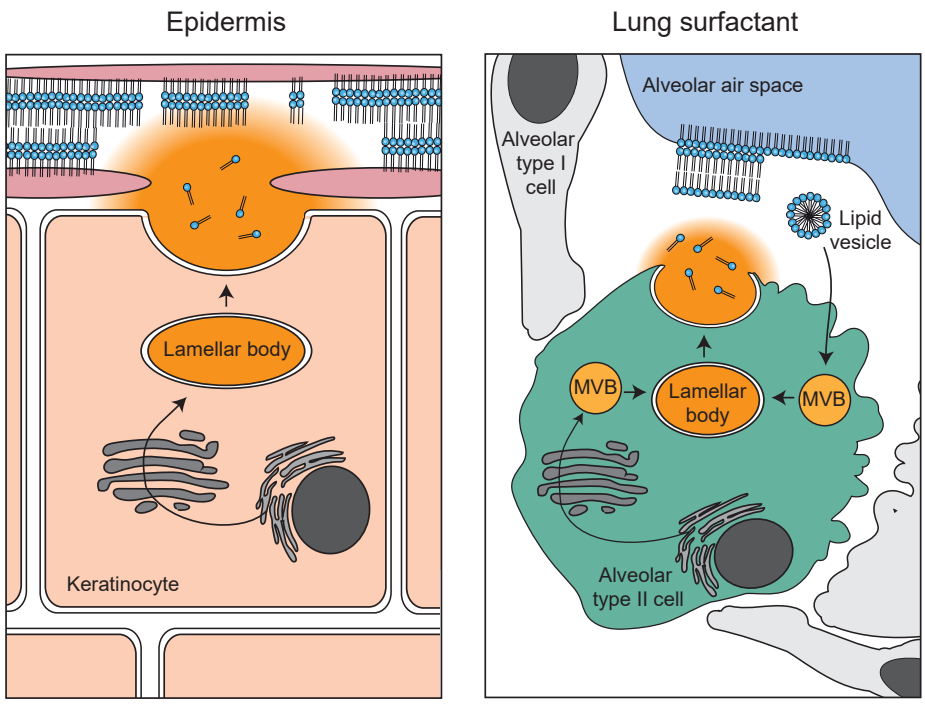

Figure 1: The similarities in the epidermal and lung lamellar body extrusion. MVB: Multivescular body.

collodion Gaucher disease patients [49-52]. Alternatively, delivery of GCase to LBs keratinocytes might take place by another, yet unidentified, receptor protein.

Apart from the skin there are other tissues where structures similar to lipid-rich LBs are formed [45]. One example of this is the lung epithelium. The alveolar system of the lung is a body barrier and is composed of two types of epithelial cells, pneumocytes I and II [53]. LBs in pneumocyte type II cells store lung surfactant that is composed of phospholipids and proteins [54, 55]. The surfactant lipid components (dipalmitoylphosphatidylcholine as major one) are extruded from LBs and form a protective layer at the alveolar air-liquid interface essential for appropriate surface tension [56]. During LB formation in pneumocytes lipids are imported by ABCA3, phylogenetically close to ABCA12 [57, 58]. An ABCA3 mutation underlies a fatal lung disease in newborns in which the surface surfactant function is impaired [59]. Thus, there is a striking parallel with the severe ichthyotic skin in patients with ABCA12 mutations [43, 44, 58]. Additionally, immediate lung alveolar collapse after birth has been demonstrated in ABCA12 deficient mice, showing it has a crucial role in both skin and lung barrier function [60]. The similarities in the lung and skin (Figure 1) spark curiosity whether glycosphingolipids also play a role in surfactant LBs and the lung barrier. Interestingly proteomic analysis of rat LB's showed significant overlap with other LRO's, but surprisingly little with LB's from the skin [61]. Moreover, little is known on lysosomal enzyme content of LBs in pneumocytes and surfactant [62]. It is therefore appealing to study in lung LBs and surfactant the presence of glycosidases using ABPs. An old study by de Vries et al. reports high amounts of lysosomal α-glucosidase (GAA), however GCase activity in LBs from the lung was low [63]. In another study with rats, six lysosomal hydrolases were identified as components of lung LBs: acid phosphatase, β-hexosaminidase, β-galactosidase, α-mannosidase, α-fucosidase and β-glucosidase. Interestingly, acute ozone stress in rats was found to result in reduced hydrolase activities voor all hydrolases, except α -mannosidase, in the LB's of alveolar type II cells [64]. More recently decreased levels of phosphatidylcholine in the lung surfactant of patients suffering from Gaucher disorder and other lysosomal storage diseases were detected, suggesting a potential link between lysosomal enzymes and barrier function [65].

LBs have also been detected in rat stomach [66] minipig kidney [67], guinea pig organ of Corte [68], canine tong papillae [69], rabbit eustachian tube [70], human oral epithelium [71] and mucosa of the nose [72]. These tissues all share an epithelial character and their LBs seem to mediate lipid transport to the extracellular space. It can be therefore attractive to research these "barrier

tissues" for glycosphingolipids and metabolizing enzymes. Another tissue in this connection of potential interest might be the placenta. The placenta is a highly specialized organ that mediates exchange of various endogenous and exogenous substances between the mother and fetus and can therefore be seen as a "barrier tissue" [73, 74]. Markedly increased GCase expression and activity has been observed in preeclamptic placenta [75]. There is still a lot unknown about this barrier in relation to lipids and lamellar bodies, but there are reports suggesting that lipid rafts in the fetal tissue are able to prevent maternal-fetal virus cell transmission [76, 77]. Blundell et al. have engineered a model that mimics structural and functional complexity of the human placenta barrier [78]. The cultured trophoblasts on their "placenta-on-a-chip" develop dense microvilli that make it possible to reconstitute the expression and localization of certain membrane transport proteins. Such models might be of interest to study in more detail regarding expression and localization of lysosomal enzymes like GCase. Besides the maternal-fetal barrier and the fetal skin, another barrier is formed during the last trimester of pregnancy: the fetus is covered in vernix caseosa, which is a protective biofilm. The vernix caseosa substitutes the immature epidermal barrier in fetal skin and forms a barrier against bacterial infection [79]. All main SC lipids have been shown to be present in the vernix caseosa [80] and research has shown 30% of the lipids in the vernix caseosa to be similar to the SC lipid content [81].

Catalytic versatility of GCase

The second section of the thesis deals with the catalytic versatility of GCase that exceeds hydrolysis of GlcCer. Expanding earlier observations [82, 83], **chapter 6** provides evidence that GCase is remarkably versatile in catalysis. It is not only able to use β-glucosides as substrate, but also β-xylosides. In addition, GCase is shown to also transxylosylate cholesterol rendering xylosylated sterol (XylChol). It was noted that recombinant GCase can even generate Xyl_2Chol and trace amounts of Xyl_3Chol. An attractive explanation for this repetitive xylosylation is the noted poor hydrolysis of XylChol by GCase, contrary to that of GlcChol. Transxylosylation is not solely a test tube phenomenon but also takes place in intact cells with lysosomal cholesterol accumulation and exposed to the sugar donor 4-metylumbelliferyl-β-xyloside (4-MU-Xyl).

β-Glucosidases are a heterogeneous group of enzymes and are known to sporadically hydrolyze other substrates that are structurally similar to β-glucosides [84-87]. Previously xylosidase activity has been reported for beta-D-glucosidases from *Stachybotrys Atra* [88], *Agrobacterium Tumefaciens* [89], *Aspergillus Niger* [90], and *Erwinia Chrysanthemi* [91]. It is also not uncommon for xylosidases to display transglycosidase activity: this has been described

for β-xylosidases from *Aspergillus Sp* [92], *Agrobacterium Tumefaciens* [89], and *Talaromyces Amestolkiae* [93]. Therefore, the observed transxylosidase activity of human GCase is not completely unexpected, nevertheless it's the first time it has been documented and characterized.

A subsequent investigation of tissues and cells revealed the presence of small but significant amounts of XylChol. Apparently, the formation of XylChol occurs also *in vivo*. A key question after the discovery of endogenous XylChol concerned the nature of β-xylosides donors that allow its formation by transxylosylation. Considered donors were exogenous β-xylosides. Indeed, XylChol was found to be formed by cultured cells after exposure to the plant derived cyanidin-β-xyloside, a colored component of berries that has been shown to accumulate in plasma after intake of berry supplements [94]. Next, endogenous β-xylosides were considered as donors. One possible candidate in this respect would be serine-linked β-xylosides arising from lysosomal degradation of proteoglycans [95]. Another considered candidate was xylosylated ceramide (XylCer). So far, there is just one report on the presence of XylCer in the salt gland of herring gull, however no follow up research on this has apparently been performed [96]. As described in **chapter 6**, tissues were found to contain small amounts of XylCer. Somewhat surprisingly, it was detected that GCS is able to use UDP-xylose (UDP-Xyl) to form XylCer, although the affinity for UDP-Xyl is much lower compared to that for UDP-Glc. It was next demonstrated that XylCer is an excellent sugar donor for GCase to generate XylChol. Therefore, at present the most likely biosynthetic pathway for formation of endogenous XylChol is the generation of XylCer by GCS followed by its use as sugar donor for GCase-mediated formation of XylChol. Consistent with this pathway is the reduced XylChol level in spleen from a type 1 Gaucher patient with a reduced GCase activity.

The identification of GlcChol in the SC of skin (**chapter 5**), prompted us to look for the possible presence of XylChol in the SC. In vital epidermis and full skin of a normal individual the presence of significant amounts of XylChol could be observed: levels of approximately 3 and 15 pmol/mg wet weight, respectively. These preliminary findings should be reproduced by analysis of samples from different subjects. Pilot studies with SC sheets from NTS patients revealed the presence of XylChol in 10 out of 13 of samples, ranging from 12 to 77 fmol/mg dry weight. This finding suggests that XylChol manages to reach the SC in diseased skin with breached barrier function.

Future investigations

Other β-glucosidases.

The discovery of significant activity of the enzyme GCase towards β-xylosidase led to investigation of similar activity of the two other cellular retaining β-glucosidases: the cytosol-facing membrane-associated GBA2 and the soluble cytosolic GBA3 (Klotho-Related Protein, KLrP) [83, 97]. GBA2 was found to exert no β-xylosidase or transxylosidase activity. In contrast, GBA3 (formerly known as 'broad-specific beta-glucosidase') is active towards β-xylosides, showing hydrolytic and transxylosylation activities similar to GCase. The physiological role of GBA3 is still not entirely clear. Common in humans is an inherited deficiency in the enzyme [98, 99]. The enzyme is thought to play a role in detoxification of toxic plant glucoside [100, 101]. A preliminary investigation has revealed that GBA3 can use 4-MU-β-galactoside and 4-MU-β-xyloside to transglycosylate 25-NBD-cholesterol. GBA3 when incubated with 4-MU-β-glucoside was only able to transglucosylate natural cholesterol but not 25-NBD-cholesterol. As observed with GCase, the ability of GBA3 to generate xylosylated products was relative prominent as compared to its ability to degrade β-xylosides. In an earlier study, Glew and co-workers did observe transgalactosylation activity of pig liver GBA3 with alcohol or another substrate molecule as acceptor, generating digalactosyl-PNP [102]. Apparently, the catalytic pocket of GBA3 can harbor (near) simultaneously two substrate molecules in the pocket. An extended careful analysis of pure GBA3 regarding transxylosylation capacity is of interest.

Another player: Acylglucosides?

The pendant CH_2OH group in a β-glucoside seems not essential be a substrate for GCase (**chapter 6**). This finding is not surprising given the observation that GCase tolerates a hydrophobic extension at C8 of cyclophellitol-epoxide (equivalent to C6 of glucose during the covalent binding to the catalytic nucleophile E340 [103]. Actually, the affinity of the suicide inhibitor is markedly improved by this modification [103]. Likewise, Vocadlo and co-workers designed a highly specific GCase substrate containing a bulky modification at the C6 of the glucoside [104].

These observations prompted the investigation whether a β-glucoside with an O-acyl extension at C6 is a suitable substrate for GCase. Four different 6-O-acyl-glucoside-methylumbelliferones (4-MU-AGlc's) were synthesized by Marta Artola (figure 2A). GCase was found to be able to hydrolyze all 4-MU-AGlc substrates showing even lower Km values than 4-MU-Glc. The Vmax of GCase was significantly higher for 4-MU-Glc than 4-MU-AGlc's. Next, the transfer of the 6-O-acylglucoside moiety from 4-MU-AG to cholesterol was confirmed by LC-MS/MS analysis. Of note, GBA2 does not accept 4-MU-AG as a substrate. Again,

this is consistent with lack of reactivity of GBA2 with a cyclophellitol with C8 modification. Meanwhile, a norbornadiene-6 glucoside-methylumbelliferone (4-MU-AG-NBD) has been generated by Artola (Figure 2B). This compound was found to be still hydrolyzed by GCase with high affinity. Such type of substrate is envisioned to be of great use to identify acceptors in transglycosylation catalyzed by GCase since the glycosylated products should be fluorescent due to the NBD attached to the sugar moiety. However, the NBD linked via an ester bond to the glucose moiety is intrinsically susceptible to hydrolysis. At the moment it is attempted to synthesize the same compound with a more stable thio-ester.

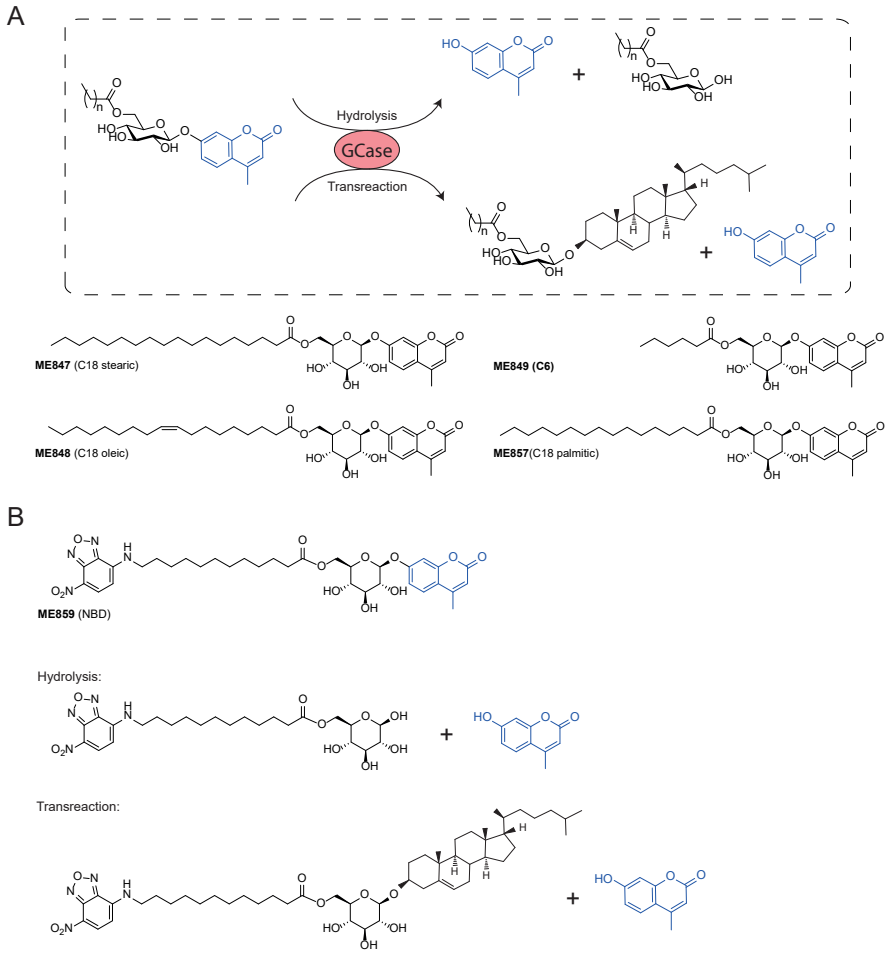

Figure 2: Acylglucosides as a substrate for GCase. A: Hydrolysis and transreaction by GCase of 4-MU glucose acylated substrates, with their acyl group differing in length and saturation. B. Chemical structure NBD-Acyl-Glucose-D-β 4-methylumbelliferyl compound (ME859) as a substrate for GCase and formed products.

The question can be raised whether 6-O-acylglucosides occur in human tissues and if so, whether they they are physiological substrates for GCase. This is amenable to investigation since in principle 6-O-acylglucosyl-cholesterol can be sensitively measured with LC-MS/MS. More than thirty years ago, Wertz and colleagues actually reported the presence of 6-O-acylated glucosylated sterol in the epidermis of chicken, being a stunning 2% of the total lipid [105]. Another research paper from around that time reports on the existence of GlcChol in snake skin [106]. The 6-O-acylated glucosylated sterols are also well known and abundant compounds in plants and usually named acyl steryl glucosides (ASGs). Several plant-derived food products are rich in ASGs, like soybean and potato [107]. Very high levels are reported for tomatoes and olive oil [108, 109]. It is conceivable that consumed ASGs (chicken skin used in snacks, various plant products) may enter intact and/or deacylated the body from the intestine [110]. Of note, oral exposure of rodents to a mixture of ASGs and SGs induces α-synucleinopathies, suggesting even their entry into the brain [110]. Likely, ASGs and de-acylated SGs are substrates of GCase and thus could interfere with endogenous GlcCer metabolism.

It will be of interest to study the presence and role of 6-O-acylglucoside sterols in the SC of human skin. Based on their chemical structure, 6-O-acylglucoside sterols might connect in a flexible way lipid lamellae, in analogy to the assumed action of very long SC ceramides [106]. It will be also exciting to look for the presence of ASG's in various cell types in the body in health and disease and to identify their precise subcellular localization.

Conclusion

This thesis describes the versatile enzyme GCase that fulfills functions inside lysosomes of cells and extracellularly in the skin. In the human skin, GCase acts as biosynthetic enzyme that produces essential SC ceramides from the precursor GlcCer. Contrarily, GCase in the lysosomes catalyzes the penultimate step in the breakdown of glycosphingolipids. The development of the accurate and sensitive *in situ* method for ABP-based detection of active GCase in skin should allow exciting novel investigation on skin in health and disease. As demonstrated in this thesis, the novel method already visualized an altered localization of GCase in AD skin in combination with an altered SC lipid composition. Using LC-MS/MS, the occurrence of GlcChol in human skin could be for the first time demonstrated. Establishing the physiological function of GlcChol in the skin will be of great interest.

The catalytic versatility of GCase is exemplified by its ability to metabolize β-xylosides. The observed natural presence of XylChol and XylCer should prompt a search for additional endogenous β-xylosides. Furtermore, the impact

of intake of food-derived exogenous β-xylosides should be investigated. In this connection, it will be particularly interesting to monitor xylosylated lipids in Gaucher disease and other conditions for which abnormal GCase imposes a risk, such as multiple myeloma and α-synucleinopathies like Parkinsonism and Lewy-body dementia [111]. Additionally, the effect of topical administration of β-glucosides, β-xylosides and sterol-like structures to the skin barrier deserves attention since it might provide clues for novel therapies.

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