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TMEM165: A Golgi Protein Implicated in a Subtype of CDG (Congenital Disorders of Glycosylation), its Function in Golgi Glycosylation, and its Connection with Manganese

Wednesday 27th march, 2024

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From the PhD defended in Lille Medical Center in September 2020 :
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Summary

I- INTRODUCTION

a) Glycosylation

- Importance in biology
- Focus on *N*-glycosylation :
  - *N*-glycans structure
  - Biosynthesis
  - Associated diseases (CDG)

b) TMEM165-CDG

- Role of TMEM165 and glycosylation
- Double link between TMEM165 and Mn^{2+}
- TMEM165 ion transport : state of the art

II- RESULTS

- Functional link between TMEM165 and SPCA1
- Identifying the peptide domains implicated in TMEM165 function in glycosylation and its manganese sensitivity

III- DISCUSSION & PERSPECTIVES

→ Current model of TMEM165

Carbohydrates

- Cell structure, metabolism, and regulation of almost all biological processes

Glycosylation

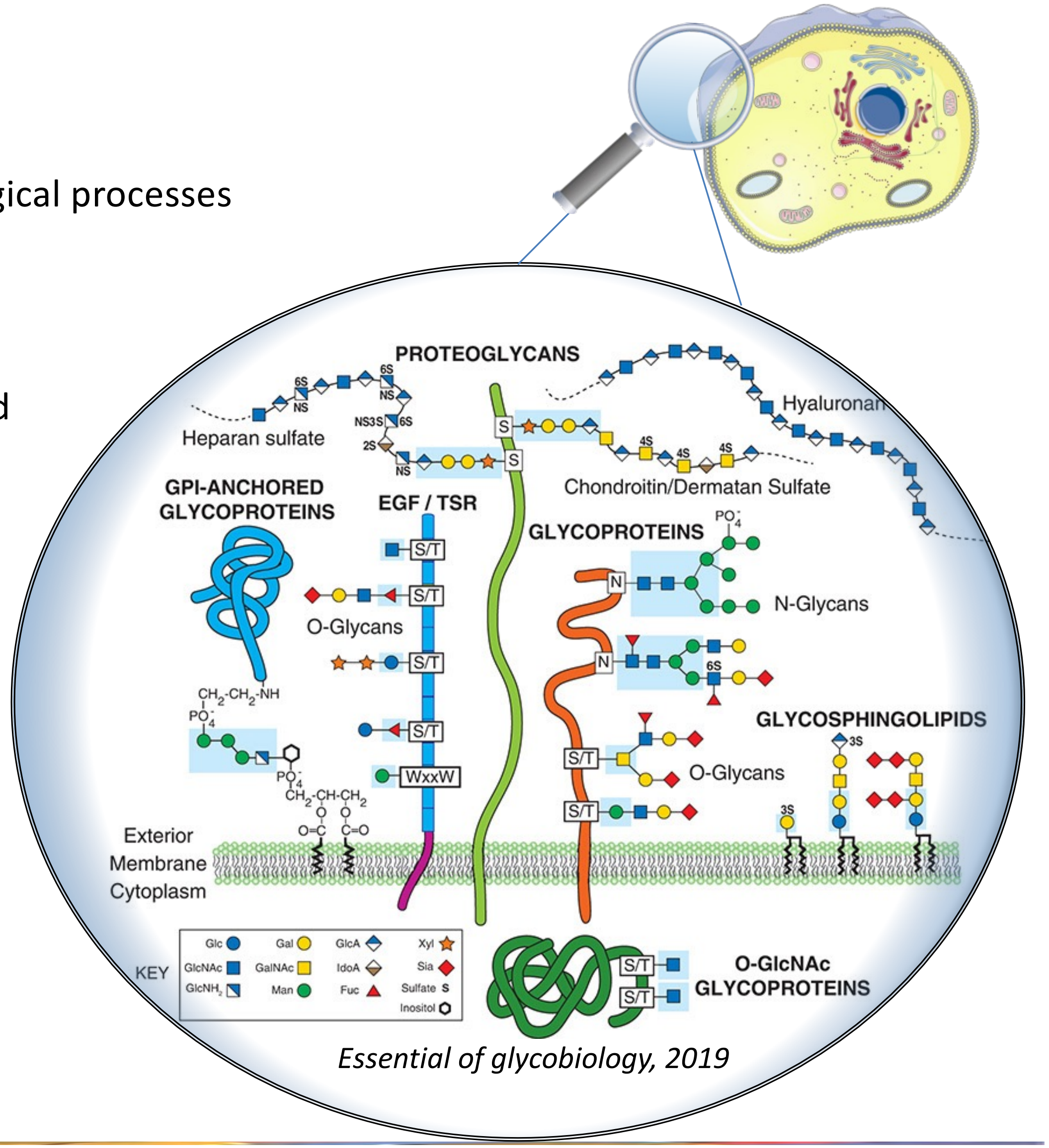
- 2% of the coding genome is dedicated to glycosylation
- Modulates proteins and lipids physicochemical properties and functions
- Various types of glycoconjugates : glycolipids, mucins, proteoglycans, glycoproteins…

Glycoproteins

- The majority of secreted and transmembrane proteins

70% of the eukaryotic proteome

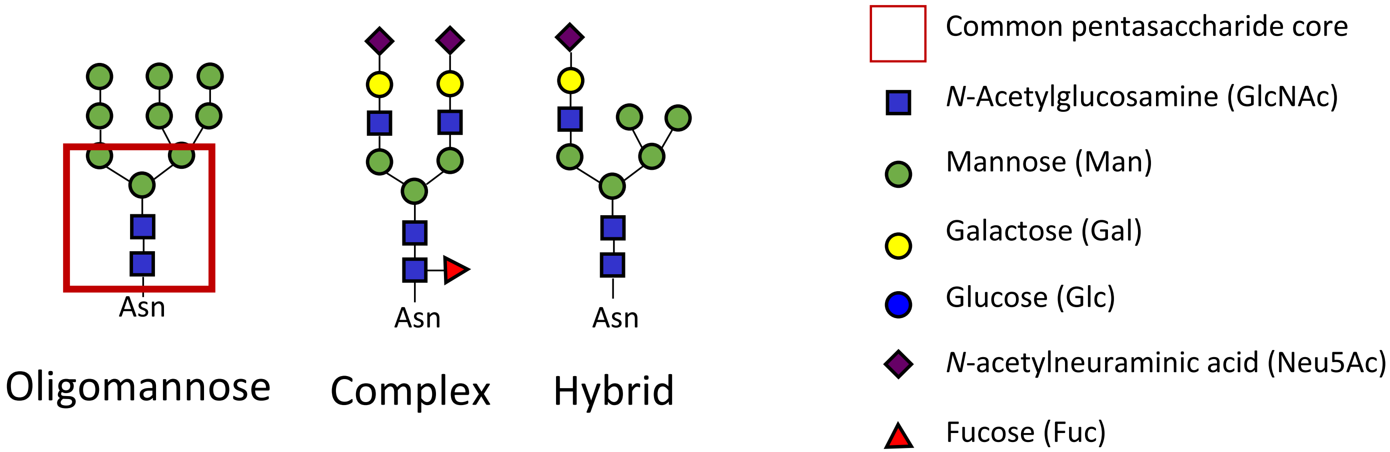
- Role in :
  - Cell-cell communications
  - Development, immunity, nervous system…
  - Pathogens adherence
- Usually *O*-Glycosylated or *N*-glycosylated
  - O-Glycosylation is generaly the attachment of a sugar to a serine or threonine residue of a protein

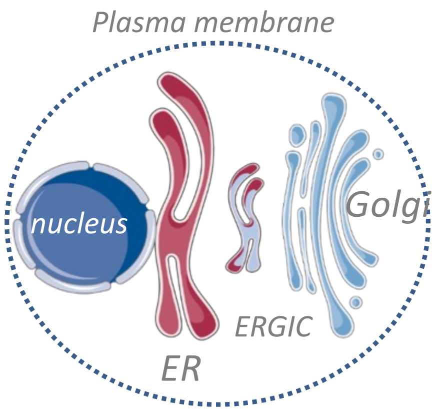


Essential of glycobiology, 2019

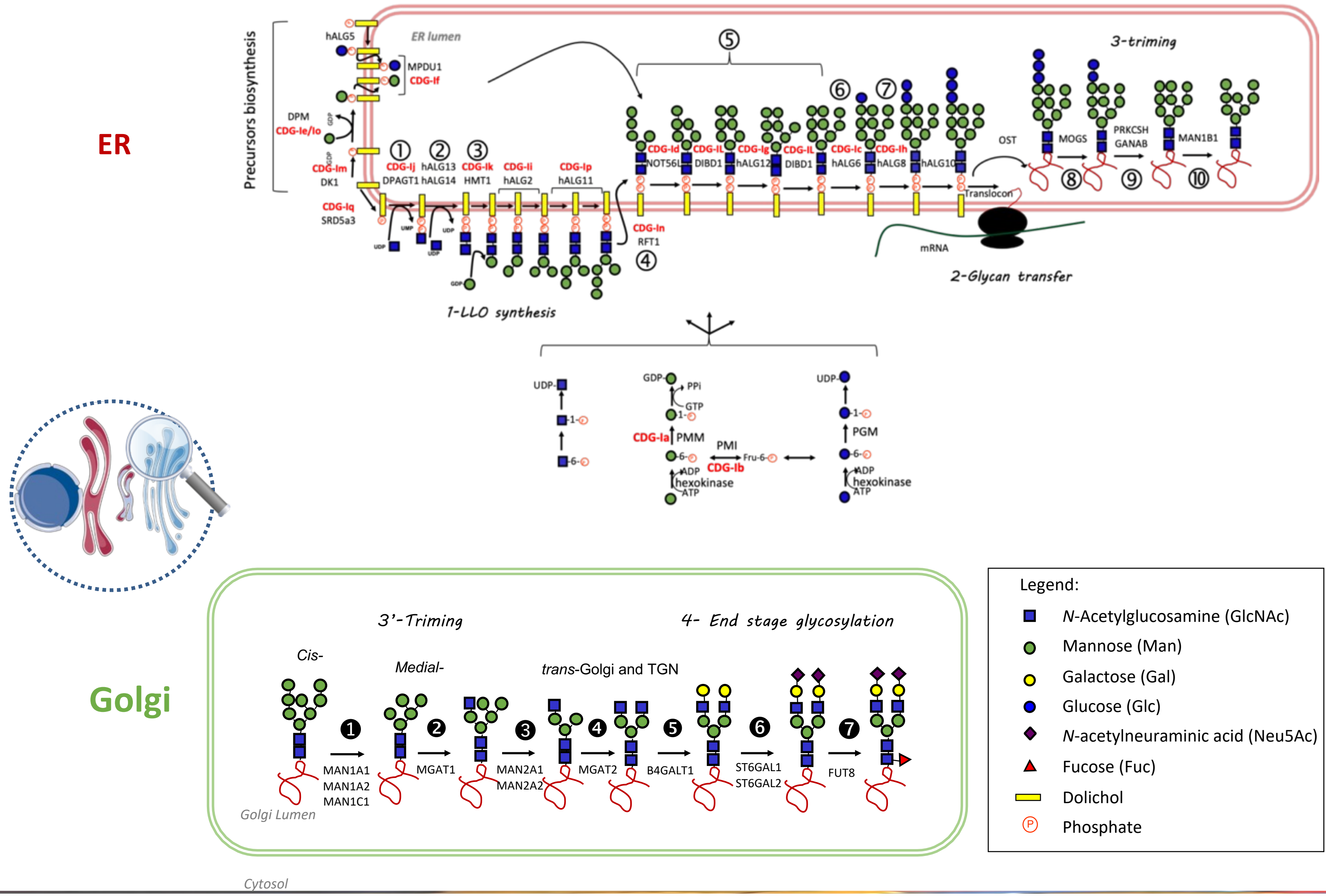
N-glycosylation

N-glycans structures

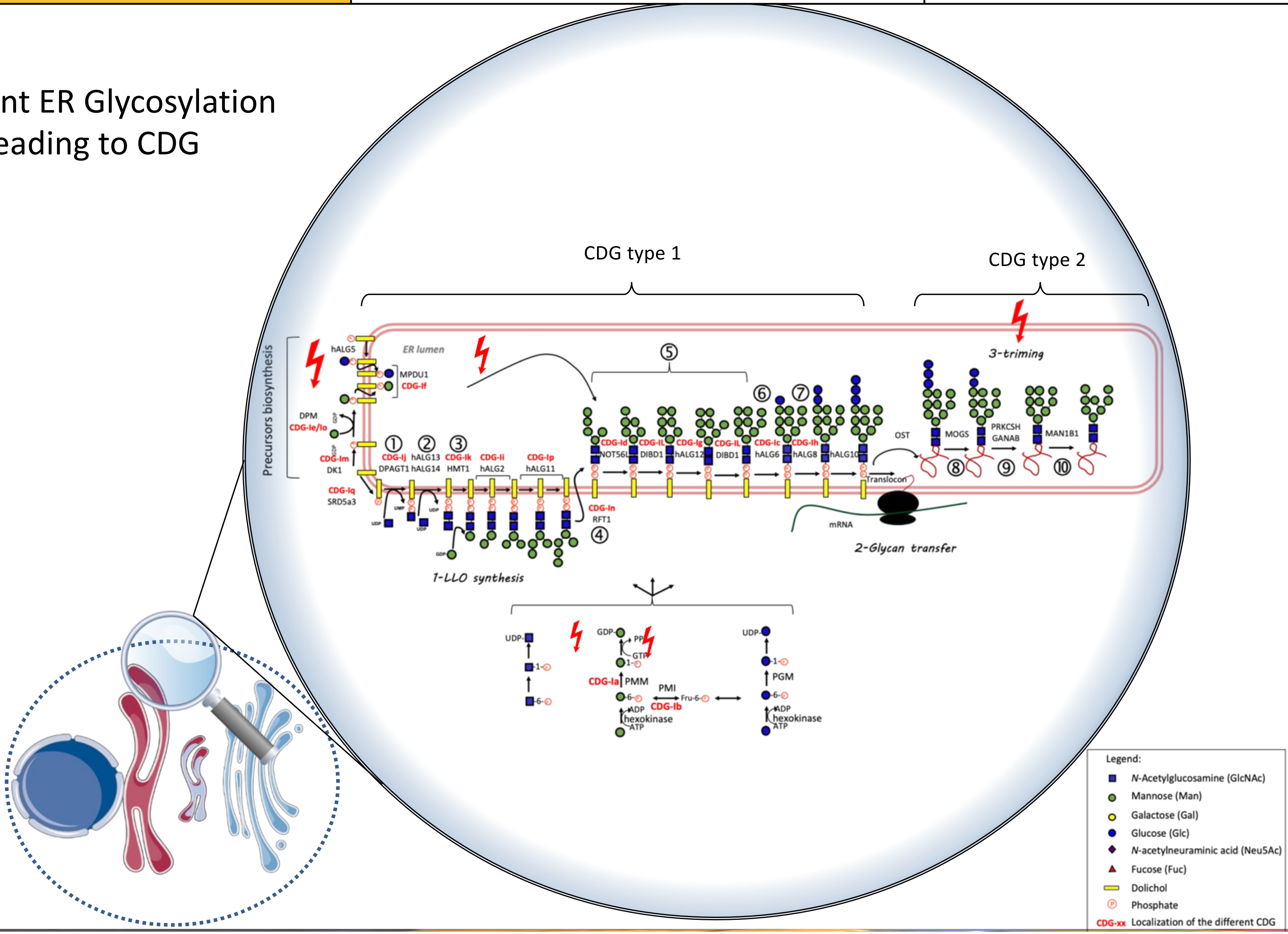




→ Biosynthesis is made in the secretory pathway : ER and Golgi

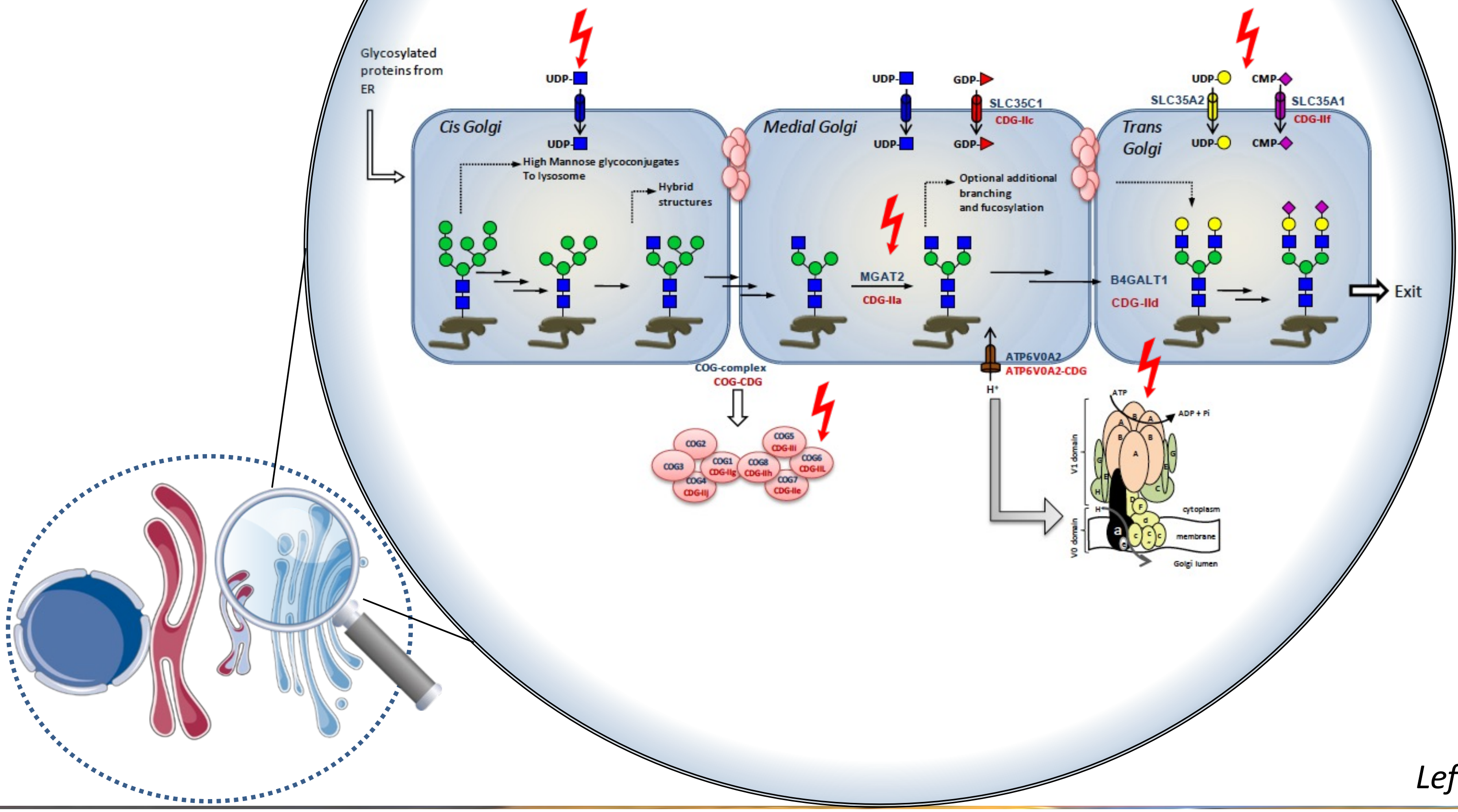

ER
Precursors biosynthesis
ER lumen
hALG5
MPDU1
CDG-If
DPM
CDG-Ie/Io
CDG-Im
DK1
CDG-Iq
SRD5a3
CDG-Ij
DPAGT1
hALG13
hALG14
CDG-Ik
HMT1
CDG-Ii
hALG2
CDG-Ip
hALG11
1-LLO synthesis
CDG-In
RFT1
CDG-Id
NOT56L
CDG-IL
DIBD1
CDG-Ig
hALG12
CDG-Ic
hALG6
CDG-Ih
hALG8
hALG10
OST
Translocon
mRNA
2-Glycan transfer
3-triming
MOGS
PRKCSH
GANAB
MAN1B1
UDP-
GDP-
PPi
GTP
CDG-Ia
PMM
PMI
Fru-6-
CDG-Ib
ADP
hexokinase
ATP
PGM
Golgi
3'-Triming
4- End stage glycosylation
Cis-
Medial-
trans-Golgi and TGN
MAN1A1
MAN1A2
MAN1C1
MGAT1
MAN2A1
MAN2A2
MGAT2
B4GALT1
ST6GAL1
ST6GAL2
FUT8
Golgi Lumen
Cytosol
Legend:
N-Acetylglucosamine (GlcNAc)
Mannose (Man)
Galactose (Gal)
Glucose (Glc)
N-acetylneuraminic acid (Neu5Ac)
Fucose (Fuc)
Dolichol
Phosphate

- Deficient ER Glycosylation steps leading to CDG



- Deficient Golgi glycosylation steps leading to CDG type II

Multiple factors :
- Glycosyltransferases
- Nucleotide sugar transporters
- Vesicular trafficking (COG)
- pH (ATP6V0A2)
- Ion homeostasis …



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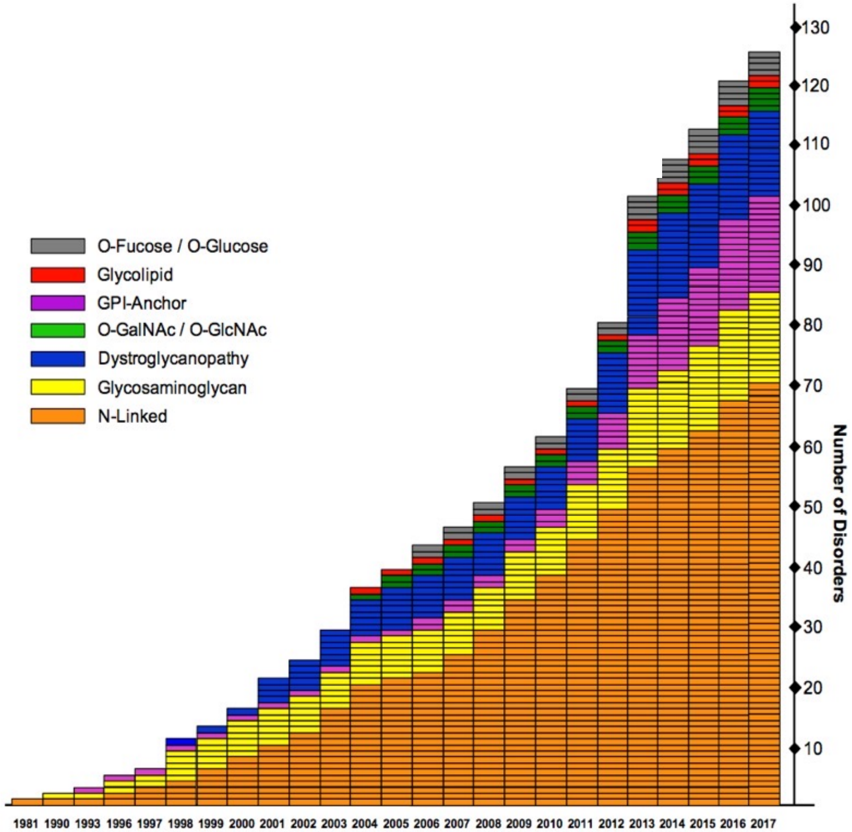
Congenital Disorders of Glycosylation (CDG)

- Rare genetic disease, estimated 1/20 000 births
- Autosomal recessive, rare X-linked cases
- First described in 1980 by Pr Jaeken
- In 2024 > 160 different CDG (dos Reis Ferreira, 2022)
- Affects glycosylation of proteins/lipids
- Variable clinical phenotype



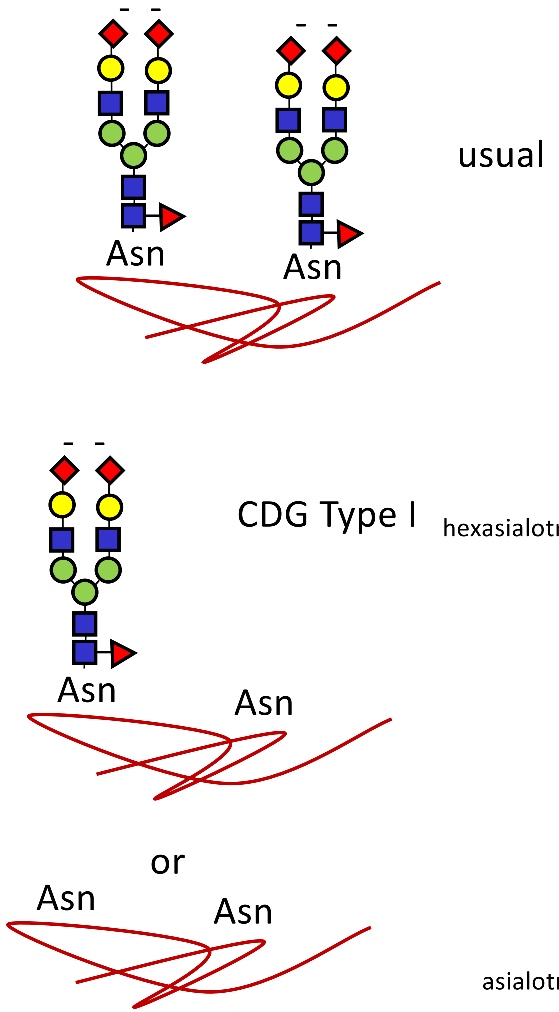
Freeze, 2018

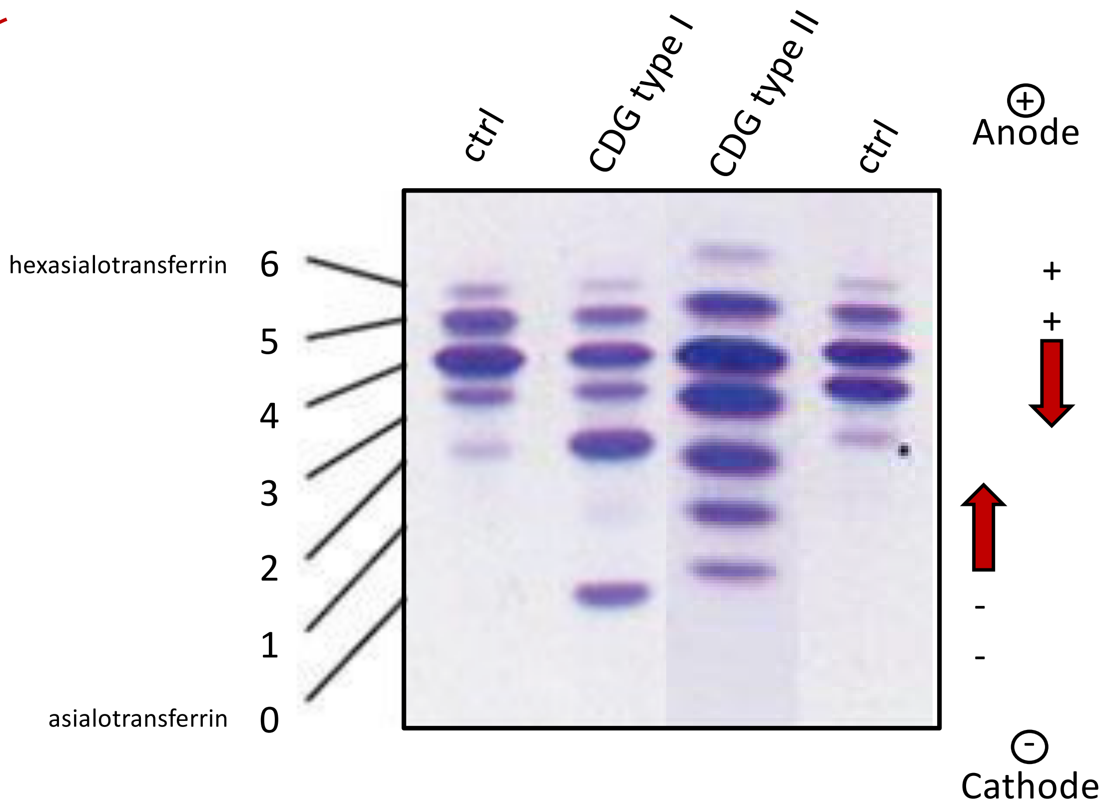
CDG Diagnostic

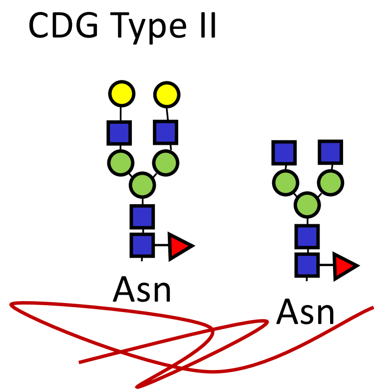
Transferrin isoelectrofocusing

Transferrin

- Serum protein
- Number of negative charges depend on sialylation
- Liver synthesis
- 2 glycosylation sites





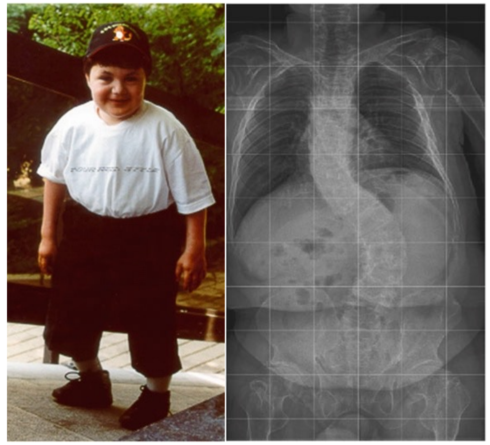


TMEM165: a Golgi protein involved in a CDG type II

- **U̲**ncharacterized **P̲**rotein **F̲**amily UPF0016
- Function unknown

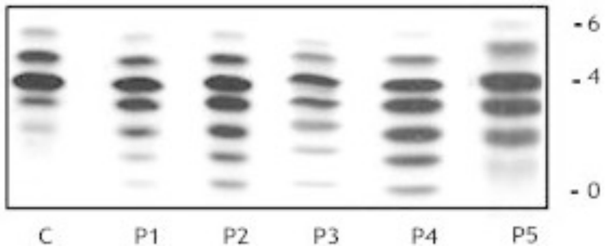
- Mutations on *TMEM165* gene: *Transmembrane Protein 165* (*Foulquier et al., 2012*)

- Clinical picture
  - Psychomotor and developmental delays
  - Bone phenotype : dwarphism, early osteoporosis, scoliosis

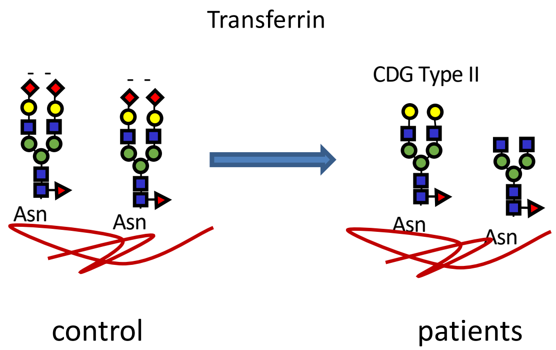


Zeevaert *et al.*, 2013

  - Type II CDG glycosylation defect identified by IEF



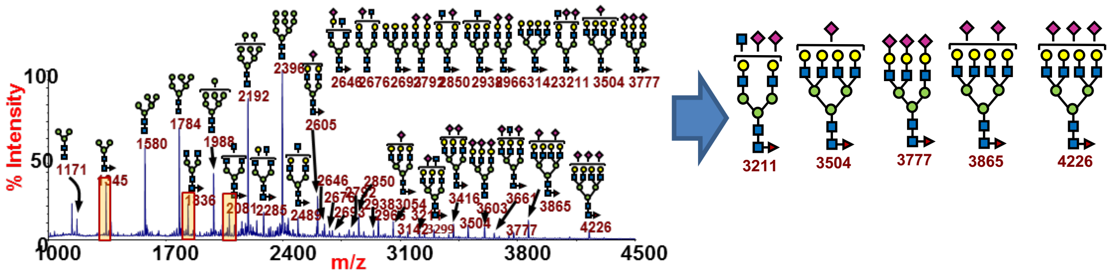
Foulquier *et al.*, 2012



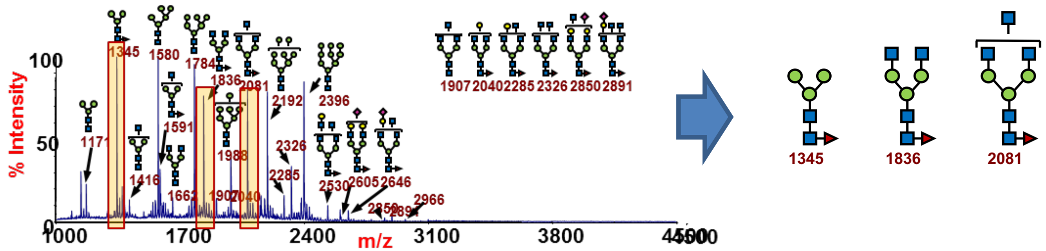
Glycosylation defect in the absence of TMEM165

Patients fibroblasts & TMEM165 KO cell lines

Ctrl

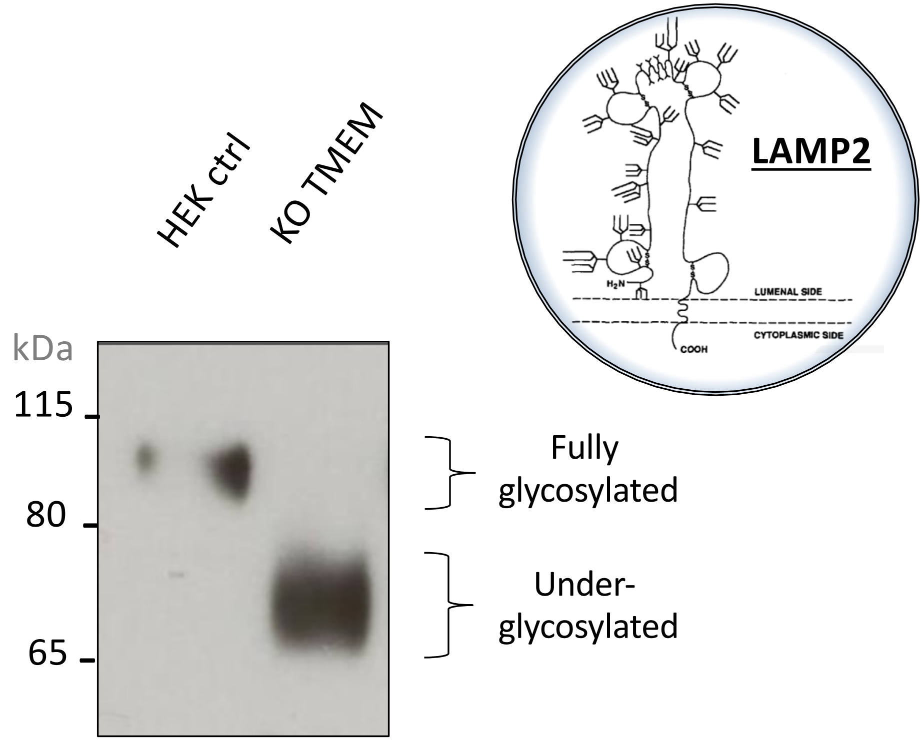


KO TMEM165



Use of LAMP2 as a glycosylation marker

LAMP2



Glycosylation defect in the absence of TMEM165

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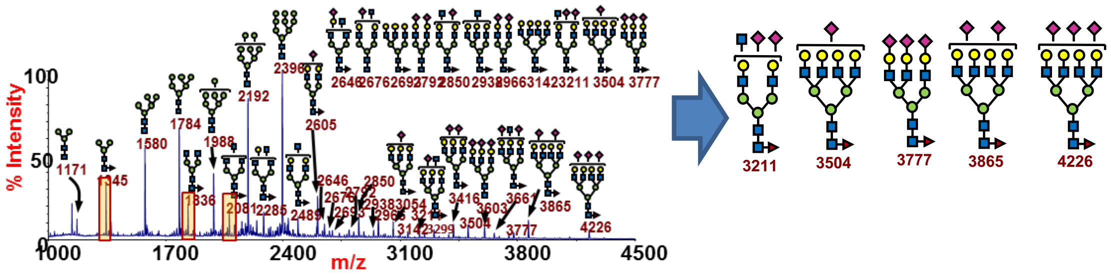
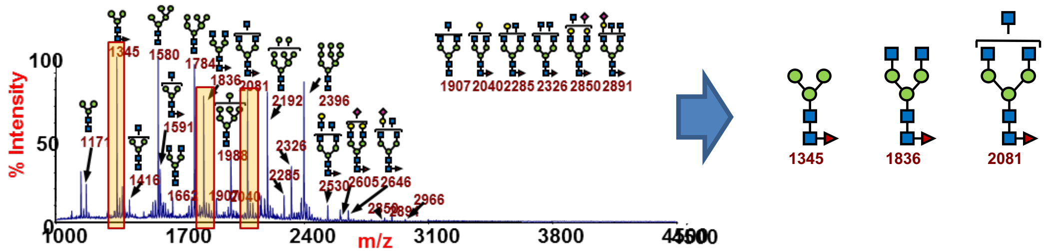
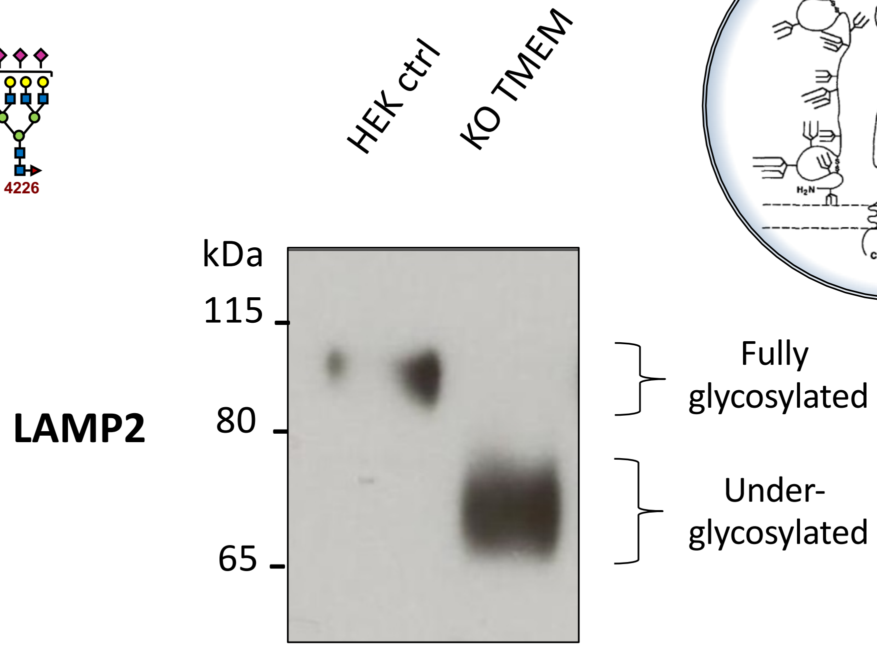
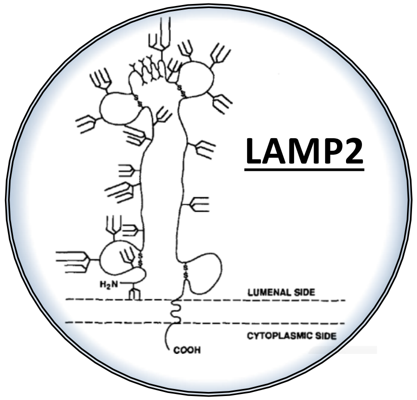


KO TMEM165



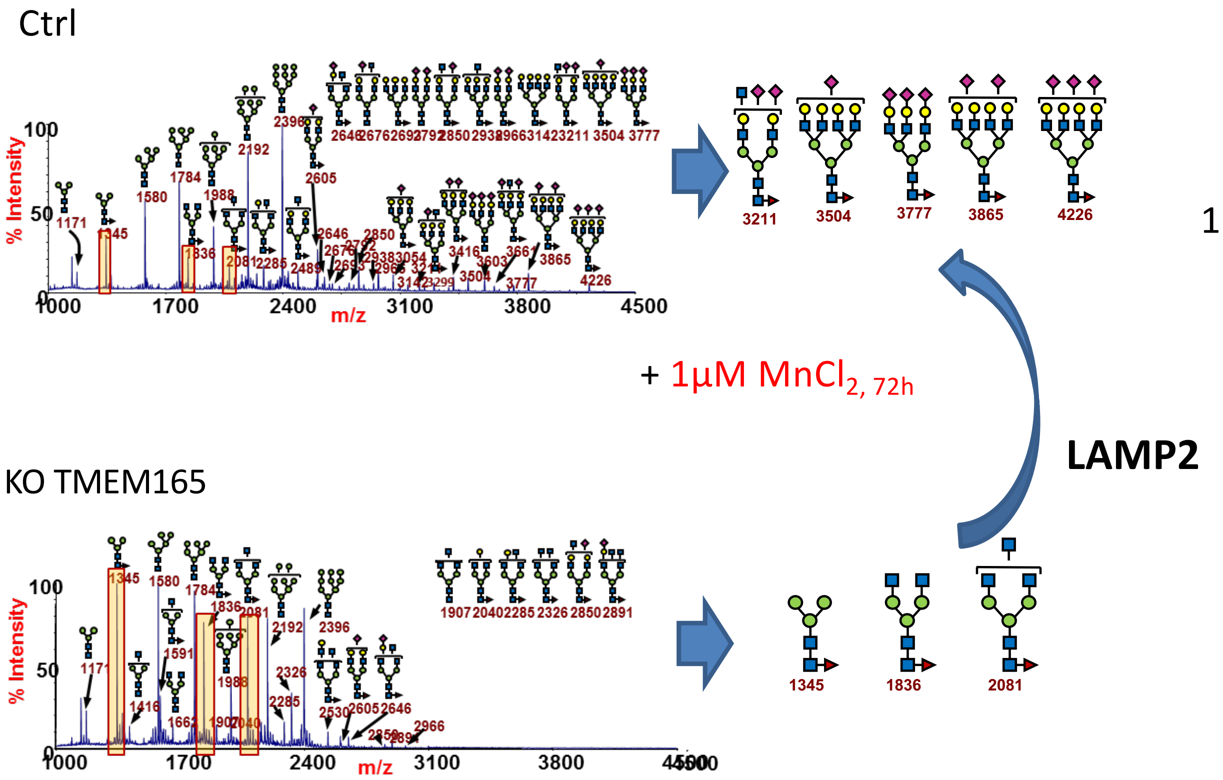
Use of LAMP2 as a glycosylation marker



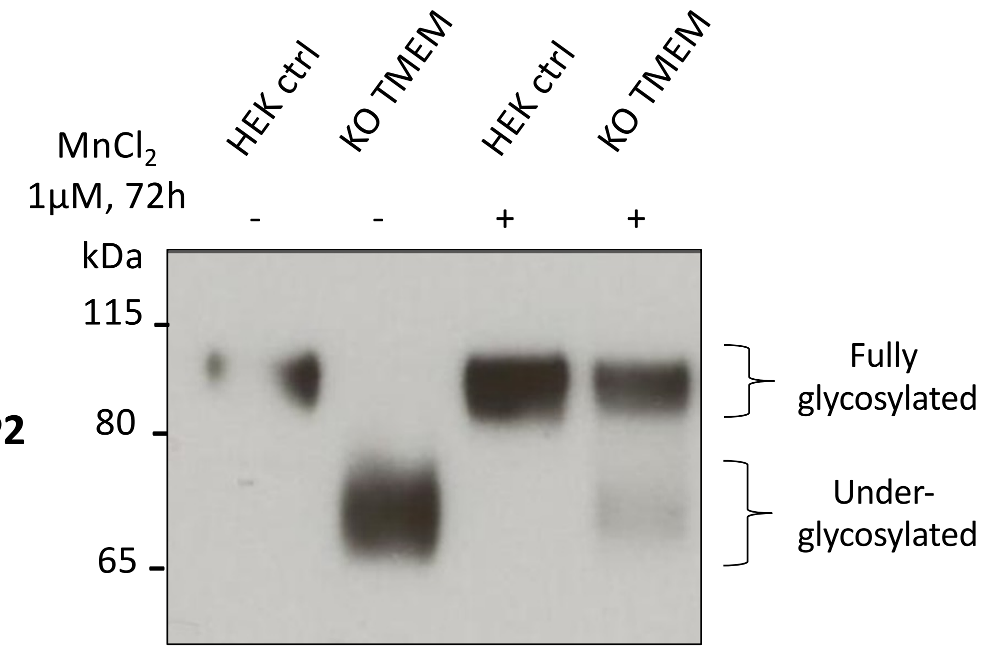


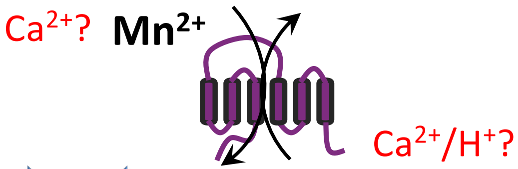
Suppression of the glycosylation defect by Mn^{2+}

Patients fibroblasts & TMEM165 KO cell lines



Use of LAMP2 as a glycosylation marker





TMEM165 ion transport : state of the art

2013

- Yeast ortholog Gdt1p : first thought to be a Ca^{2+}/H^{+} exchanger (Demaegd, 2013 [Morsomme/Foulquier teams])

2016

- Plant ortholog, PAM71 function as a Ca^{2+}/Mn^{2+} cation antiport transporter localized in the thylakoid membranes system (Schneider, 2016)

2017

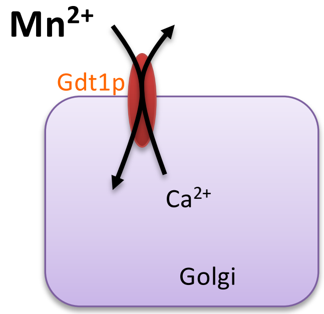
- Our studies suggested the function of Gdt1p as a Ca^{2+}/Mn^{2+} cation antiport transporter (Dulary, 2017 [Foulquier team])

2018

- **Mn^{2+} transport confirmed** by the first team (Thines, [Morsomme team], 2018)

Yeast

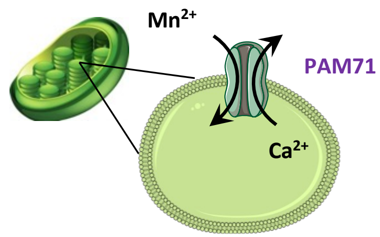
Saccharomyces cerevisiae



Dulary et al, 2017

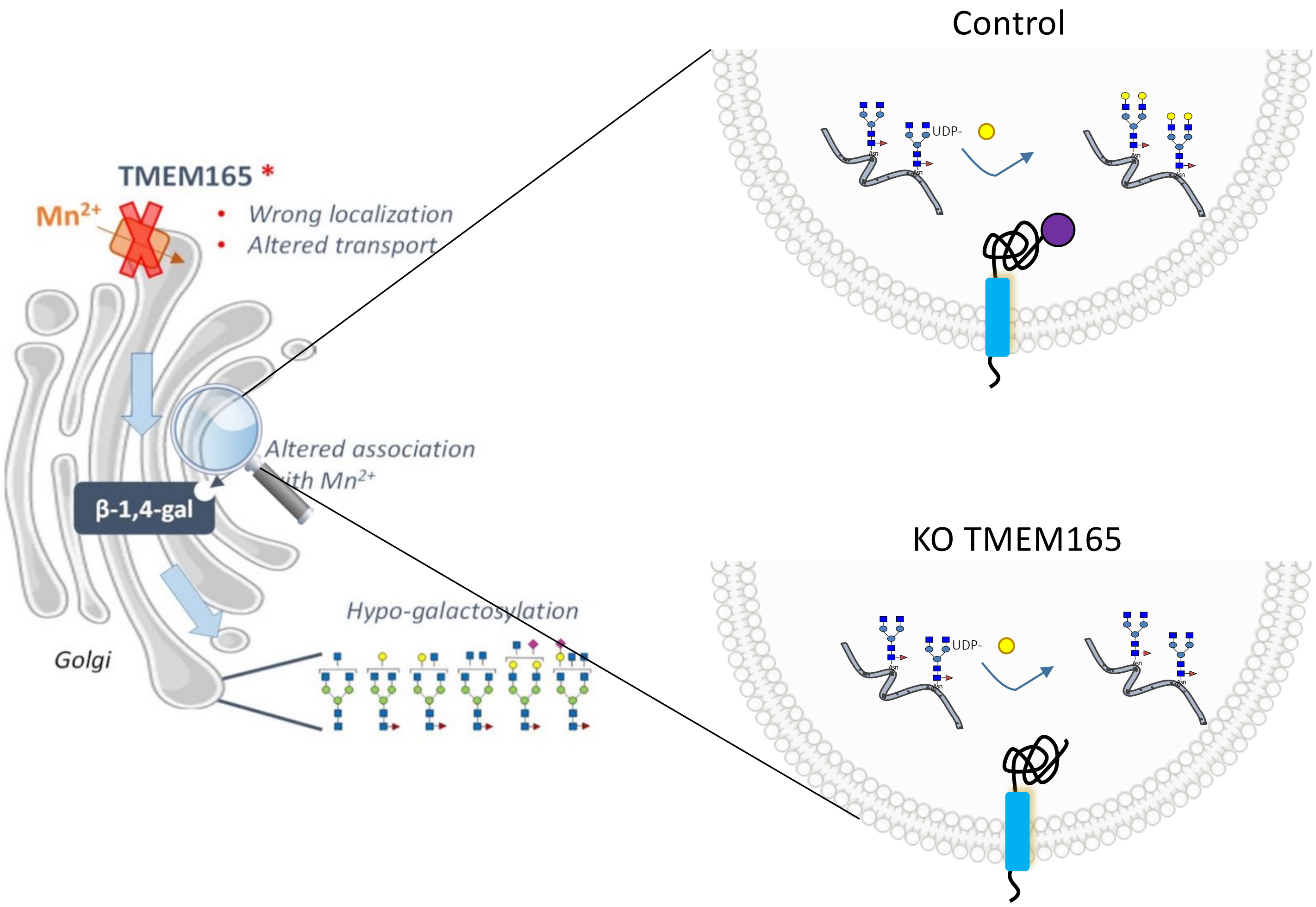
Plant

Arabidopsis thaliana



Schneider, 2016

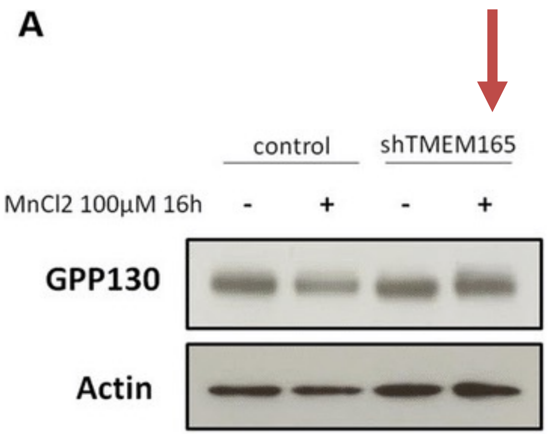
TMEM165 and glycosylation : hypothetic function

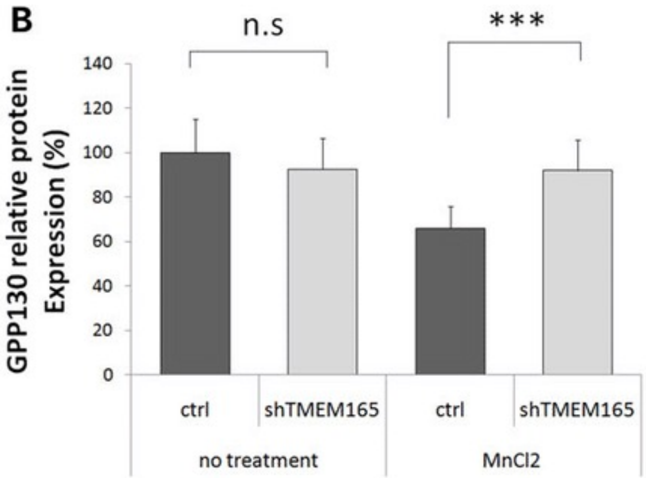


→ Glycosylation defect

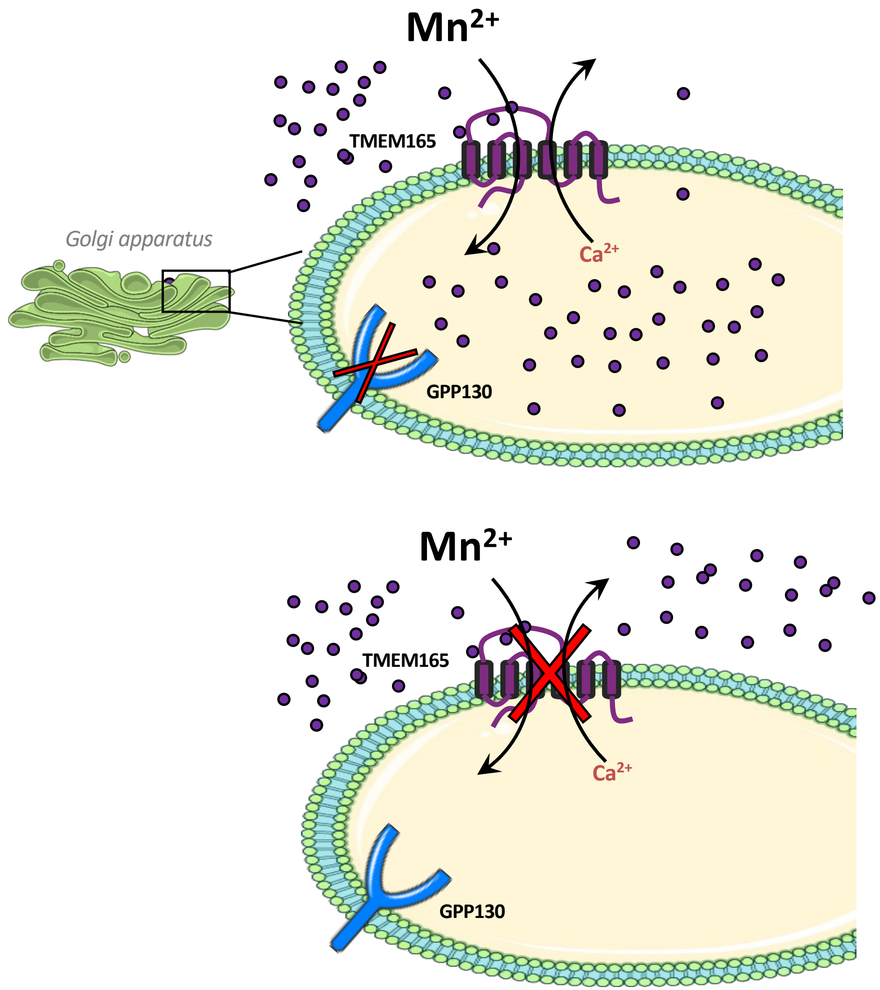
Confirmation of TMEM165 manganese import

- GPP130 : Golgi protein sensitive to Golgi luminal manganese concentration





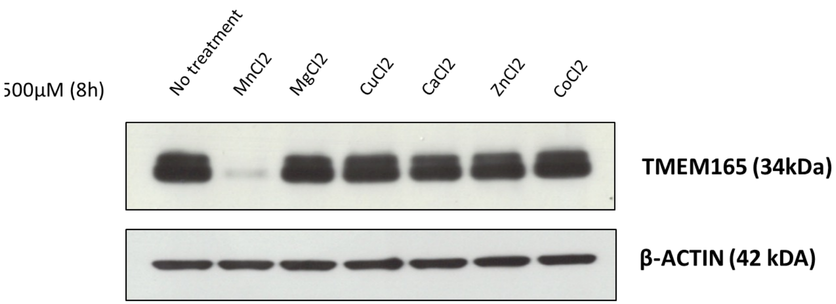
Potelle et al., 2016

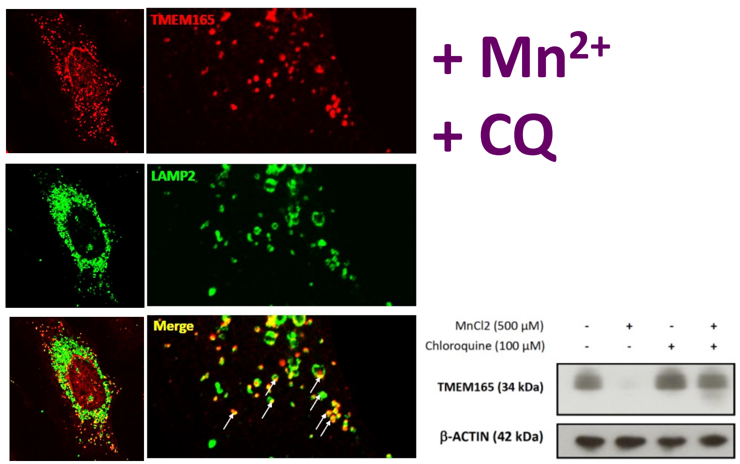


→ **Downregulation of TMEM165 prevent GPP130 manganese-induced degradation**

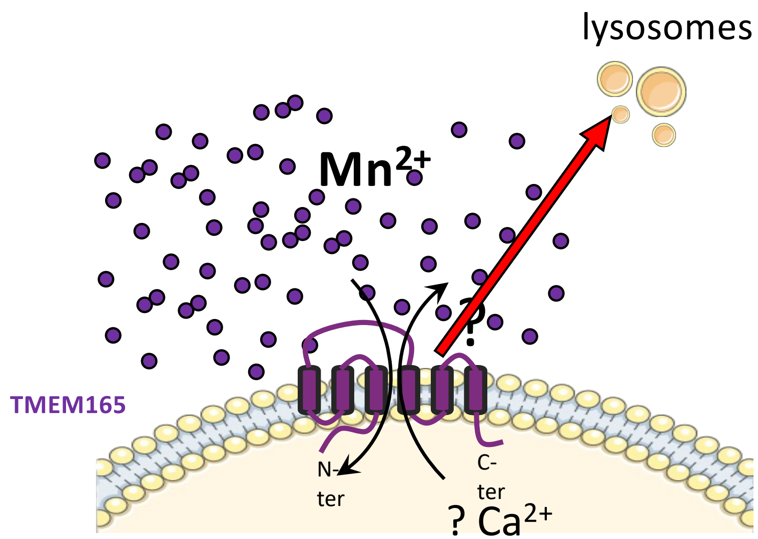
Another link between TMEM165 and cellular Mn^{2+} homeostasis

- TMEM165 is specifically degraded by Mn^{2+}





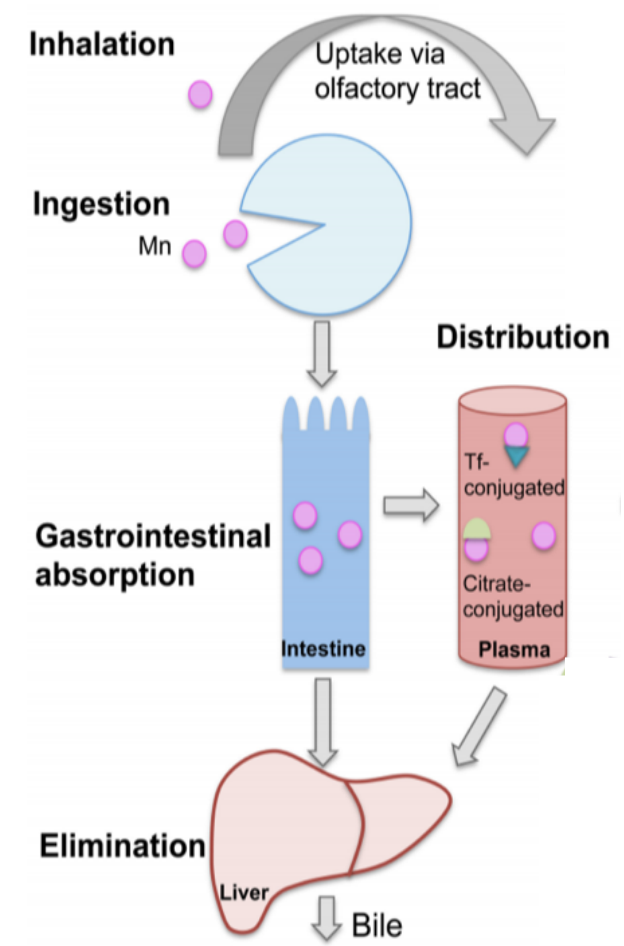
→ TMEM165 is degraded in lysosomes



Link between TMEM165 and cellular/Golgi Mn^{2+} :

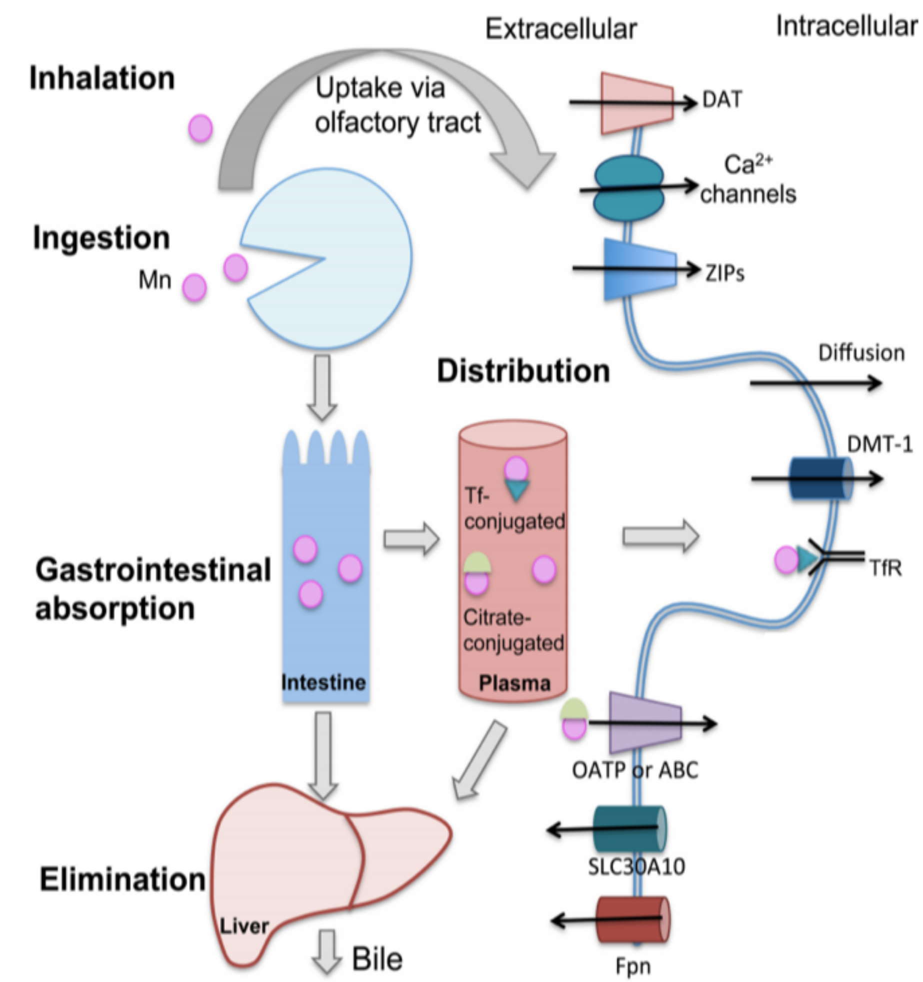
1) Restoration of Golgi glycosylation by Mn^{2+} supplementation
2) TMEM165 Mn^{2+} -induced degradation
3) Absence of GPP130 Mn^{2+} -induced degradation in TMEM165 depleted cells

Manganese homeostasis



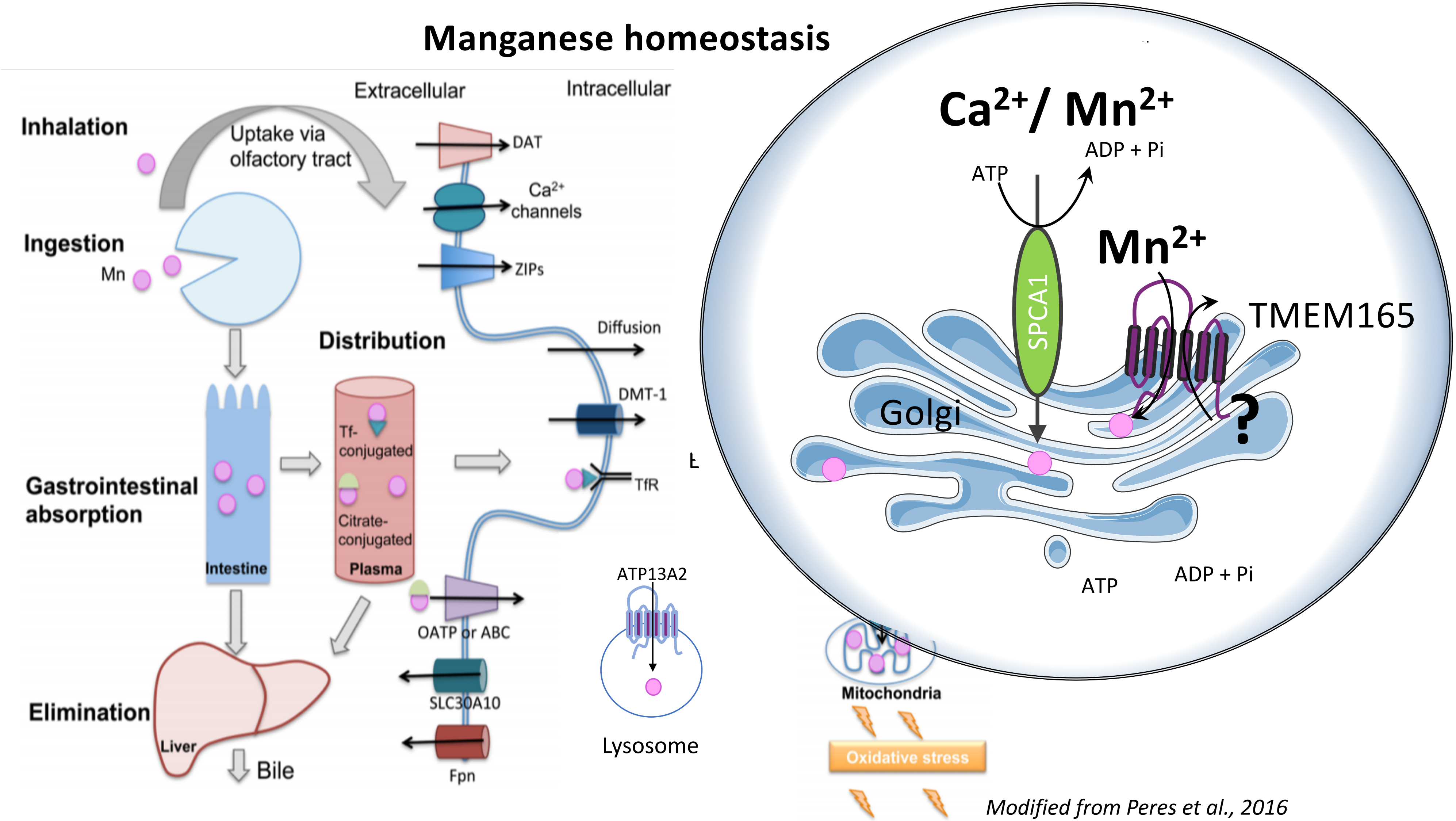
Modified from Peres et al., 2016

Manganese homeostasis



Modified from Peres et al., 2016

Manganese homeostasis



Modified from Peres et al., 2016

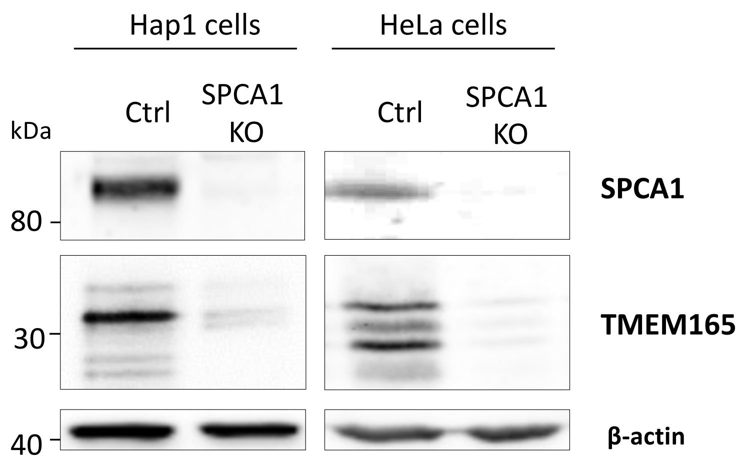
Objectives

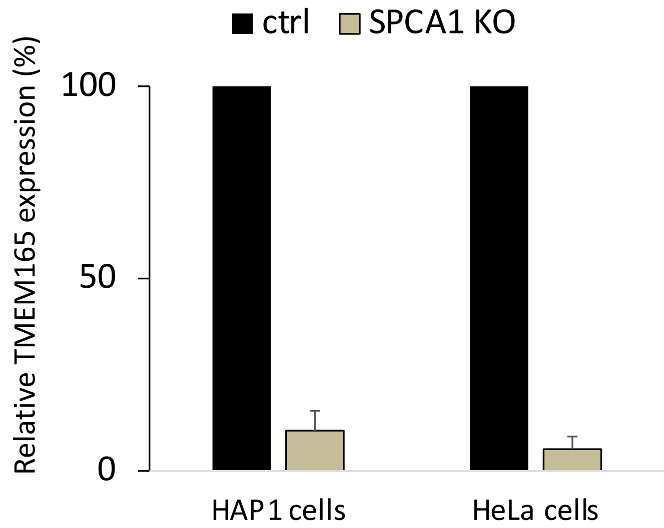
1) Link between TMEM165 and SPCA1?

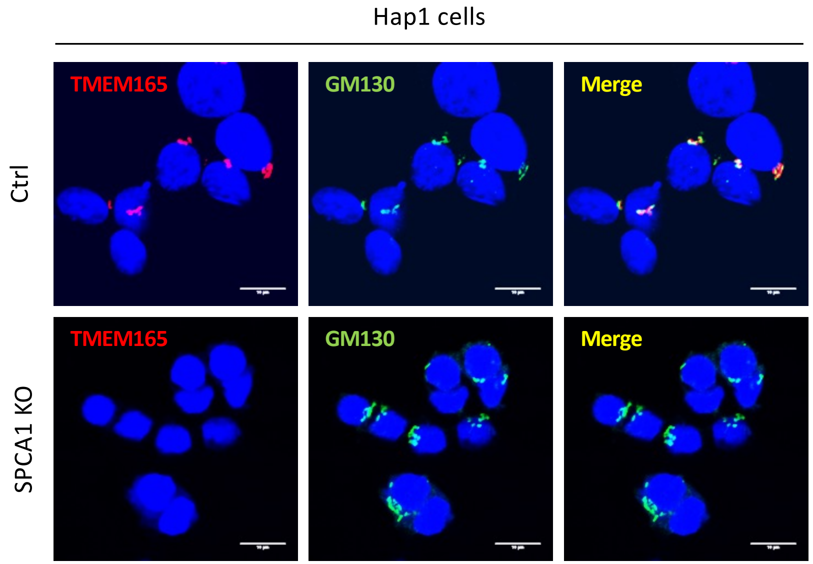
- **To better understand the role of TMEM165 in the maintenance of Golgi ion homeostasis**

2) What are the amino acids implied in glycosylation function of TMEM165 and manganese sensitivity?

TMEM165 expression in KO SPCA1 cells

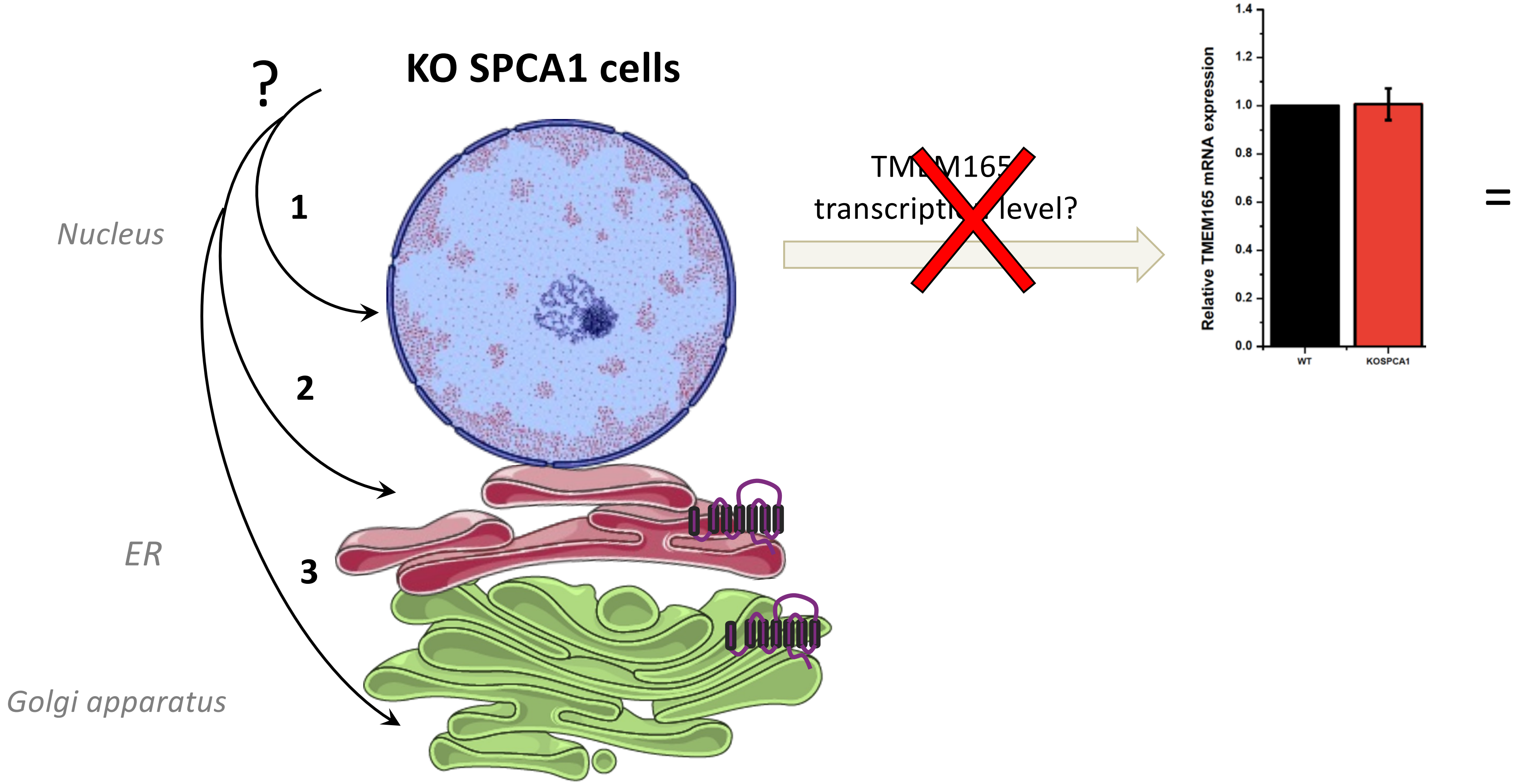




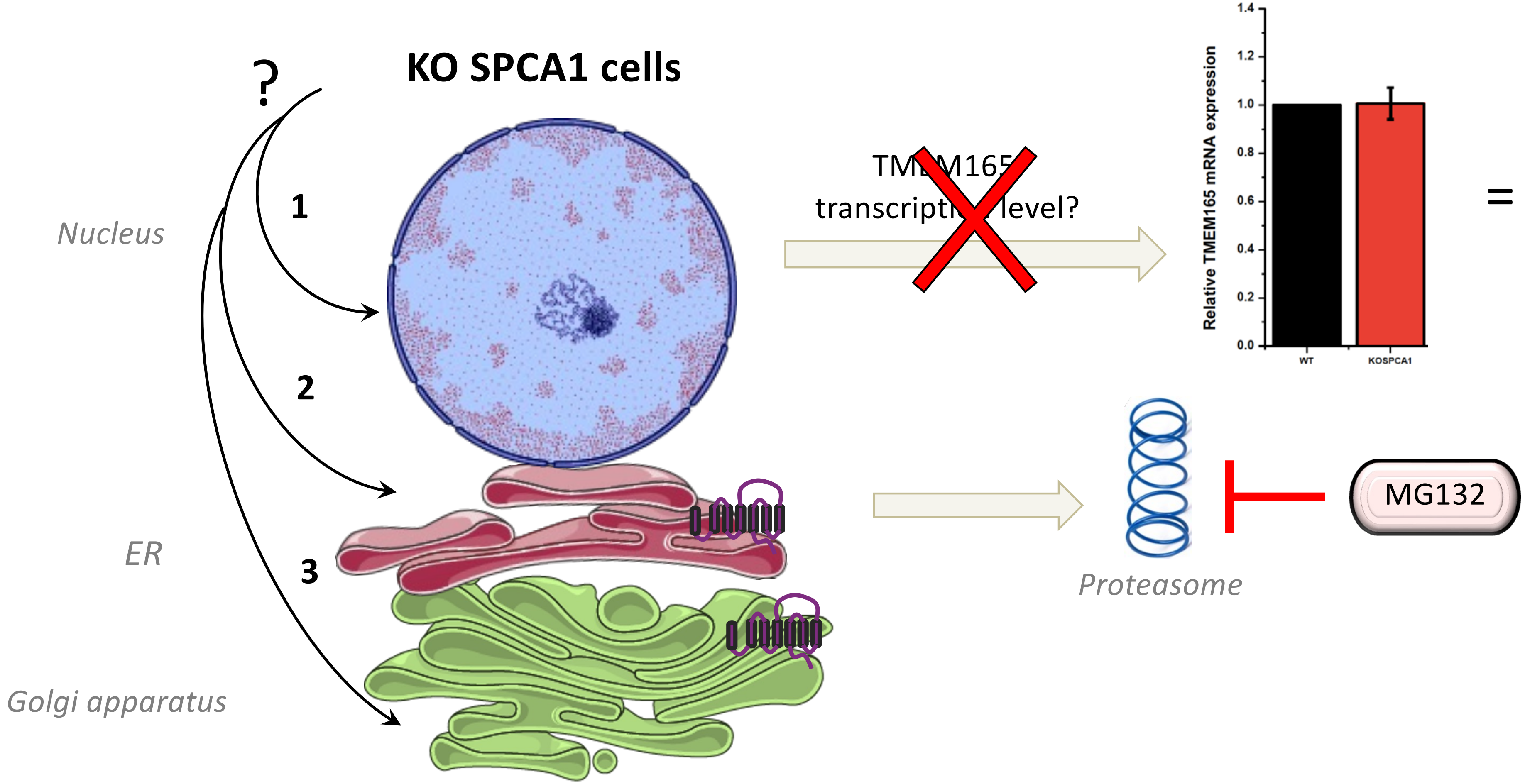


→ Loss of 80% of the expression level of TMEM165 in KO SPCA1 cell lines

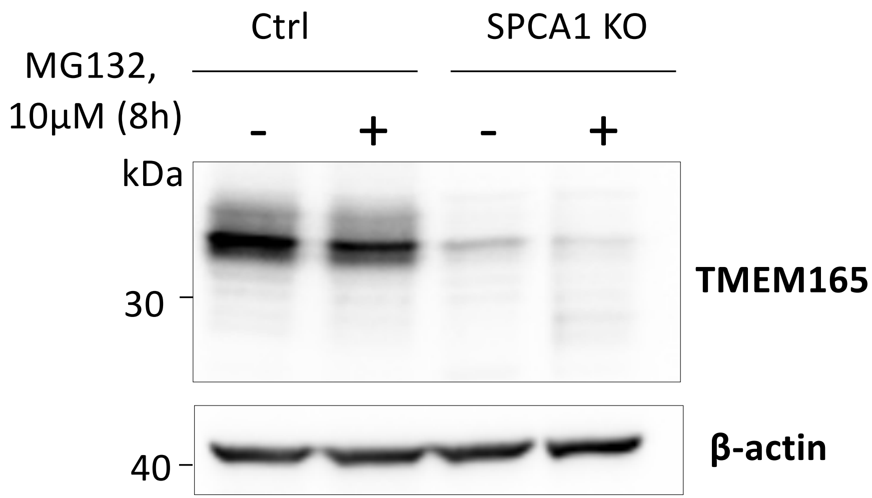
Hypothetic degradation pathways of TMEM165 in KO SPCA1 cells

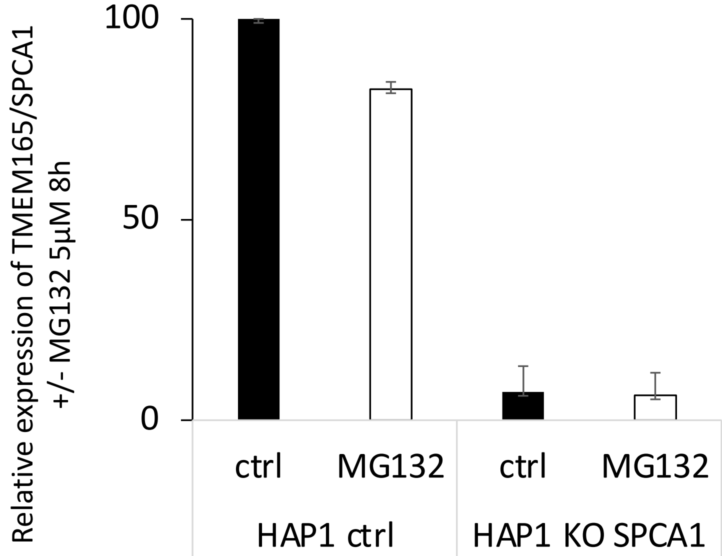


Hypothetic degradation pathways of TMEM165 in KO SPCA1 cells



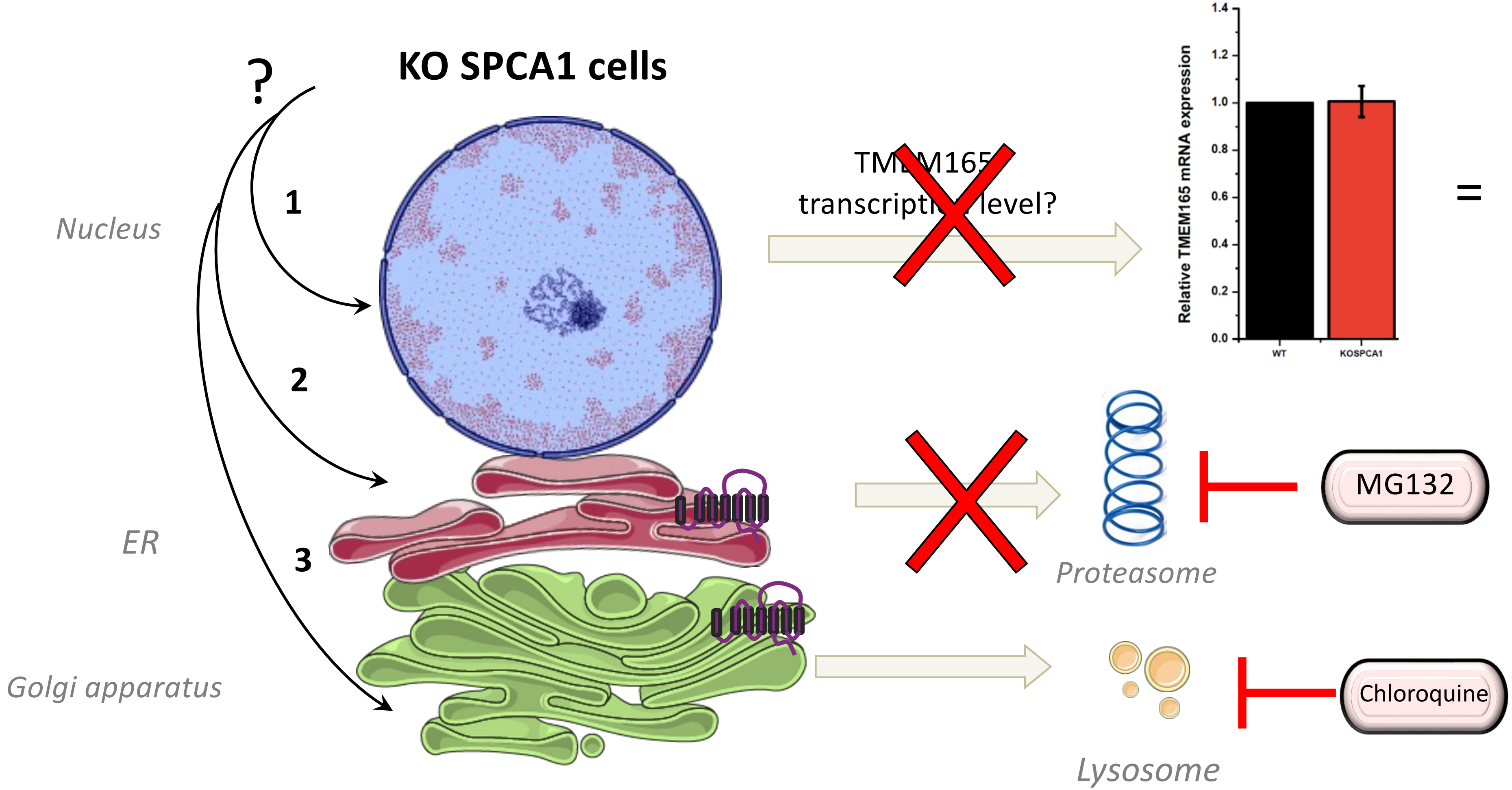
Effect of MG132 on TMEM165 level of expression in KO SPCA1 cells



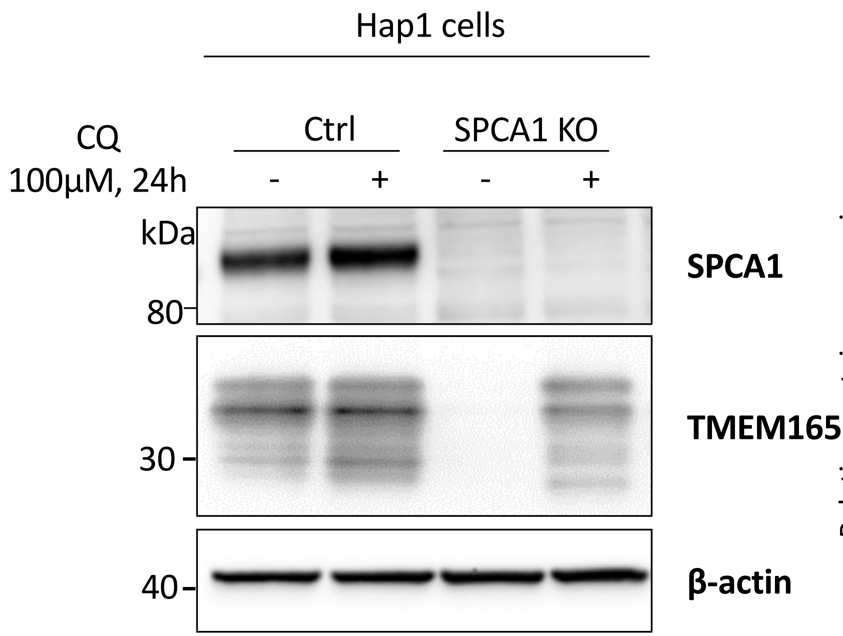


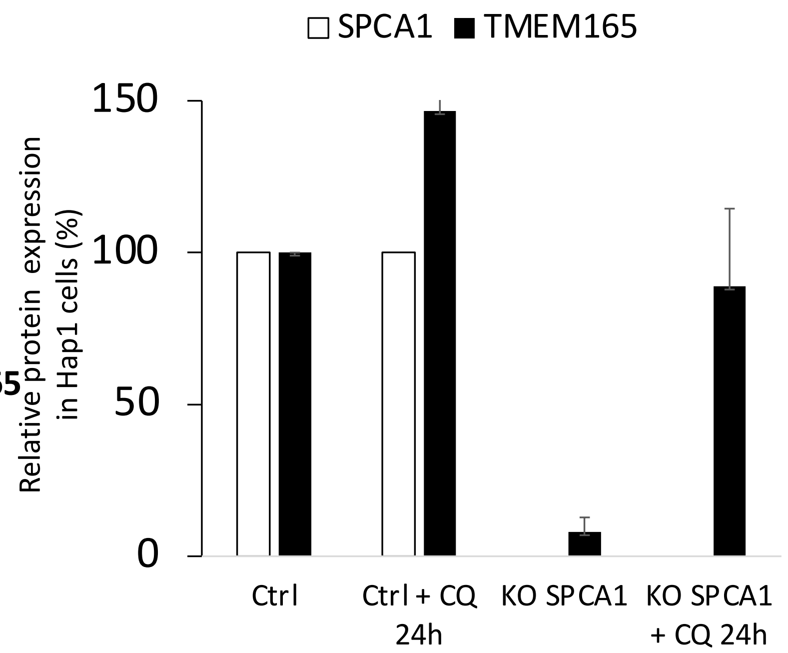
→ **No restoration of TMEM165 expression level by MG132**

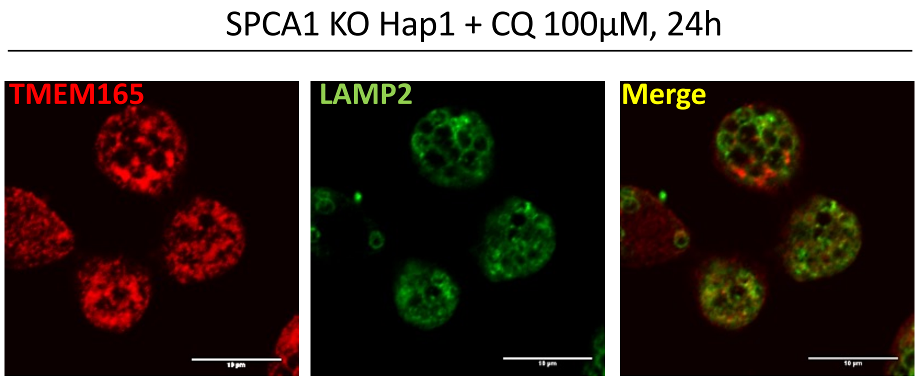
Hypothetic degradation pathways of TMEM165 in KO SPCA1 cells



Effect of CQ on TMEM165 level of expression in KO SPCA1 cells

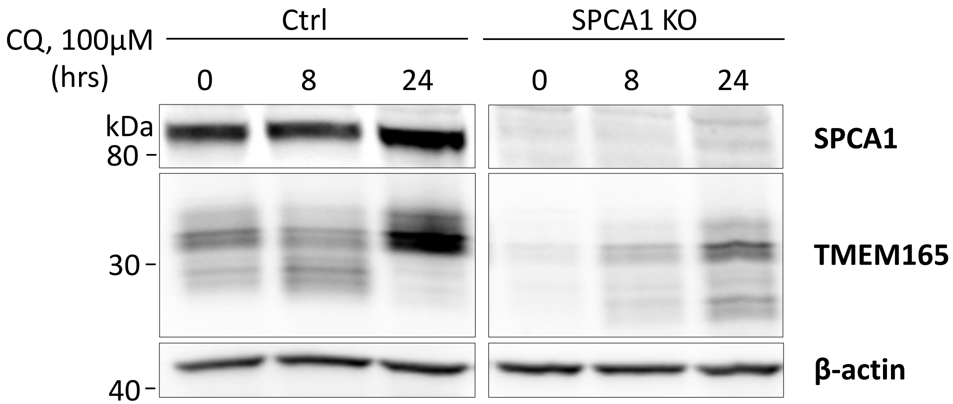


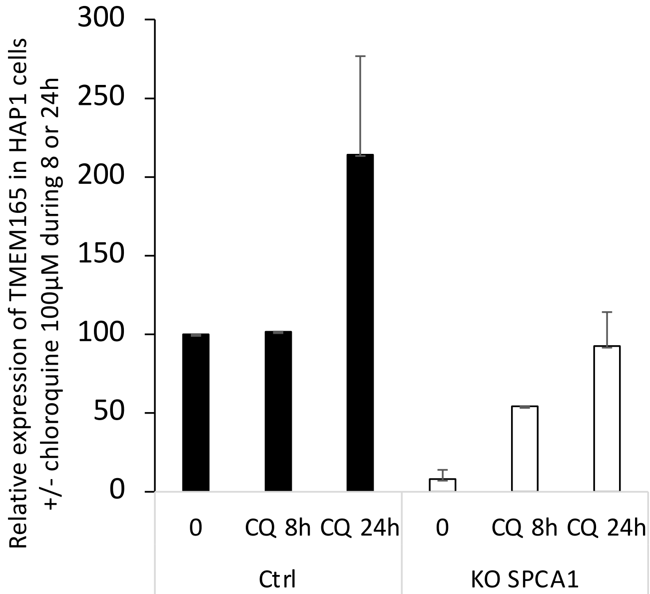




→ **Lysosomal degradation of TMEM165 in the absence of SPCA1**

Effect of CQ on TMEM165 level of expression in KO SPCA1 cells

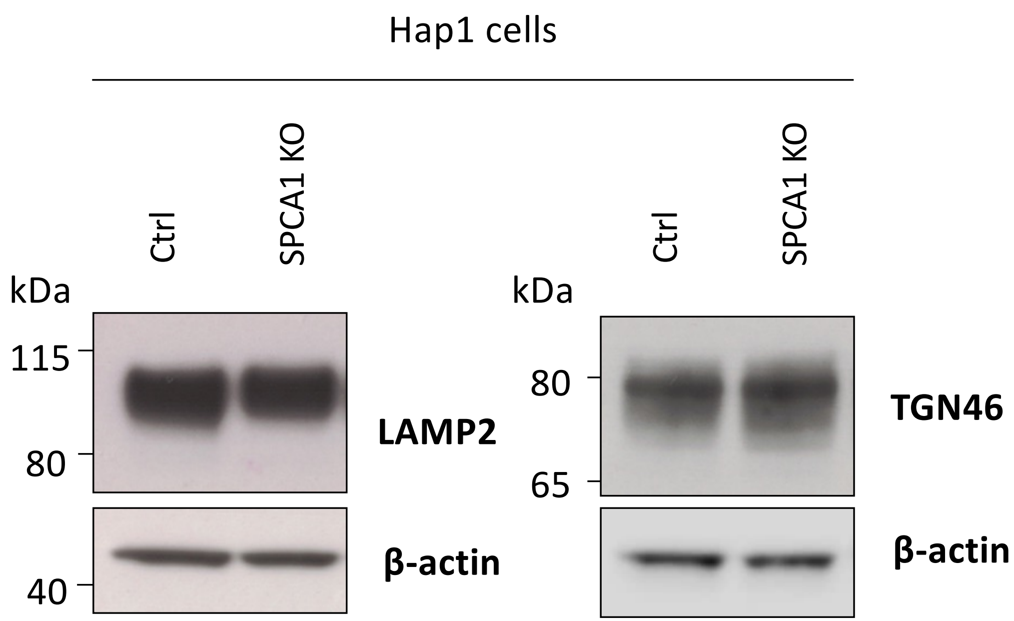




→ The restauration of TMEM165 expression level by CQ is time-dependant

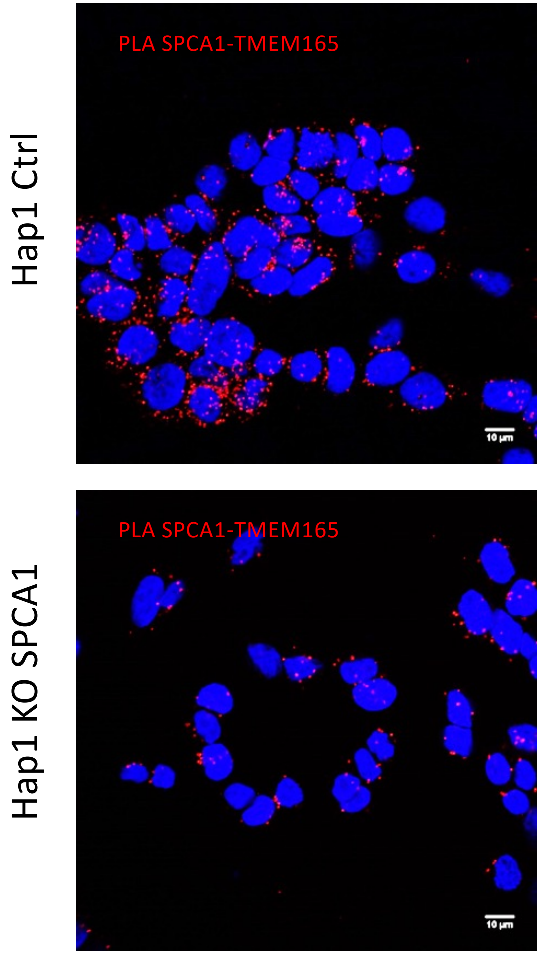
Glycosylation status of these cells?

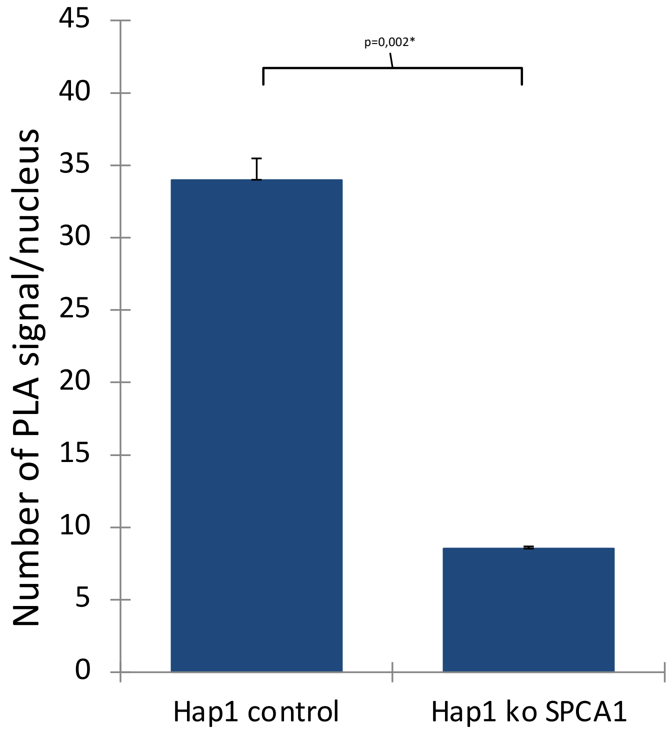
Glycosylation in KO SPCA1 cells



→ Absence of glycosylation defect

Protein–protein proximity between TMEM165 and SPCA1

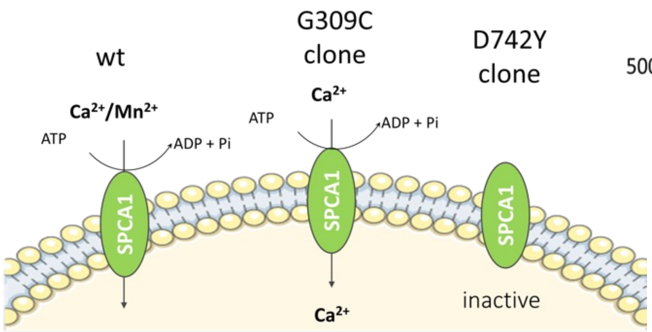


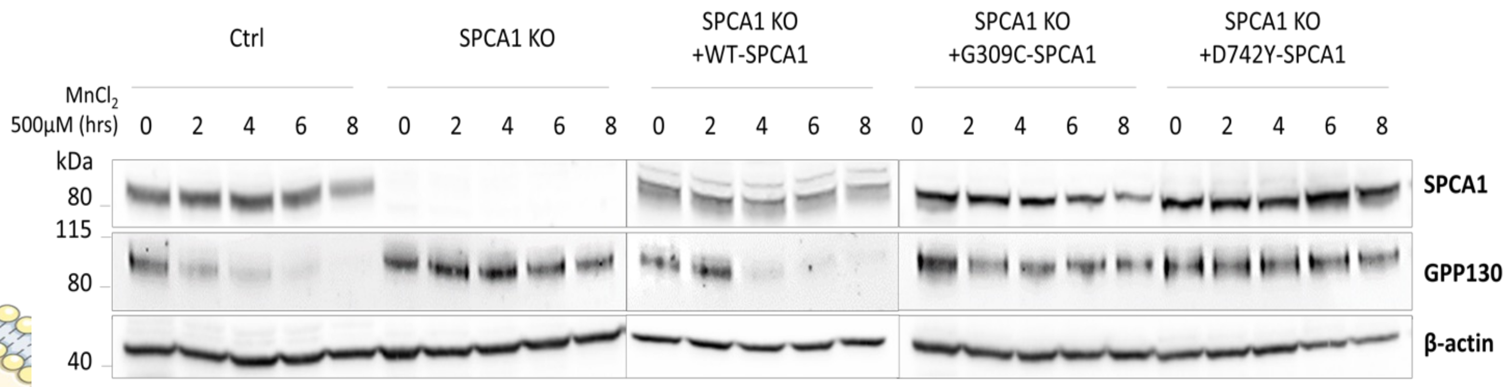


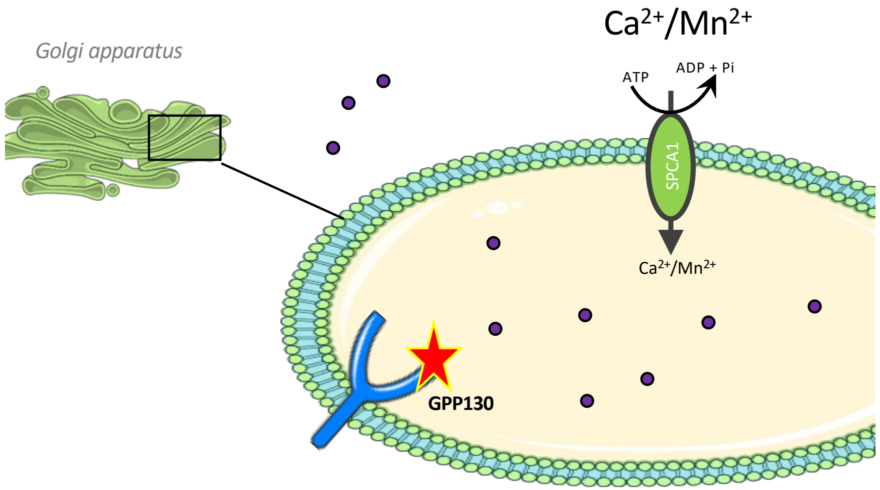
→ Distance between TMEM165 and SPCA1 < 40nm

Use of SPCA1 clones : evidence of their functionality

- GPP130 is sensitive to <u>Golgi luminal</u> manganese concentration



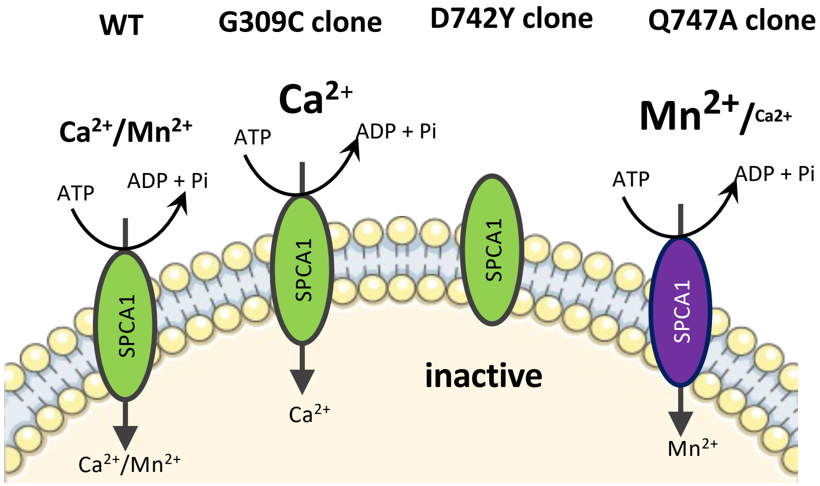


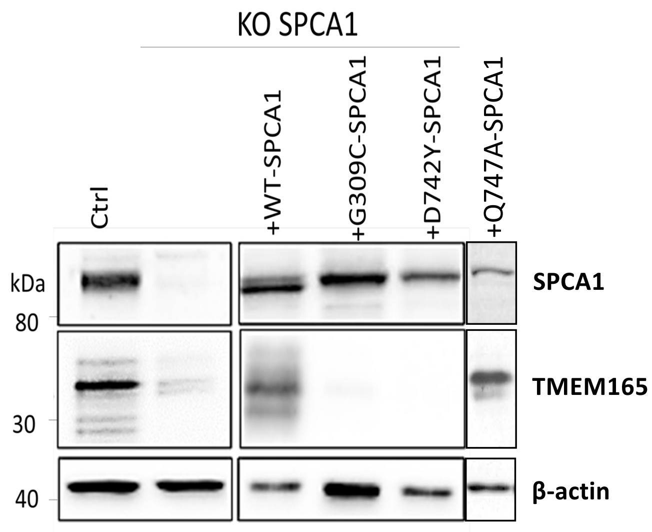


If SPCA1 does not import Mn^{2+}
➘ Golgi [Mn2+]
→ GPP130 is stable

★ manganese sensor sequence localization

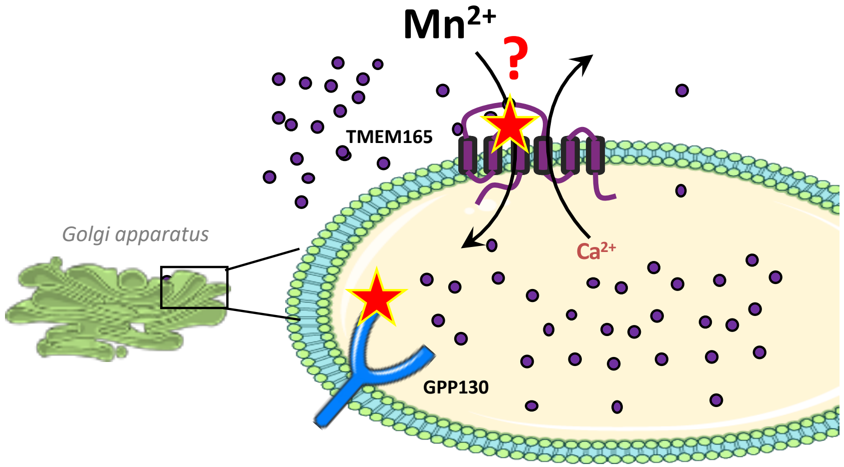
Effect of SPCA1 ion transport on TMEM165 expression in KO SPCA1 cells





→Conclusion article 1 : TMEM165 expression depends on SPCA1 ability to import Mn^{2+} inside the Golgi

Objectives



1) Link between TMEM165 and SPCA1?

- To better understand the role of TMEM165 in the maintenance of Golgi ion homeostasis
- *In fine,* unveal cellular and molecular functions of TMEM165
- Long term : developping new therapeutics

2) What are the amino acids implied in glycosylation function of TMEM165 and manganese sensitivity?

Dissection of TMEM165 function in Golgi glycosylation and its Mn^{2+} sensitivity

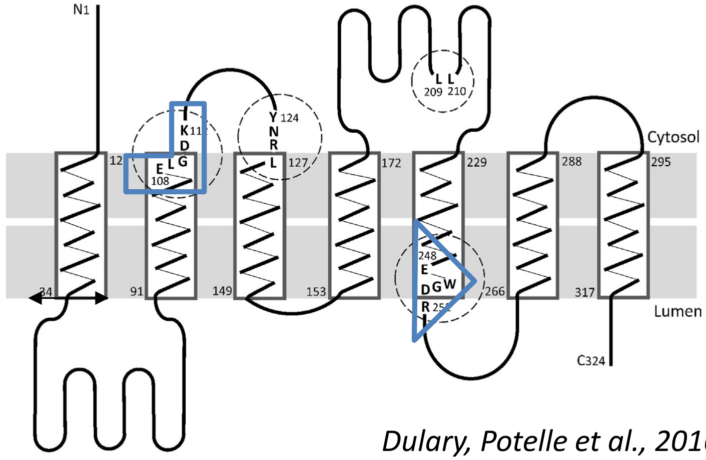
Elodie Lebredonchel[a,b], Marine Houdou[a], Sven Potelle[a], Geoffroy de Bettignies[a], Céline Schulz[a], Marie-Ange Krzewinski Recchi[a], Vladimir Lupashin[c], Dominique Legrand[a], André Klein[a,b], François Foulquier[a,*]

[a]Univ. Lille, CNRS, UMR 8576 – UGSF - Unité de Glycobiologie Structurale et Fonctionnelle, F-59000, Lille, France

[b]Centre de Biologie et Pathologie, UAM de Glycopathologies, Lille Medical Center, University of Lille, 59000, Lille, France

[c]Department of Physiology and Biophysics, College of Medicine, University of Arkansas for Medical Sciences, Biomed 261-2, Slot 505, 200 South Cedar St., Little Rock, AR, 72205, USA

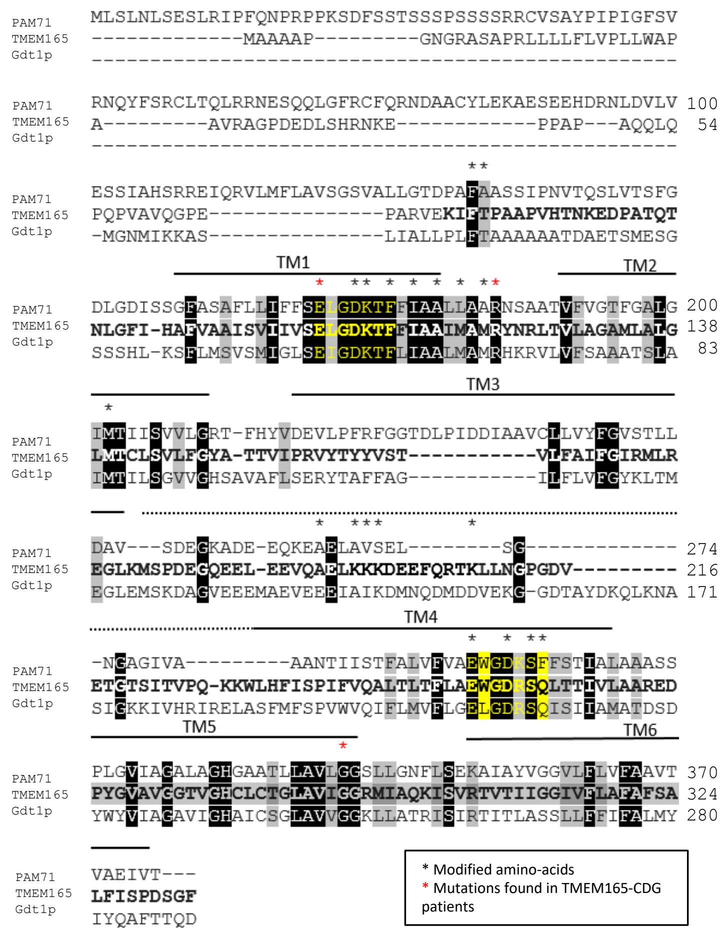
TMEM165 structure



Dulary, Potelle et al., 2016

- 324 AA
- 6 or 7 transmembrane domains
- Highly conserved throughout evolution
- Especially two domains
  - E-x-G-D-K-[TF] and E-x-G-D-R-[SQ]
  - Signature motifs of UPF16 (**U**ncharacterized **P**rotein **F**amily UPF0016)

Sequences alignment



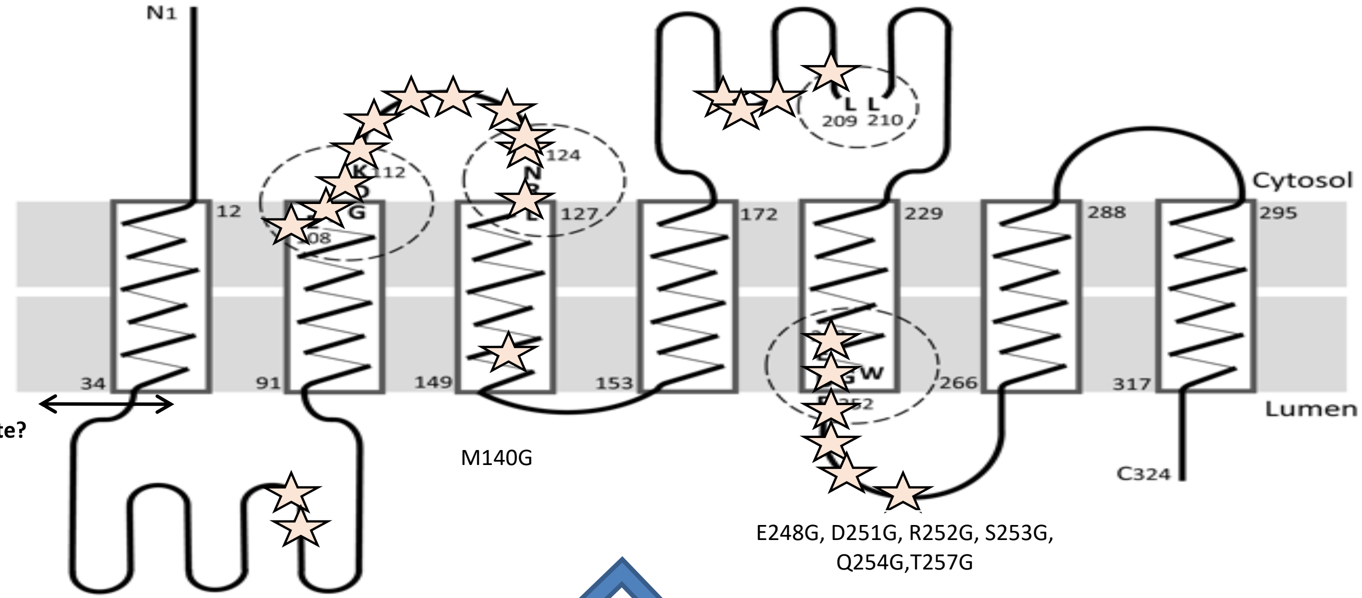
Uncover the AA implied in TMEM165 function and/or manganese-induced sensitivity

- **Method**

☆ Mutation

E108G, D111G, K112G, T113G, F114G, I116G, M120G, M122G, R123G, Y124G, R126G

K198R, K199R, K200R, K198-200R, K208R



Cleavage site?

M140G

E248G, D251G, R252G, S253G, Q254G,T257G

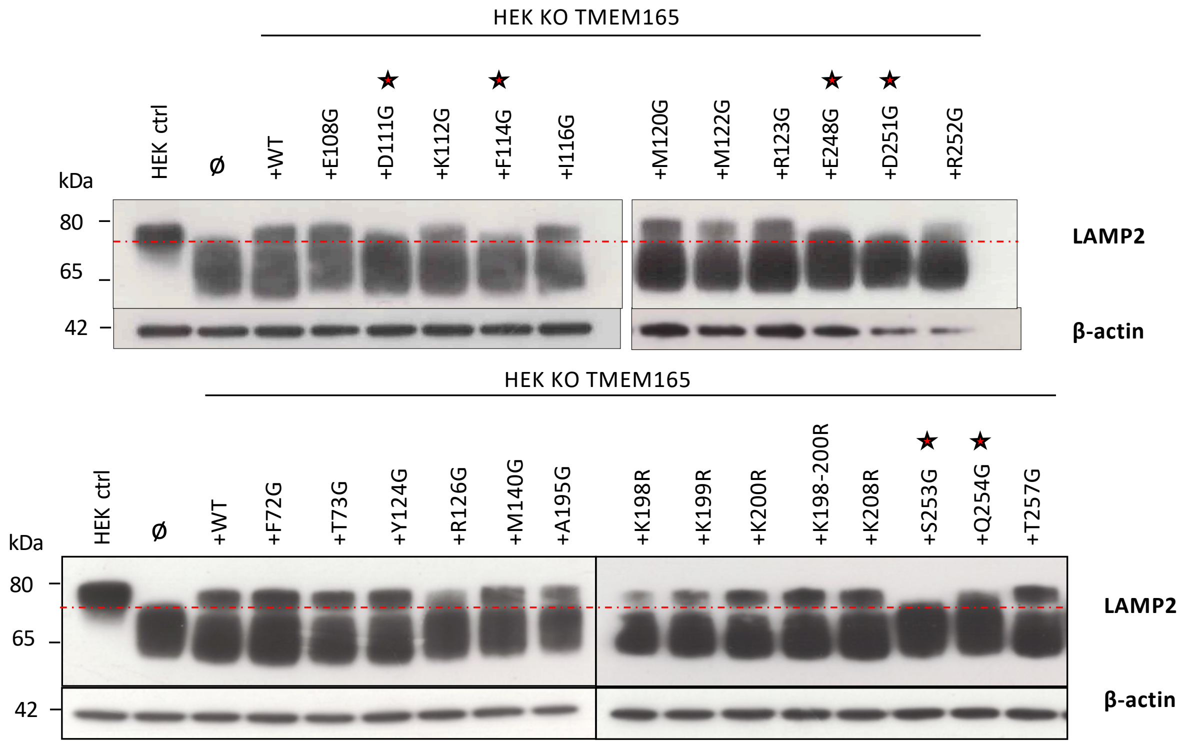
F72G, T73G

1) Role in glycosylation?

2) Role in manganese sensivity?

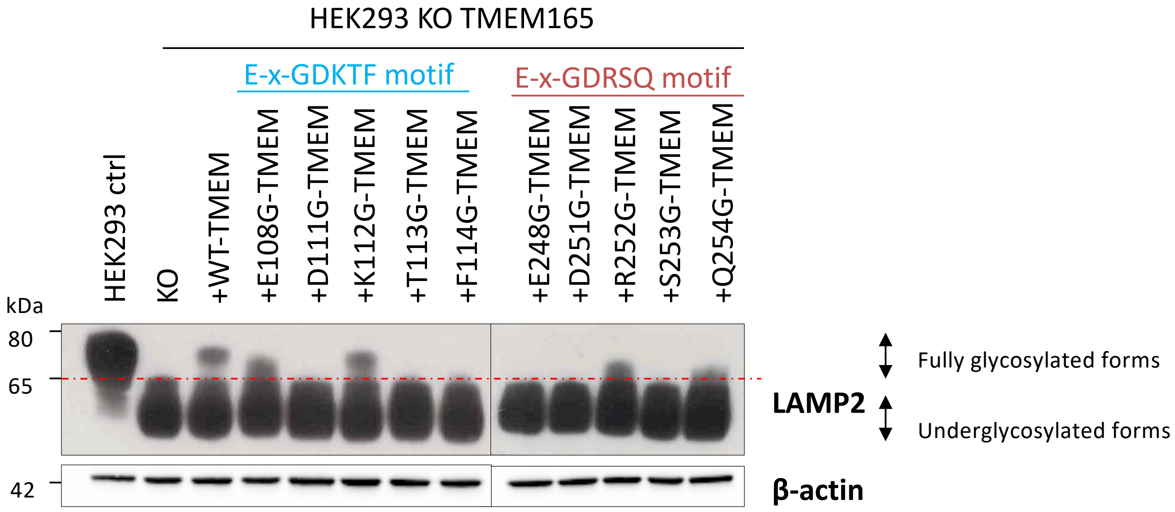
- Study of LAMP2 profile for each mutants
- Stability of TMEM165 after Mn^{2+} supplementation

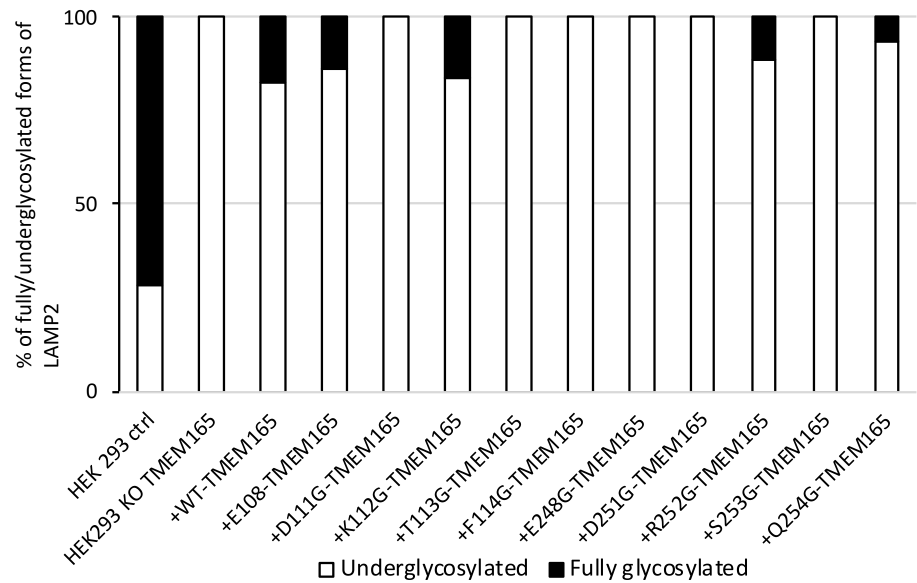
Mutants glycosylation study



→Mutants unable to restore glycosylation seem more likely localized in the 2 conserved sequences.

Glycosylation study of TMEM165 mutants in ExGDKTF and E xGDRSQ sequences



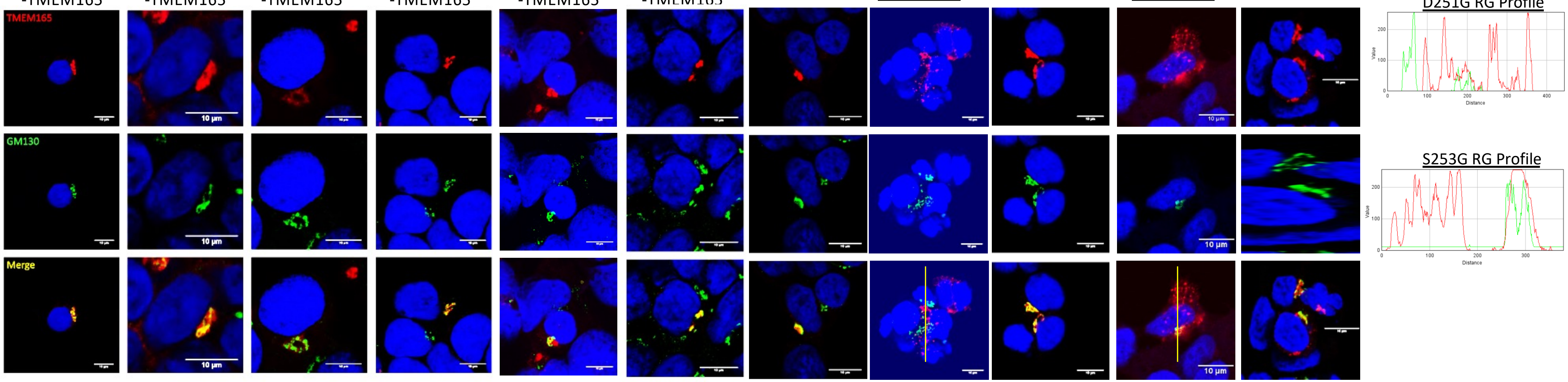


→Almost all unable to restore fully glycosylated forms of LAMP2

Mutants subcellular localization

E-x-GDKTF motif | E-x-GDRSQ motif

WT -TMEM165 | E108G -TMEM165 | D111G -TMEM165 | K112G -TMEM165 | T113G -TMEM165 | F114G -TMEM165 | E248G -TMEM165 | **D251G -TMEM165** | R252G -TMEM165 | **S253G -TMEM165** | Q254G -TMEM165

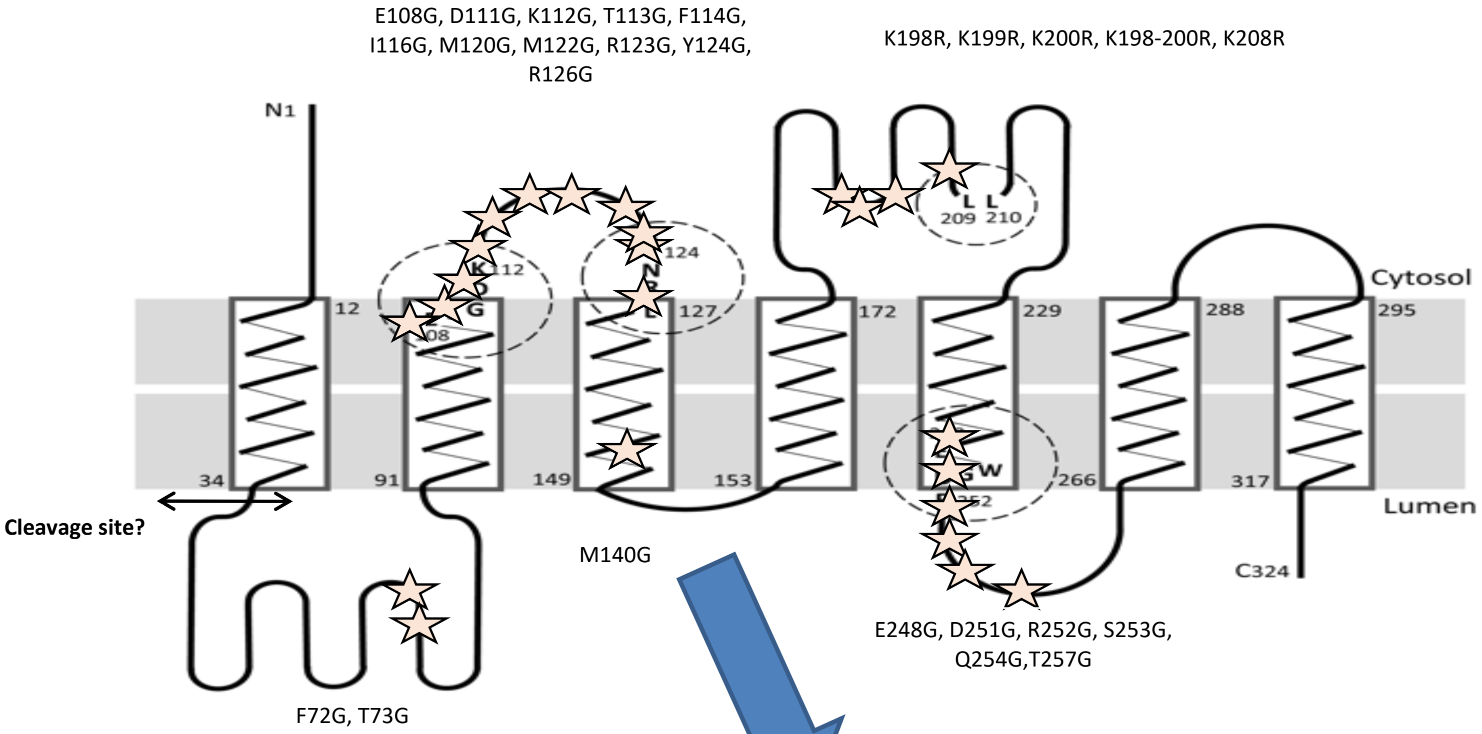


Scale bar : 10µm

→Every mutant is Golgi localized except D251 and S253 that are lysosomal

Uncover the AA implied in TMEM165 function and manganese-induced sensitivity

☆ Mutation

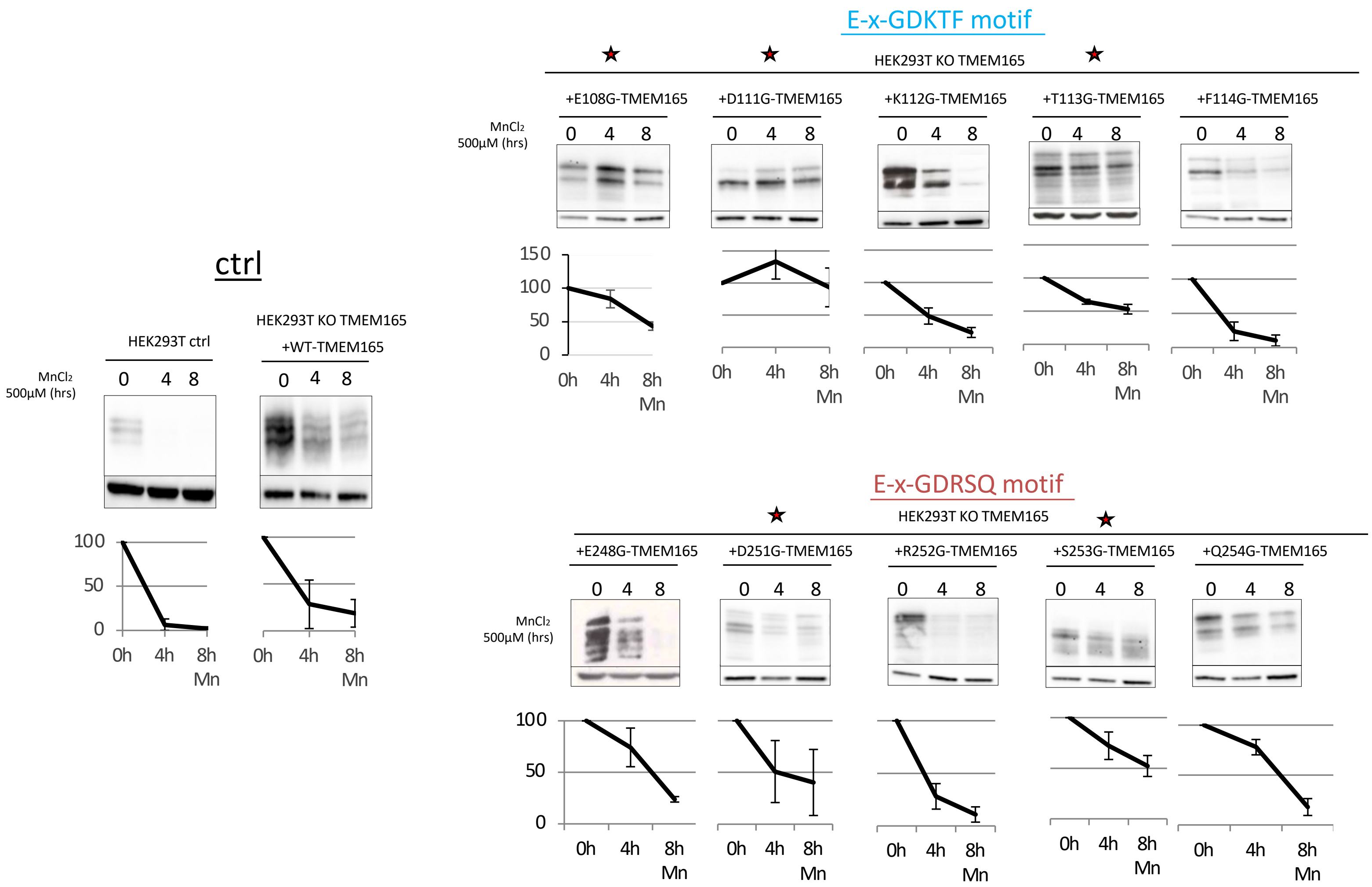


1) Role in glycosylation?

2) Role in manganese sensivity?

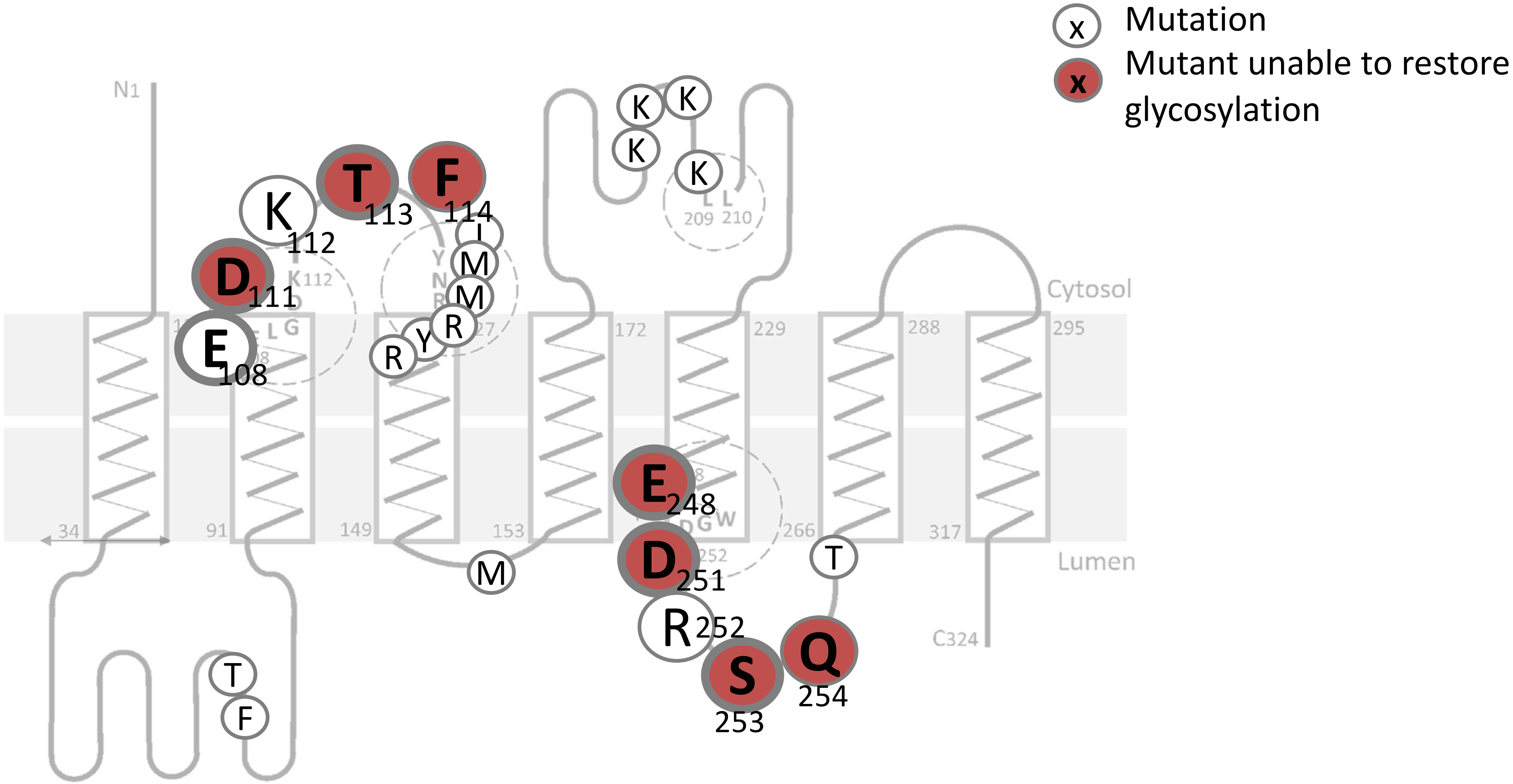
- Study of LAMP2 profile for each mutants
- Stability of TMEM165 after Mn^{2+} supplementation

Manganese sensitivity study



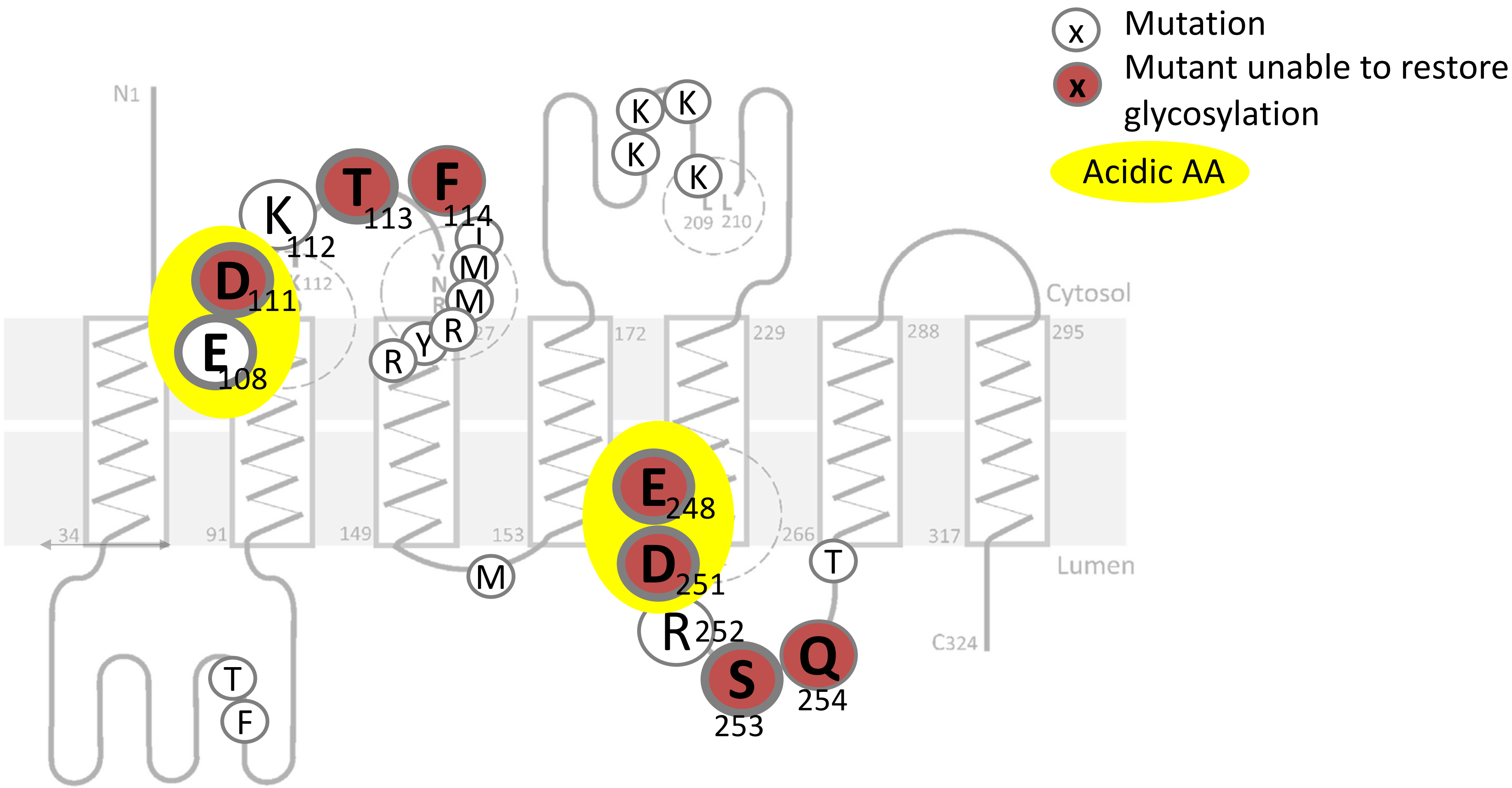
→Some mutants present a partial resistance to manganese-induced degradation

- **Summary**



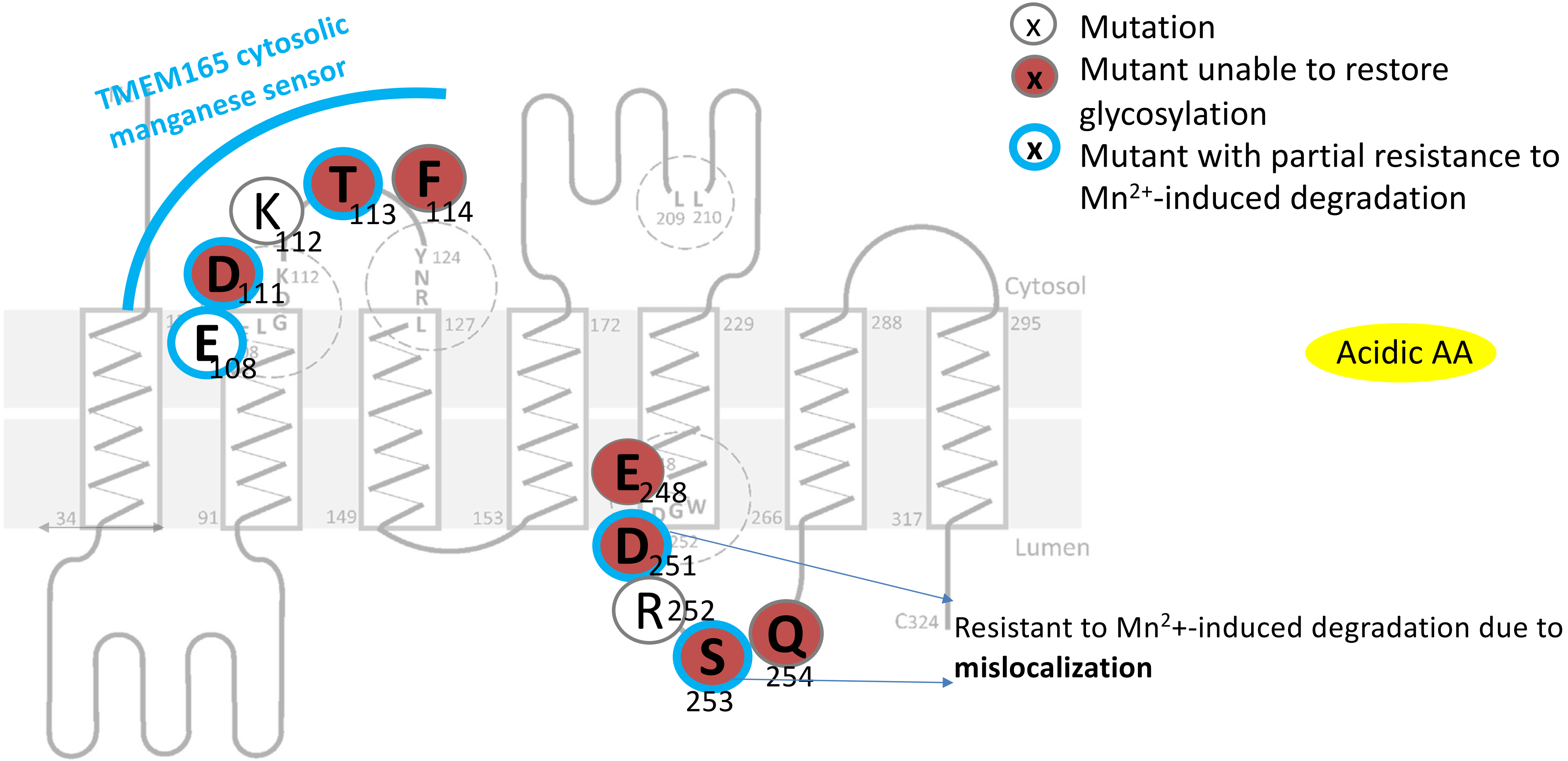
1^{st} **observation** : mutants unable to **restore glycosylation** are more likely to be localized in the 2 signatures motifs

- **Summary**



The 2 signatures motifs contains acidic AA (E/D) → cation binding site
Role in cation affinity or pocket conformation change

- **Summary**



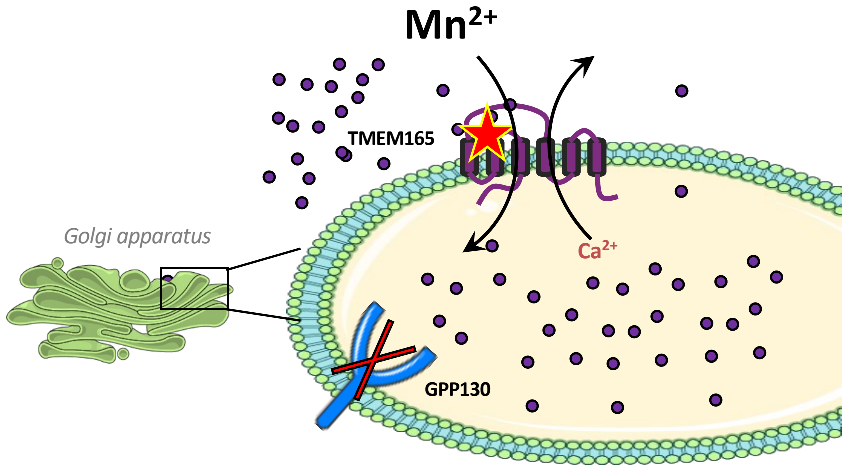
→ **1st motif : governs Golgi ion homeostasis**

Conclusions (1)

Identification of :

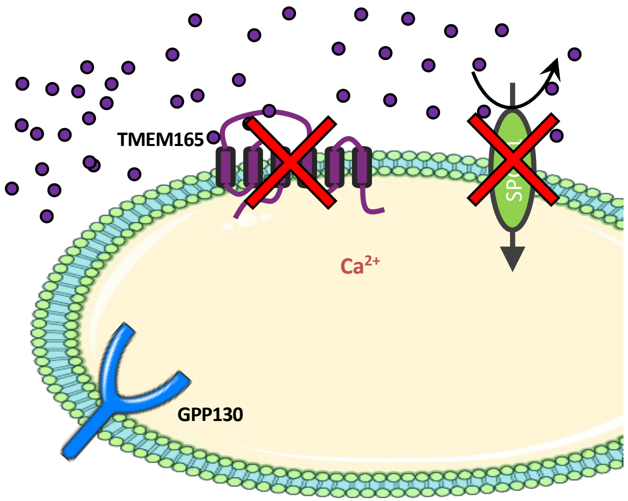
- the key domains for the function of TMEM165 in glycosylation
- the AA implicated in the manganese sensitivity of TMEM165

→ TMEM165 is a cytosolic manganese sensor



Consistent with previous statements:

- TMEM165 Mn^{2+} sensitivity is confered by AA between AA number 69 and 172 (Potelle et al., 2017)
- GPP130 Mn^{2+} -induced degradation is affected by the absence of SPCA1 (BJ, 2019)
- GPP130 Mn^{2+} -induced degradation is affected by the absence of TMEM165 (Potelle et al., 2016)
- TMEM165 degradation is not affected by the depletion of GPP130



Conclusions (2)

There is a functionnal link between TMEM165 and SPCA1

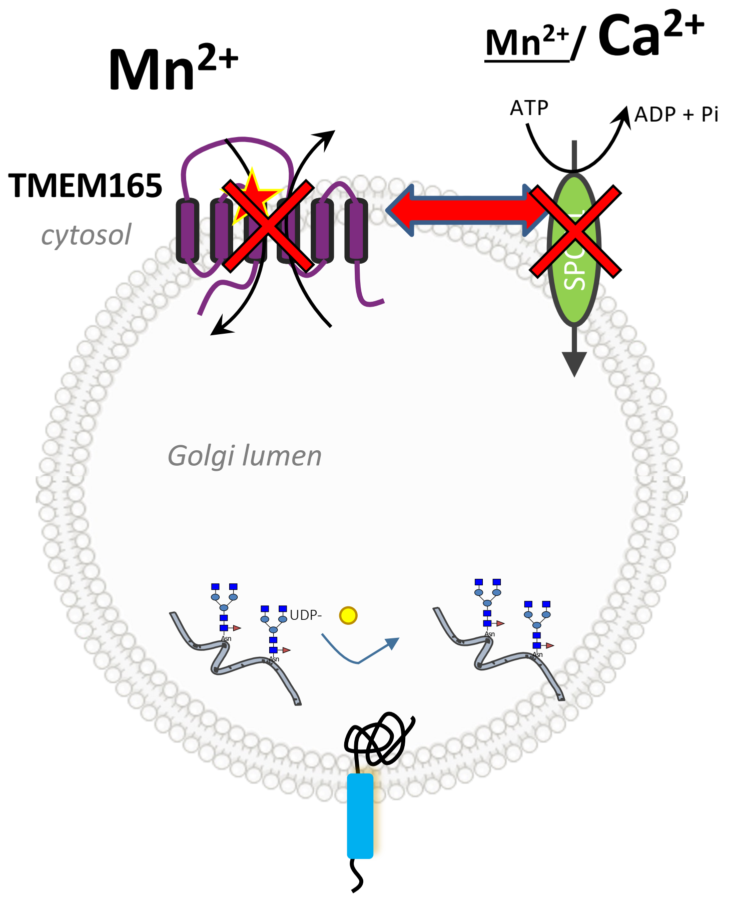
→ First evidence of a link between these two proteins

→ TMEM165 presence depends on **the ability of SPCA1 to import manganese**

→ No glycosylation defect in the absence of SPCA1

→ Glycosylation defect in the absence of TMEM165

→ TMEM165 **one major manganese importer** in the Golgi apparatus in humans



Discussion

Recent findings opening up on the nature of the counterion

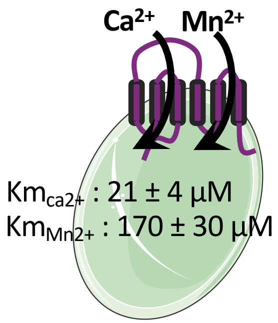
Ca^{2+} arguments

- Phylogeny : functions of yeast, plant orthologs
- Signature motifs are symetric and conserved

→ Sens?

- Truncated forms of TMEM165 transfected

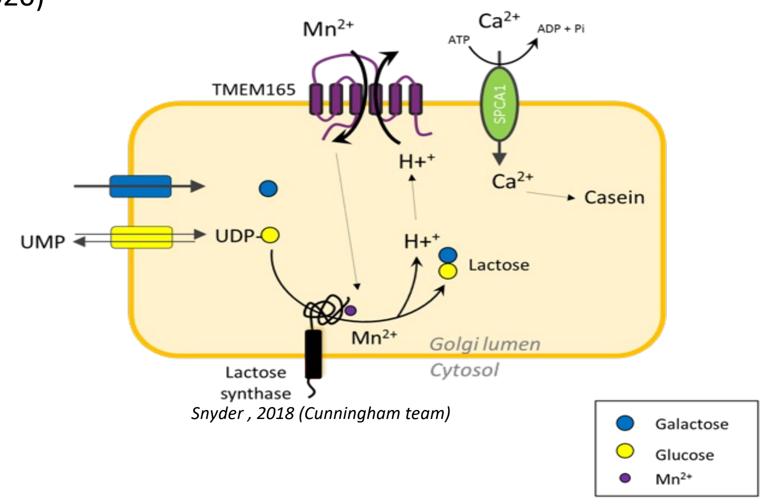
in bacteria → Km Ca^{2+} = ++ (Stribny, 2020)



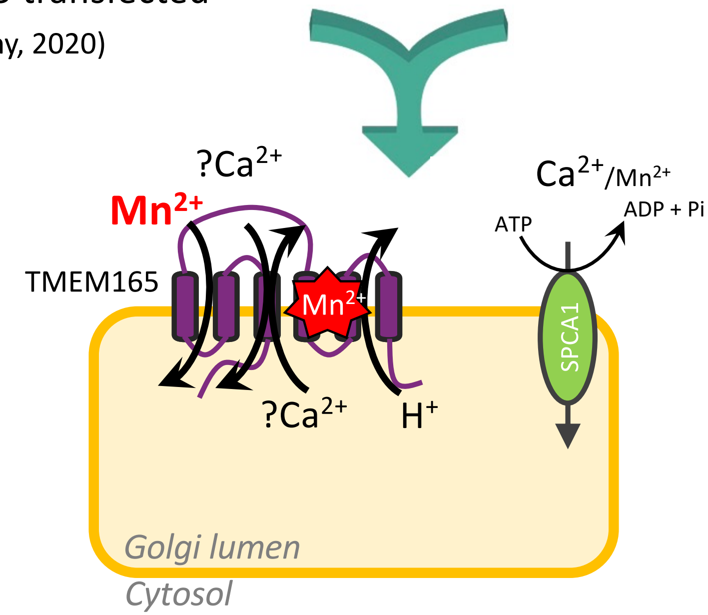
Stribny, 2020 (Morsomme team)

H^+ arguments

- Mammary cells TMEM165x25 → export H^+ (Snyder, 2018)
- Decrease of Golgi pH in TMEM165 depleted cells (Wang, 2020)



Snyder , 2018 (Cunningham team)



This undeniable link *between* TMEM165 and manganese lead us to consider manganese as a supplementation therapy for TMEM165-CDG patient.

2017-2019

Publications

- **Dissection of TMEM165 function in Golgi glycosylation and its Mn^{2+} sensitivity**

Lebredonchel, E., Houdou, M., Potelle, S., de Bettignies, G., Schulz, C., Krzewinski Recchi, M.-A., Lupashin, V., Legrand, D., Klein, A., and Foulquier, F. (2019) Biochimie *165*, 123–130.

- **Investigating the functional link between TMEM165 and SPCA1**

Lebredonchel, E.*, Houdou, M.*, Hoffmann, H.-H., Kondratska, K., Krzewinski, M.-A., Vicogne, D., Rice, C.M., Klein, A., and Foulquier, F. (2019) Biochem. J. *476*, 3281–3293.

- **Involvement of thapsigargin and cyclopiazonic acid sensitive pumps in the rescue of TMEM165-associated glycosylation defects by Mn^2**

Houdou, M., Lebredonchel, E., Garat, A., Duvet, S., Legrand, D., Decool, V., Klein, A., Ouzzine, M., Gasnier, B., Potelle, S., et al. (2019) FASEB J. *33*, 2669–2679.

- **Manganese-induced turnover of TMEM165**

Potelle, S., Dulary, E., Climer, L., Duvet, S., Morelle, W., Vicogne, D., Lebredonchel, E., Houdou, M., Spriet, C., Krzewinski-Recchi, M.-A., et al. (2017) Biochem. J. *474*, 1481–1493.

> 2019

- **Efficacy of oral manganese and D-galactose therapy in a patient bearing a novel TMEM165 variant.**

Durin Z, Raynor A, Fenaille F, Cholet S, Vuillaumier-Barrot S, Alili JM, Poupon J, Oussedik ND, Tuchmann-Durand C, Attali J, Touzé R, Dupré T, Lebredonchel E, Akaffou MA, Legrand D, de Lonlay P, Bruneel A, Foulquier F.Transl Res. 2024 Apr;266:57-67. doi: 10.1016/j.trsl.2023.11.005. Epub 2023 Nov 25.PMID: 38013006

- **New insights into the pathogenicity of TMEM165 variants using structural modeling based on AlphaFold 2 predictions.**

Legrand D, Herbaut M, Durin Z, Brysbaert G, Bardor M, Lensink MF, Foulquier F.Comput Struct Biotechnol J. 2023 Jun 17;21:3424-3436. doi: 10.1016/j.csbj.2023.06.015. eCollection 2023.PMID: 37416081

- **Insights into the regulation of cellular Mn(2+) homeostasis via TMEM165.**

Vicogne D, Beauval N, Durin Z, Allorge D, Kondratska K, Haustrate A, Prevarskaya N, Lupashin V, Legrand D, Foulquier F.Biochim Biophys Acta Mol Basis Dis. 2023 Aug;1869(6):166717. doi: 10.1016/j.bbadis.2023.166717. Epub 2023 Apr 14. PMID: 37062452

- **Differential Effects of D-Galactose Supplementation on Golgi Glycosylation Defects in TMEM165 Deficiency.**

Durin Z, Houdou M, Morelle W, Barré L, Layotte A, Legrand D, Ouzzine M, Foulquier F.Front Cell Dev Biol. 2022 May 26;10:903953. doi: 10.3389/fcell.2022.903953. eCollection 2022.PMID: 35693943

- **TMEM165 a new player in proteoglycan synthesis: loss of TMEM165 impairs elongation of chondroitin- and heparan-sulfate glycosaminoglycan chains of proteoglycans and triggers early chondrocyte differentiation and hypertrophy.**

Khan S, Sbeity M, Foulquier F, Barré L, Ouzzine M.Cell Death Dis. 2021 Dec 20;13(1):11. doi: 10.1038/s41419-021-04458-1.PMID: 34930890

- **Biometals and glycosylation in humans: Congenital disorders of glycosylation shed lights into the crucial role of Golgi manganese homeostasis.**

Foulquier F, Legrand D.Biochim Biophys Acta Gen Subj. 2020 Oct;1864(10):129674. doi: 10.1016/j.bbagen.2020.129674. Epub 2020 Jun 26.PMID: 32599014

- **SPCA1 governs the stability of TMEM165 in Hailey-Hailey disease.**

Roy AS, Miskinyte S, Garat A, Hovnanian A, Krzewinski-Recchi MA, Foulquier F.Biochimie. 2020 Jul;174:159-170. doi: 10.1016/j.biochi.2020.04.017. Epub 2020 Apr 23.PMID: 32335229

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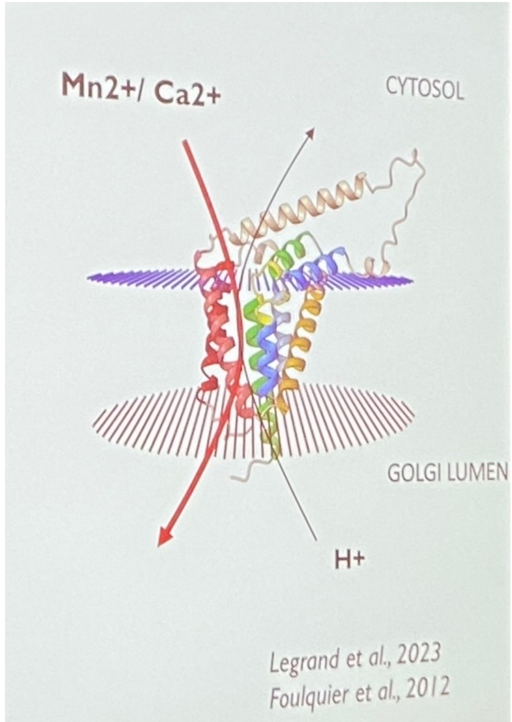
Research Article

New insights into the pathogenicity of TMEM165 variants using structural modeling based on AlphaFold 2 predictions

Dominique Legrand [a], Mélissandre Herbaut [a], Zoé Durin [a], Guillaume Brysbaert [a], Muriel Bardor [a,b], Marc F. Lensink [a], François Foulquier [a,*]

[a] Univ. Lille, CNRS, UMR 8576 – UGSF - Unité de Glycobiologie Structurale et Fonctionnelle, F-59000 Lille, France
[b] Université de Rouen Normandie, Laboratoire GlycoMEV UR 4358, SFR Normandie Végétal FED 4277, Innovation Chimie Carnot, F-76000 Rouen, France



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Efficacy of oral manganese and D-galactose therapy in a patient bearing a novel TMEM165 variant

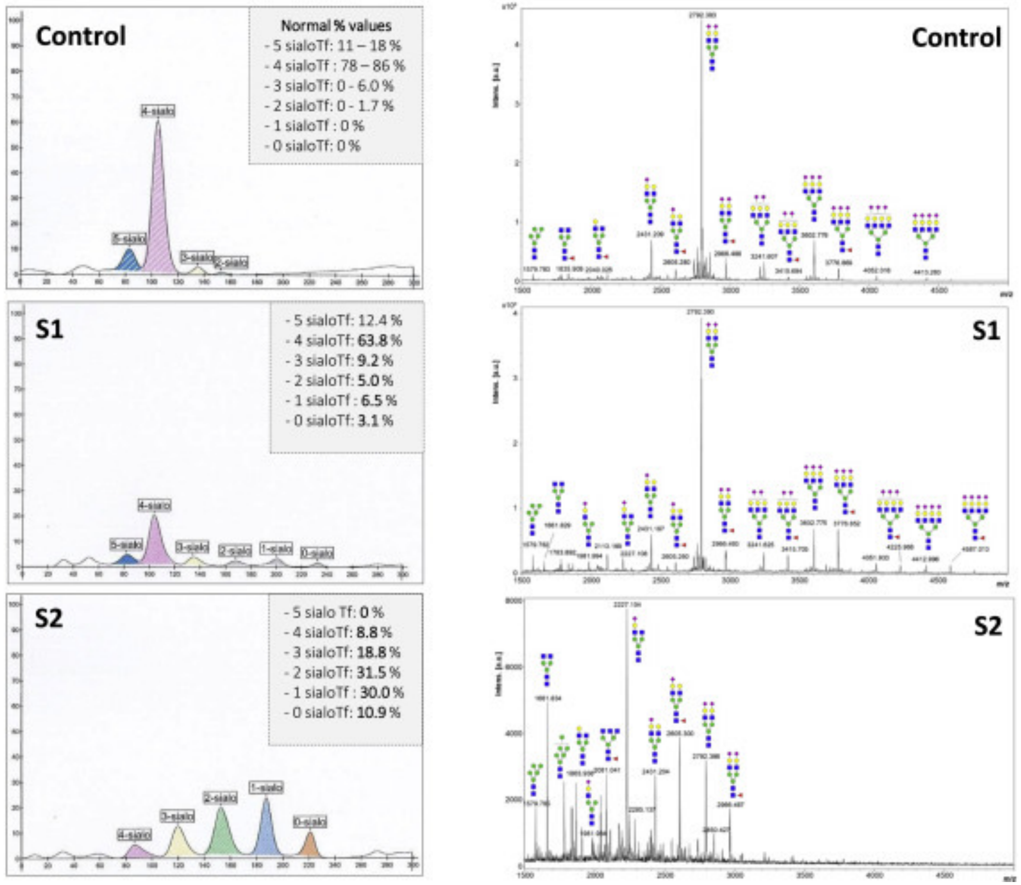
Zoé Durin[a,1], Alexandre Raynor[b,1], François Fenaille[c], Sophie Cholet[c], Sandrine Vuillaumier-Barrot[b,d], Jean-Meidi Alili[e], Joël Poupon[f], Nouzha Djebrani Oussedik[f], Caroline Tuchmann-Durand[g], Jennifer Attali[h], Romain Touzé[i], Thierry Dupré[b], Elodie Lebredonchel[b], Marlyse Angah Akaffou[b], Dominique Legrand[a], Pascale de Lonlay[e,j,2,***], Arnaud Bruneel[b,k,2,**], François Foulquier[a,2,*]

A

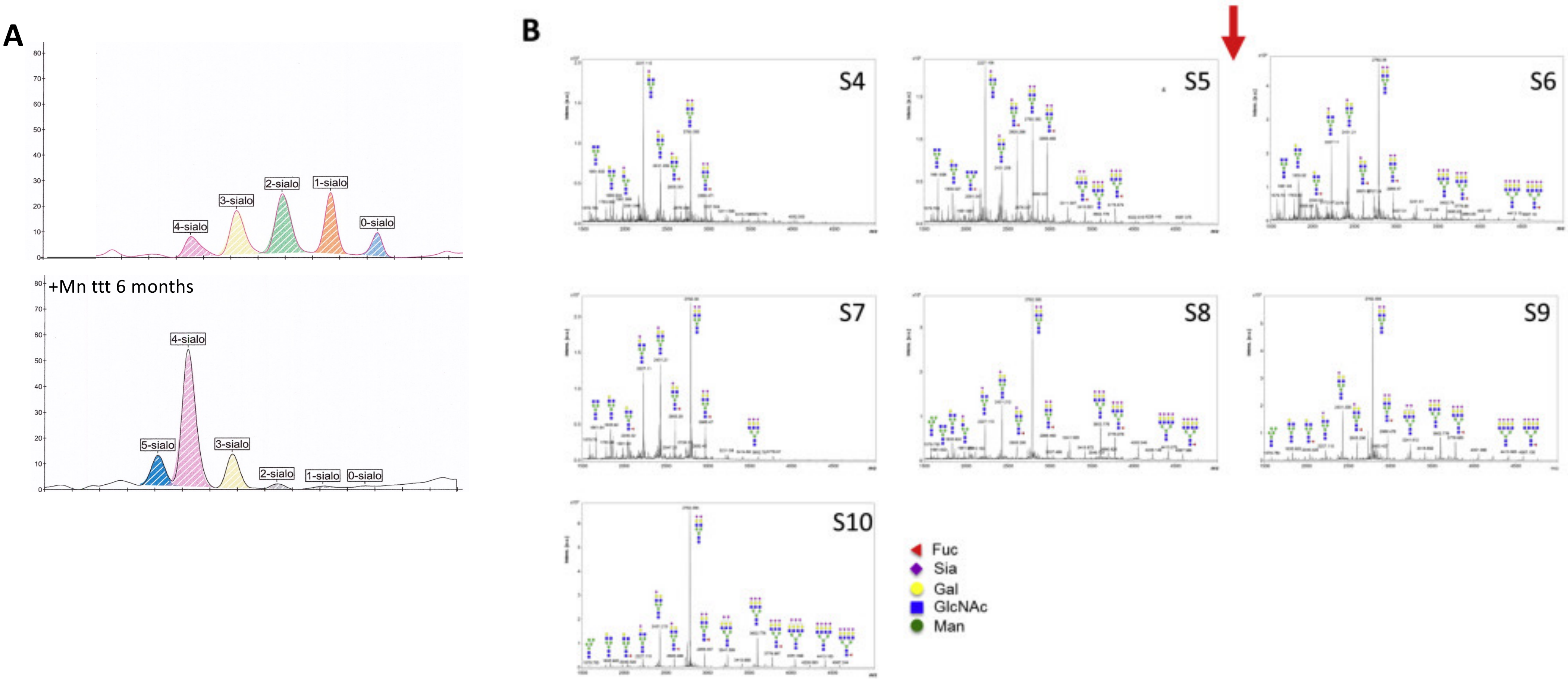
B

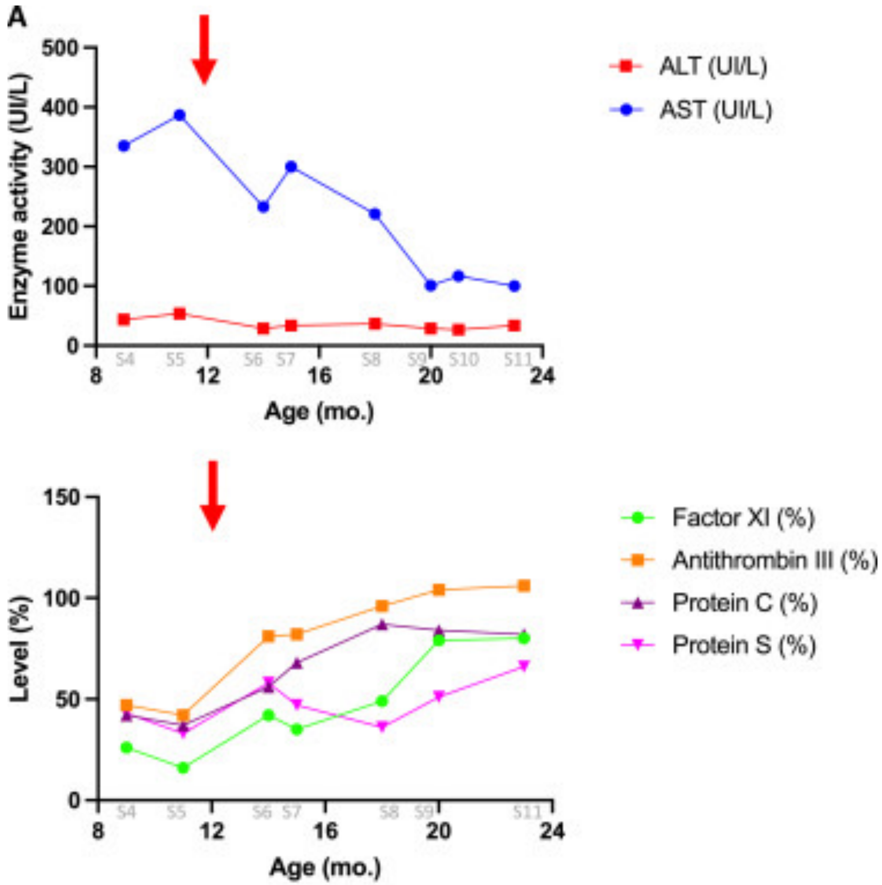
C

D



- Mn2+ supplementation from 2 mg/day to 10 mg/Kg/day.
- D-Galactose (D-Gal, magistral preparation) from 4 g to 12g/day.




A
Enzyme activity (UI/L)
500
400
300
200
100
0
S4 S5 S6 S7 S8 S9 S10 S11
8 12 16 20 24
Age (mo.)
ALT (UI/L)
AST (UI/L)
Level (%)
150
100
50
0
S4 S5 S6 S7 S8 S9 S11
8 12 16 20 24
Age (mo.)
Factor XI (%)
Antithrombin III (%)
Protein C (%)
Protein S (%)

Acknowledgements

UGSF 020 Team

Dr. François Foulquier
Dr. André Klein

Dr. Geoffroy de Bettignies
Dr. Sandrine Duvet
Dr. Marie-Ange Krzewinski
Dr. Dominique Legrand
Pr. Willy Morelle
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