4. DISCUSSION

4.1 GO is caused by loss-of-function of the golgin protein SCYL1BP1

By genetic mapping in several consanguineous Mennonite families with multiple cases of GO, our group identified mutations in the gene Scyl1bp1. SCYL1BP1 was initially identified as an interaction partner of SCYL1 by yeast-two hybrid screening, and both proteins show evolutionary conservation (Di et al., 2003). SCYL1 is a widely expressed protein with N-terminal kinase-like domain that probably has no kinase activity (Liu et al., 2000a). The function of SCYL1 in mitosis was indicated by its localization in the centrosome (Kato et al., 2002), however, mutations in the Scyl1 gene causing a recessive form of spinocerebellar neurodegeneration support a possible role for SCYL1 in intracellular transport (Schmidt et al., 2007). Additionally, Pirh2, a p53 ubiquitin ligase, that promotes p53 degradation in a p53-inducing manner was also reported to interact with SCYL1BP1 (Leng et al., 2003; Zhang et al., 2005).

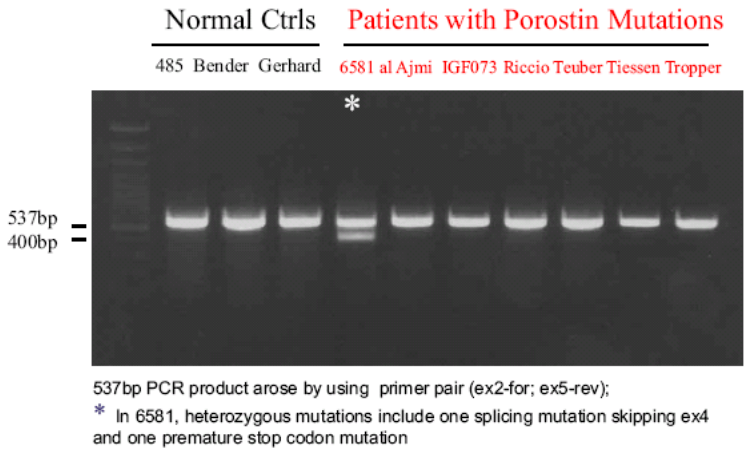
SCYL1BP1 is predicted to have multiple potential phosphorylation sites and two coiled-coil domains that are covered by DFU662 domain of unknown function. We have shown that the coiled-coil domains are both necessary and sufficient for the interaction with Rab6. We believe that the potential phosphorylation sites might play a regulatory role such as a switch between different forms. SCYL1BP1 protein in denaturing SDS-PAGE gel with a bigger WM than predicted might result from heavy phosphorylation.

An open reading frame of 394 codons is predicted for the human Scyl1bp1 gene, however, the failure to detect Porostin protein by immunofluorescence and Western blot in the fibroblasts derived from the patient with Met26Leu mutation indicated that it should be the real start codon. In line with this assumption, the orthologs from most other species also possess the start codon corresponding to this methionine. Therefore, we conclude that the Met26Leu mutation disrupts the start codon, thereby blocking the initiation of protein translation. We argue that human SCYL1BP1 protein consists of 369 aa, rather than 394 aa, similar to mouse protein 368 aa.

In the fibroblasts derived from the GO patients with the premature termination codon (PTC) mutations, SCYL1BP1 protein was not detected either by immunofluorescence or

Western blot. Therefore, these PTC mutations in the Scyl1bp1 led to complete loss of the protein rather than producing truncated versions. It is widely believed that the mRNA harboring PTC mutaions (except in the last exon) is subject to nonsense-mediated mRNA decay. However, our RT-PCR result showed that Scyl1bp1 mRNA is present in all GO patients as well as in Ctls (**Fig. 1**), indicating a more likely mechanism that the mRNA harboring PTC mutations was not well processed, leading to the failure of protein translation. It is also plausible that truncated proteins were synthesized, but were subsequently recognized by the cell and incurred the degradation program. In light of autosomal recessive inheritance of GO and loss of SCYL1BP1 protein in all our GO patients, loss of function of Scyl1bp1 should account for this genetic disease.

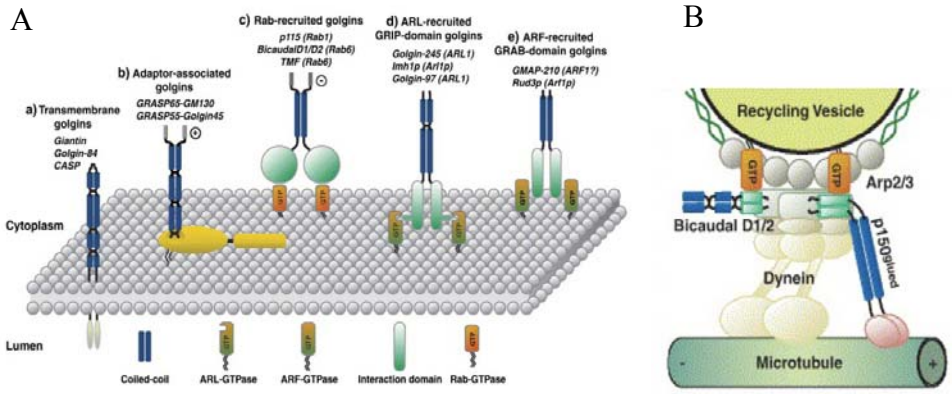
By different Golgi markers, we could clearly classify SCYL1BP1 as a novel Golgi protein. In a yeast two-hybrid screening we were able to demonstrate a specific interaction with Rab6, one member of small G proteins. Given the Golgi localization, the presence of coiled-coil domains and the interaction with a Rab protein, SCYL1BP1 can be defined as a new member of the golgin family, which give identity and structure to the Golgi apparatus in animal cells (Barr and Short, 2003).



Discuss-Fig. 1. RT-PCR in normal and patient HAF. Using primer pair (ex-2-for; ex5-rev) with Forward and Reverse primers located at exon-2 and exon-5 respectively, one PCR product (537bp) was amplified in all samples tested, indicative of the presence of Scyl1bp1 mRNA even in patient cells . In 6581, one additional product (400 bp) was amplified owing to the splicing mutation skipping exon-4.

4.2 How does SCYL1BP1 function as a golgin?

The golgins were originally characterized as a family of Golgi-localized autoantigens, using antibodies derived from the sera of patients with various autoimmune disorders (Barr and Warren, 1996; Fritzler et al., 1993; Kooy et al., 1992). Coiled-coil domains are common protein motifs contained in all golgins. Apart from the Golgi localization and the presence of coiled-coil regions, the other feature for the golgin family is the interaction with small GTPases. Different mechanisms are used by a variety of golgins to target to Golgi membranes (**Fig. 2A)**. Some golgin such as Giantin, Golgin-84 and CASP dock into the membrane via their transmembrane domain (**Fig. 2A-a**). Other golgins are peripheral membrane proteins and associate with the membranes via interaction with adaptor protein (**Fig. 2A-b**) or small GTPases such as Rab (**Fig. 2A-c**), ARL (**Fig. 2A-d**) and ARF (**Fig. 2A-e**).



Discuss-Fig. 2. Model for golgin association and function. **A:** Golgins associate with Golgi membranes in various ways. (a) Some have a transmembrane domain near their C-terminus . (b) Peripheral membrane golgins may associate with the membrane by an interaction with an adaptor protein of the GRASP family. Other golgins are recruited to Golgi membranes in a nucleotide-dependent manner by small GTPases of the (c) Rab, (d) ARL, and (e) ARF families. **B:** The role of Bicaudal-D in tethering vesicles to microtubule cytoskeleton under Rab6. Activated Rab6 recruits the dynein motor to Golgi membranes and transports vesicles via multiple interactions with the dynactin complex and the golgin Bicaudal-D. Bicaudal-D acts as an attachment factor for the dynactin complex, and binds Rab6 via its C-terminal domain. In addition Rab6 interacts with the dynactin subunit p150glued. It was speculated that dynactin at microtubule tips can capture Rab6 bearing Golgi vesicles, and that dynein then transports these membranes towards the microtubule minus end. (Modified from Short et al. 2005)

By Y2H and GST pulldown, the specific interaction between SCYL1BP1 and Rab6 was demonstrated. Therefore, it is reasonable to speculate that the SCYL1BP1 might be targeted to the Golgi membranes via the tight interaction with Rab6, in accordance with the same sub-domains of Golgi apparatus (media and trans) where both SCYL1BP1 and Rab6

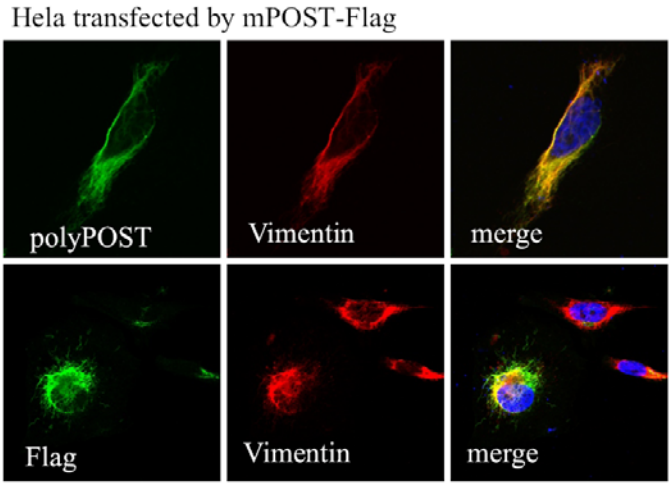
are located. However, the result from the siRNA knock down experiment demonstrated that depletion of Rab6 could not affect the localization of SCYL1BP1 in the Golgi, indicating that some other molecules on the membrane might associate with SCYL1BP1 as well. In agreement with this proposal, the interaction between SCYL1BP1 and one member of Arf family was manifested in our Y2H screen (data not shown). Therefore, we believe that SCYL1BP1 is localized to Golgi membrane via the association with several partners.

One of the best-characterized function of golgins is their role in membrane tethering events, evidenced by p115, GM130 and giantin (Short et al., 2005). For this purpose, it is important and necessary for one golgin to interact with multiple molecules and even form various complex with different GTPases (Rosing et al., 2007). p115 was the first characterized Rab1-interacting protein, which also binds to the Golgi-associated proteins GM130 and Giantin (Allan et al., 2000; Nakamura et al., 1997; Sonnichsen et al., 1998). P115 is a peripheral membrane protein mainly localized to the vesicular-tubular clusters of ER to Golgi transport intermediates (VTCs) and the cis- Golgi (Nelson et al., 1998). GM130 is also a Rab1 effector and localized to cis-Golgi membranes via its tight binding to an adaptor protein GRASP65. GM130 is predicated to contain extensive coiled-coil regions forming a homodimer and had a basic motif at its N-terminus binding to the acidic C-terminus of p115 (Nakamura et al., 1997). Giantin is an integral membrane protein attached to Golgi membranes by a putative C-terminal membrane anchor and contains an extensive coiled-coil regions. Apart from the direct interaction with Rab1, giantin could bind p115 via its N-terminus (Sonnichsen et al., 1998). In light of the presence of giantin in COPI vesicles and the above mentioned direct interactions on Golgi membranes, a giantin-p115-GM130 ternary complex model is preferred for the trafficking between ER and the Golgi although some contradiction still exists (Linstedt et al., 2000). Recently the other subpopulation of COPI vesicles was defined by golgin-84-CASP (Malsam et al., 2005) and was believed to run independent of giantin-p115-GM130 system that is regulated by Rab1.

Rab1 is a GTPase that regulates the transport of endoplasmic-reticulum-derived vesicles in eukaryotic cells by coordinating a variety of downstream effectors exemplified by giantin-p115-GM130 model. However, other golgins perform different roles contributing to transport insides Golgi apparatus by interacting with other GTPases such as Rab6. The Rab6 family reside in Golgi apparatus and cytoplasmic vesicles and regulate protein

transport between the Golgi, endoplasmic reticulum (ER), plasma membrane, and endosomes (Del Nery et al., 2006; Girod et al., 1999; Grigoriev et al., 2007; Jasmin et al., 1992; Martinez et al., 1997; Martinez et al., 1994; Opdam et al., 2000; Utskarpen et al., 2006; White et al., 1999; Young et al., 2005). Two related golgins Bicaudal-D1 and Bicaudal-D2 are localized to trans-Golgi through the association with Rab6 (Matanis et al., 2002; Short et al., 2002). Given that fact that Golgi is positioned in a dynein dependent manner (Corthesy-Theulaz et al., 1992; Sandoval et al., 1984), and that Bicaudal-D proteins interact with dynactin, an adaptor for motor protein dynein (Hoogenraad et al., 2001), Bicaudal-D probably acts as a Rab6 effector to tether vesicles and some Golgi membranes to the microtubule cytoskeleton (**Fig. 2B**).

As a Rab6 effector, SCYL1BP1 might participate in this tethering process as well, in accordance with the presence of SCYL1BP1 in the Golgi and some vesicles. Interestingly, we observed the perfect co-localization between Porostin and vimentin in the cells transfected by exogenous Porostin (**Fig. 3**), which might argue some role for vimentin, one component of intermediate filaments in vesicle tethering/trafficking process.



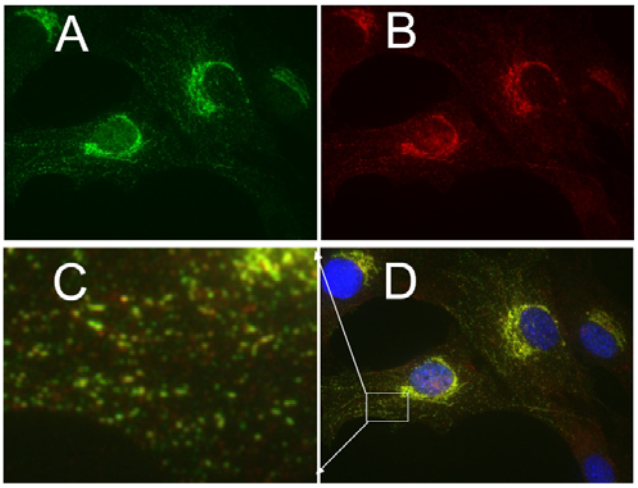
Discuss-Fig. 3. Fibrous formation involving Porostin in Hela cells transfected by mPOST. Hela cells produce fibre- structural signal where both Porostin and Vimentin are located 48 h after transfection of pCMV-mPOST-Flag. In most cells, complete colocalization between Porostin and Vimentin (upper panel) was observed, with partial colocalization (lower panel) in the rest population.

4.3 Membrane trafficking and GO

Small G proteins are typically between 20–25 kDa in size and cycle between an inactive GDP-bound conformation and an active GTP-bound conformation, which is regulated by a multitude of GEFs and GAPs to ensure signaling specificity (Bos et al., 2007). Rab family have been demonstrated to play an essential role in membrane trafficking. Rabs drive cargo collection into nascent transport vesicles, link vesicles to motor proteins, and recruit tethers to vesicles to facilitate membrane trafficking (Pfeffer, 2007). Identifying the molecules

recruited by each Rab to form functional microdomains will be one of the most important tasks for our understanding of the mechanism and regulation of membrane trafficking (Pfeffer, 2007).

Rab6 with 3 isoforms is a central player in cellular membrane trafficking mainly residing in the trans-Golgi network. One important function of Rab6 is to recruit motor proteins that promote vesicle movement along microtubules (as discussed in previous section). Apart from the role of Rab6 in the retrograde transport of toxins from endosomes to the Golgi, recent study has demonstrated a general role of Rab6 in Golgi membrane trafficking in secretory pathway (Grigoriev et al., 2007). As a new effector of Rab6, SCYL1BP1 might therefore play some role in transporting cargo by interacting with Rab6 through coiled-coil domains. Besides Rab6a and Rab6b, one member of Arf family was also demonstrated to be specific interaction partner of SCYL1BP1 in our Y2H screen (data not shown), and all of them are involved in membrane trafficking. Therefore, we speculate that GO syndrome is caused at least in part by some defect in membrane trafficking.



Discuss-Fig. 4. Vesicle recognition by anti-Porostin antibodies. Both polyclonal and monoclonal (#54) antibodies recognized some vesicle structure in primary mouse embryonic fibroblasts. (A) Green: polyclonal Ab; (B) red: mono#54; (C) high magnification of part of merged image. (D) merged signal recognized by polyclonal and monoclonal antibodies.

Both tissues affected in GO, skin and bone, require extensive matrix production and secretion for their respective homeostasis. Moreover, we observed some vesicles recognized by both anti-Porostin polyconal and monoclonal #54 antibodies in cultured MEF (**Fig. 4**). In light of the essential role of Rab6 in retrograde transport and exocytosis, secretion of extracellular matrix might be affected by loss of Scyl1bp1. However, the secretion test in skin fibroblasts based on Fibulin-5, one component of extracellular matrix with abundant amount secreted into the culture medium, did not reveal an obvious delay. The deposition of Fibulin-4, 5 and Elastin also occurred normally in the tissues of skin and

lungs from the *Scyl1bp1*$^{Gt(Bgeo)/Gt(Bgeo)}$. Nevertheless, it is still worthwhile to test this possibility by investigating fibulins as well as other candidates such as fibrillins and collagens in more detail.

4.4 Lung development and respiratory distress

We attribute the lethality of Scyl1bp1 deficient mice to unmature lung development, however, they displayed relatively mild lung hypoplasia in comparison with the reported cases, which should be insufficient to cause neonatal lethality. Moreover, homozygous fetuses obtained from Caesarean section at E18.5 were successful in breathing despite the exhaustive effort they need, and could survive up to 3 hours in warm surroundings (longer time not tested). Close monitoring of E18.5 embryos in several litters revealed certain criteria for homozygotes: **1.** exhaustive effort to breathe; **2.** stretched skin with pale color; **3.** enlarged belly.

The embryonic lung arises from the laryngo-tracheal groove of the mouse foregut at E9. The genetic programs that determine axis and branching patterns are defined earlier. The left-right (L-R) axis of the lung is specified and the difference is further developed as airways undergo branching and are assembled into lobes by the visceral pleura (lobation), which result in more lobes in the right lung (mouse, four; human, three) than in the left (mouse, one; human, two) (Cardoso, 2001). Histologically, mouse lung development can be divided into four chronological stages in mouse: (1) pseudoglandular stage (E9.5±16.6), the bronchial and respiratory tree develops and an undifferentiated primordial system forms; (2) canalicular stage (E16.6±17.4), terminal sacs and vascularization develop in this period; (3) terminal sac stage (E17.4 to postnatal day 5 (P5)), the number of terminal sacs and vascularization increase and type I and II cells differentiate; and (4) alveolar stage (P5-P30), terminal sacs develop into mature alveolar ducts and alveoli (Warburton et al., 2000).

Many different genetic defects have been shown to affect respiratory organogenesis at different stages. Foxa2 deficient mice show a defect of anterior foregut differentiation (Ang and Rossant, 1994). The expression of a dominant negative FGF receptor 2 (Fgfr-2) in the distal respiratory epithelium directed by the surfactant protein C (SP-C) gene promoter completely blocks airway branching and epithelial differentiation, without prohibiting outgrowth (Peters et al., 1994). EGF receptor (Egfr) null mutants have impaired branching and deficient alveolization and septation (Miettinen et al., 1997).

Fibroblast growth factor 9 (Fgf9) null mutant lungs exhibit reduced mesenchyme and decreased branching of airways (Colvin et al., 2001). PDGF-A deficiency leads to failure of alveolar smooth muscle cell formation (Lindahl et al., 1997). Fgfr3/Fgfr4 double deficient mice are completely blocked in alveogenesis (Weinstein et al., 1998). Transcription factor $Sp3^{-/-}$ mice die shortly after birth, apparently of respiratory failure, with only slight morphological alterations of their lungs (Bouwman et al., 2000). $Nfib^{-/-}$ mice died early after birth of respiratory failure associated with pulmonary atelectasis and lungs from both heterozygous and homozygous mice are immature, but to a different extent, with only heterozygous mice surviving (Grunder et al., 2002). Apart from skeletal defect, pulmonary hypoplasia was demonstrated in the *Ctgf*-deficient newborns and both of them might contribute to respiratory failure (Baguma-Nibasheka and Kablar, 2008).

These data revealed that the respiratory distress can be caused by a variety of factors at different developmental stages. In accordance with the principle role of elastic fibres in lung function, the ablation of Fibulin5 or Fibulin4, the components of elastic fibres, causes some lung abnormality, and the latter succumbed to prenatal lethality (McLaughlin et al., 2006; Nakamura et al., 2002). Interestingly, the phenotype that most resembles Scyl1bp1 deficient mice is caused by a defect in N-glycan processing, pointing out a critical role of N-glycosylation in pulmonary development (Akama et al., 2006; Tremblay et al., 2007).

Whereas GO patients do not suffer from pulmonary diseases, our mutant mice exhibit respiratory insufficiency, which might be due to species difference. As yet, the exact mechanism underlying is unclear. Although the defect of N-glycan processing was demonstrated in the skin tissues, such a change was not evident for the lungs either by lectin blots or Maldi-Tof-MS. This would otherwise be a reasonable explanation, consistent with the mice lacking the enzymes involved in N-linked oligosaccharide biosynthesis (Akama et al., 2006; Tremblay et al., 2007). Nevertheless, it remains likely that some mild affection of N-glycan processing indeed exists, however, below the threshold for above-mentioned detection assays. Alternatively, an impaired secretory pathway might affect the secretion of some ECM molecules involved in normal lung function such as components of elastic fibres. Since surfactant proteins in the air/liquid interface of the lung are essential factors to lower the surface tension for air entry, reduced secretion of surfactant proteins might also contribute to the respiratory distress. It is also possible that some brain defect might act as the basis of lethality since its reported

interaction partner Scyl1 deficient mice displayed neural degeneration and ataxia (Di et al., 2003; Schmidt et al., 2007).

4.5 Glycosylation defect

Congenital disorders of glycosylation (CDG) represent a heterogeneous group of genetic diseases owing to deficient or increased glycosylation of glycoconjugates (mainly glycoproteins and glycolipids). There are two means by which the sugar structures are covalently attached to proteins: N-linked (to the amide group of asparagine via an N-acetylglucosamine residue) or O-linked (to the hydroxyl group of serine or threonine via an N-acetylgalactosamine or other monosaccharide residue). The synthesis of the N-glycans encompasses a much longer pathway than that of the O-glycans because N-glycosylation, apart from an assembly pathway, also comprises a processing pathway that is lacking in O-glycosylation (Jaeken and Matthijs, 2007). Three cellular compartments including the cytosol, the endoplasmic reticulum (ER), and the Golgi are involved in N-glycosylation. N-glycan assembly is initiated on the cytoplasmic and then on the lumenal side of the ER, which results in the formation of the lipid-linked oligosaccharide dolichylpyrophosphate-GlcNAc2Man9Glc3 followed by transferring the oligosaccharide moiety of this compound to selected asparagines of the nascent proteins. Subsequently, the glycan of the newly formed glycoprotein is processed in the ER by trimming off the three glucoses before entering the Golgi for further modification by trimming off six mannoses and replacing these with two residues each of N-acetylglucosamine, galactose, and sialic acid.

Classical characterization of CDG is based on the glycosylation status of transferrin, a major serum protein. Abnormal transferrin can be detected by the isoelectric focusing (IEF) patterns. As yet, IEF of serum transferrin is the most widely used screening test for N-glycosylation disorders. An association of a cutis laxa phenotype with CDG has been previously described (Morava et al., 2005), and wrinkly skin has been observed in an individual with a defect in the COG complex (Wu et al., 2004). However, we did not view an abnormality in our GO patients compared with normal Ctl by such a test. Therefore, GO has been initially precluded from CDG.

There are approximately 500 cases of all types of CDG worldwide, which probably only reflect a few percent of the total patients. It is safely believed that the entire group of CDG

is severely underdiagnosed in that CDG patients are often misdiagnosed because of its wide-spectrum and variable symptoms, which resemble some other genetic disorders.

Surprisingly, we demonstrated a defect of N-glycan synthesis in our mutant mouse skin by lectin staining/blot, which was subsequently corroborated by Maldi-Tof-MS analysis. Notably, such a defect exists only in the skin and perichondrium, but not in other tissues such as liver, lung and the whole embryo. Considering the ubiquitous expression profile of Scyl1bp1, it remains a mystery how this tissue-specific defect of glycosylation is accomplished. Interestingly, by lectin blot we did not reveal such a defect in cultured skin fibroblasts derived from the skin of either GO patients or mutant mice. The same holds true for cultured fibroblasts derived from WSS patient skin samples even though WSS patients show a clear CDG II by serum test (Kornak et al., 2008). The failure to detect the difference in the cell culture by lectin blot might indicate that the fibroblasts in cell culture condition did not recapitulate the features of N-glycans biosynthesis in vivo (Andersen and Goochee, 1994), consistent with the observation that N-glycans profile can be altered under various physiological and pathological circumstances (Arnold et al., 2007).

N-glycans can have important regulatory function. On average receptors mediating growth responses (e.g. FGF receptors) have more N-glycosylation sites than those responsible for the induction of differentiation (e.g. Tgfβ receptors), indicating a differential regulation of the degree of N-glycan branching for different proteins. Accordingly, mice deficient for N-acetylglucosaminyltransferase V, a Golgi protein required for N-glycan branching, show impaired weight gain, reduced muscle mass and osteopenia (Cheung et al., 2007). Interestingly, we observed the strongest porostin expression and the most striking glycosylation changes in structures (basal cells, perichondrium) that contain dividing cells responsible for tissue growth and renewal, which explains the confined phenotype to the skin and bone. Glycosylation changes causing progeroid phenotypes are supported by the finding that serum protein glycosylation is altered in a similar way in aged individuals and in WRN patients (Vanhooren et al., 2007).

4.6 GO provides a distinct mechanism for progeroid syndromes

Wrinkly skin is the most obvious feature of GO patients, especially the sagging face which appears much older than the chronological age. The premature appearance together with osteoporotic bone easily associates GO with physiological ageing. Based on the criteria of

progeroid syndromes, it is reasonable to describe GO as a "segmental progeroid syndrome" given the joint occurrence of osteoporosis and the skin lesions (Martin, 1978).

Progeroid syndromes are a group of genetic disorders mimicking clinical features of ageing at an early age. The research on Werner syndrome and HGPS, the most extensively studied examples, uncovered the molecular basis of this sort of diseases and shed some light on the pathology of ageing (Martin, 2005). All the characterized Progeroid syndromes can be separated in subcategories corresponding to (i) genes encoding DNA repair factors, in particular, DNA helicases, such as Werner syndrome, Bloom syndrome (BS), Rothmund–Thomson syndrome (RTS), Cockayne syndrome (CS) syndrome, xeroderma pigmentosum (XP) or trichothiodystrophy (TTD) and (ii) genes encoding lamins A/C or partners such as HGPS or restrictive dermopathy (RD) (Navarro et al., 2006). Recently, several lines of evidence indicated a functional link between DNA repair and A-type lamins-associated syndromes, evidencing a common mechanism for these syndromes.

Surprisingly, our result revealed that the molecular basis of GO syndrome is mutations in a Golgi resident protein. The identification of rab6 and one member of Arf family as its interaction partners raises a speculative role for SCYL1BP1 in membrane trafficking. In addition, the tissue specific defect in N-glycan maturation was demonstrated in the skin of mutant mouse. Both aspects are correlated to the fundamental function of Golgi apparatus. Since GO syndrome resembles ageing mainly concerning the tissues of skin and bone. We assume that mutations in some Golgi proteins might contribute to some progeroid syndromes, especially the conditions manifested by wrinkled skin or osteoporotic bone. Consistent with this speculation, mutations in the vesicular H+-ATPase subunit ATP6V0A2, were identified by our group to account for Wrinkly skin syndrome (WSS; OMIM 278250), one genetic disorder with a significant overlap with GO syndrome (Kornak et al., 2008). In accordance with GO syndrome, both trafficking defect and CDG type II was demonstrated in WSS (Kornak et al., 2008). Therefore, we argue that impairment of Golgi function is a distinct mechanism for progeroid syndromes.

4.7 Emerging roles of Golgi in ageing

The loss of elastic fibre structure is associated with several aspects of the ageing phenotype, including the loss of skin elasticity, a marked decrease in arterial compliance, and the onset of a form of chronic lung disease (emphysema) (Bailey, 2001; Labat-Robert

and Robert, 1988; Pasquali-Ronchetti and Baccarani-Contri, 1997). Some mutations in the components of elastic fibres such as Elasin, Fibulin-4&5 have been identified in cutis laxa patients with premature ageing appearance owing to decreased elasticity of the skin. The mutations in collagens, the most abundant extracellular matrix, were found in numerous skeletal dysplasias (Olsen, 1995).

Interestingly, glycosylation alteration was also observed in skin fibroblasts from some HGPS patients (Clark and Weiss, 1995). More recently, it was demonstrated that N-glycan profiles of the serum from healthy individuals start to change after the age of 40-50 years, and these changes also occur in one progeroid syndrome WRN patients (Vanhooren et al., 2007). Alterations in the attachment or structure of oligosaccharides on proteins might be the biochemical basis at least in part contributing to progeria.

This study clearly showed that loss of Porostin in mice results in a phenotype similar to GO syndrome, which might be due to combined impairment of membrane trafficking and N-glycan processing. Wrinkly skin syndrome (WSS), one genetic disorder with a significant overlap with GO syndrome, was recently linked to mutations in the vesicular H+-ATPase subunit ATP6V0A2 (Kornak et al., 2008). In accordance with GO syndrome, both trafficking and N-glycan processing glycosylation of Golgi function are impaired in WSS (Kornak et al., 2008). Some mutations in subunit of COG complex (conserved oligomeric Golgi) that is involved in protein transport within the Golgi cause CDG that includes wrinkled skin and bone phenotype (Wu et al., 2004).

These data point out some role of Golgi such as trafficking (secretion) and oligosaccharide modification in progeroid syndromes, likely reflecting the importance of Golgi apparatus in usual ageing. The fact that the collagen, the most abundant protein secreted by Golgi, is of cosmetic relevance can be certainly accepted. We are tending to propose one general role of this organelle in ageing (maybe mainly concerning skin and bone, where large amounts of extracellular matrix deposit). The shaping link between Golgi apparatus and progeroid syndromes is extending our knowledge of normal ageing to several aspects of the fundamental role of Golgi. It is likely that the Golgi apparatus in usual ageing (mainly concerning skin and bone) is comparable to the mitochondria in the longevity.