5. SUMMARY

Geroderma osteodysplastica (GO; OMIM 231070) is an autosomal recessive segmental progeroid syndrome characterized by cutis laxa and osteoporosis. By genetic mapping mutations in SCYL1BP1 had been identified as the molecular basis of this disease. Co-localization studies using polyclonal and monoclonal antibodies generated by immunization with different SCYL1BP1 fragments revealed a localization of SCYL1BP1 in the medial and/or trans Golgi compartment. By a Y2H screening against a library of small GTPases, we identified the activated form of Rab6 as a specific interaction partner, a central regulator of anterograde and retrograde Golgi trafficking. Deletion mutants showed that the coiled-coil domain of SCYL1BP1 is sufficient to mediate Rab6 binding. Therefore, SCYL1BP1 belongs to the Golgin protein family.

The mouse model generated by insertion of a gene trap cassette into the first intron of the murine *Scyl1bp1* gene recapitulated the skin and bone phenotype of human GO. However, a thorough analysis of the phenotype was hampered by perinatal lethality of homozygous mutants that was attributed to a defect in lung development. Staining with different lectins demonstrated a dramatic reduction of complex N-glycans in the dermis and in the perichondrium adjacent to the growth plate of Scyl1bp1 deficient mice. MALDI-TOF analysis of skin lysates corroborated a striking rarefaction of complex N-glycans while some high mannose and hybrid N-glycans were more abundant. In contrast, no major glycosylation abnormalities could be identified in liver, lung or other tissues. Therefore, a tissue-specific glycosylation defect is correlated to the connective tissue abnormality in GO.

Collectively, our results show that two common ageing phenomena, skin wrinkling and osteoporosis can be associated with mutations in a novel golgin, SCYL1BP1. Deficiency of Scyl1bp1 in mice is associated with a segmental alteration of glycosylation that is confined to skin and bone. Our data indicate that tissue-specific glycosylation changes can be associated with premature ageing.