iBioSeminars: Part 3
Protein secretion and human disease

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Mutations in a Sar1 GTPase of COPII vesicles are associated with lipid absorption disorders

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Dietary fat is an important source of nutrition. Here we identify eight mutations in *SARA2* that are associated with three severe disorders of fat malabsorption. The Sar1 family of proteins initiates the intracellular transport of proteins in COPII (coat protein)-coated vesicles. Our data suggest that chylomicrons, which vastly exceed the size of typical COPII vesicles, are selectively recruited by the COPII machinery for transport through the secretory pathways of the cell.

g

a
b
c
d
e
f

CLSD mutation: Alignment with yeast sequence and structure

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SEC23A   TGGYMVMGDSFNTSLFKQTFQRVFTKDMHGQFKMGF
SEC23B   TGGYMVMGDSFNTSLFKQTFQRIFTKDFNGDFRMAF
Sec23p   TGGVLLLTDAFSTAIFKQSYLRLFAKDEEGYLKMAF
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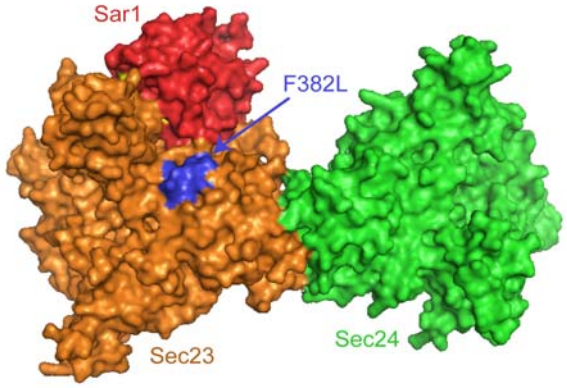
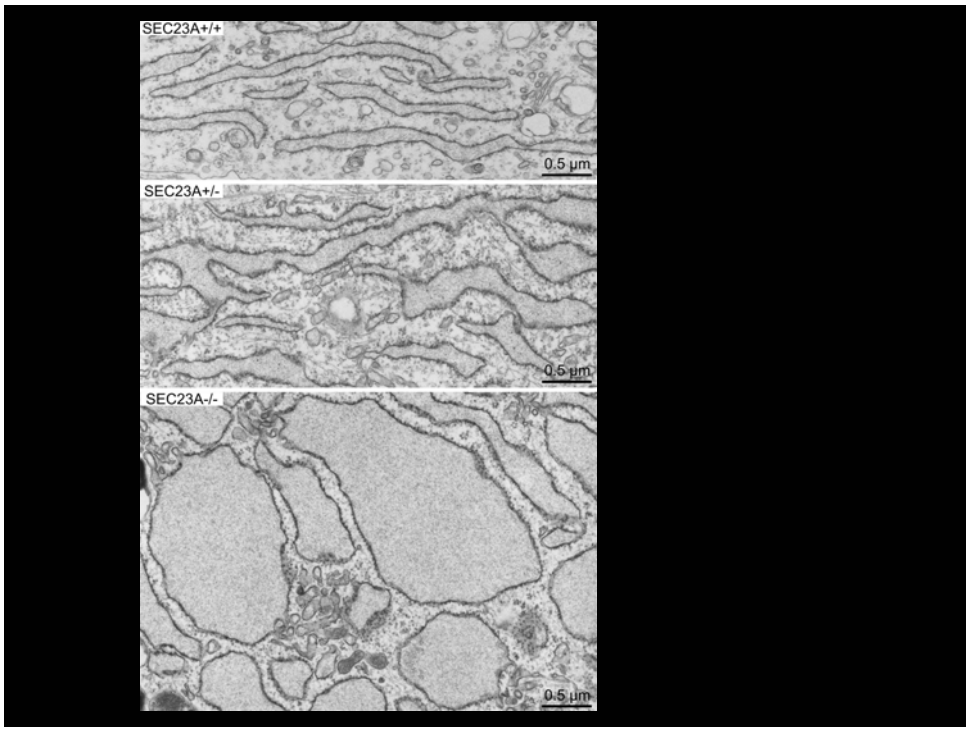
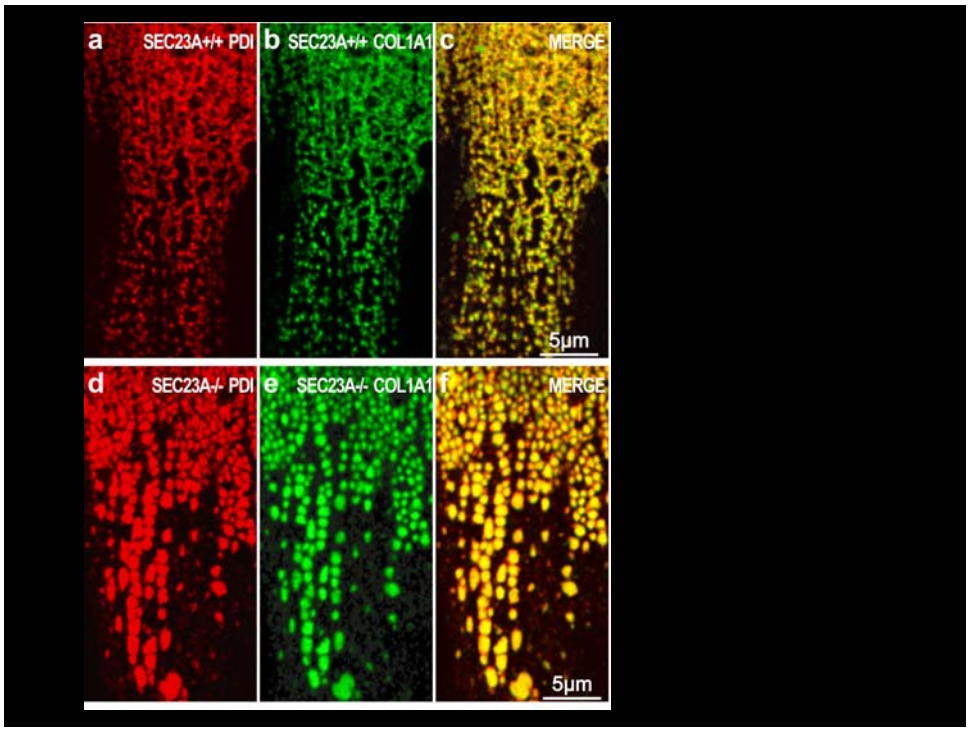
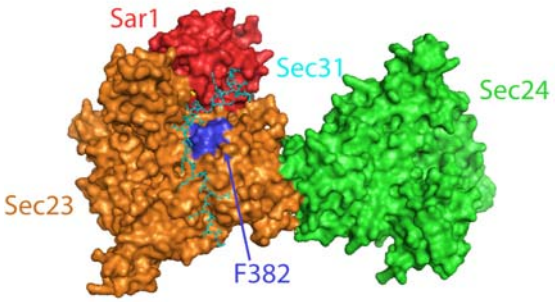
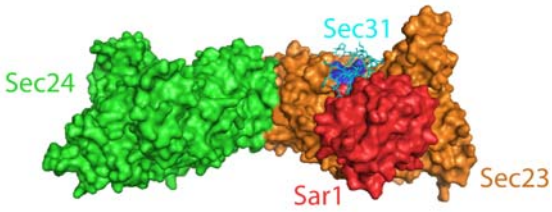



SEC23A+/+
0.5 µm
SEC23A+/-
0.5 µm
SEC23A-/-
0.5 µm

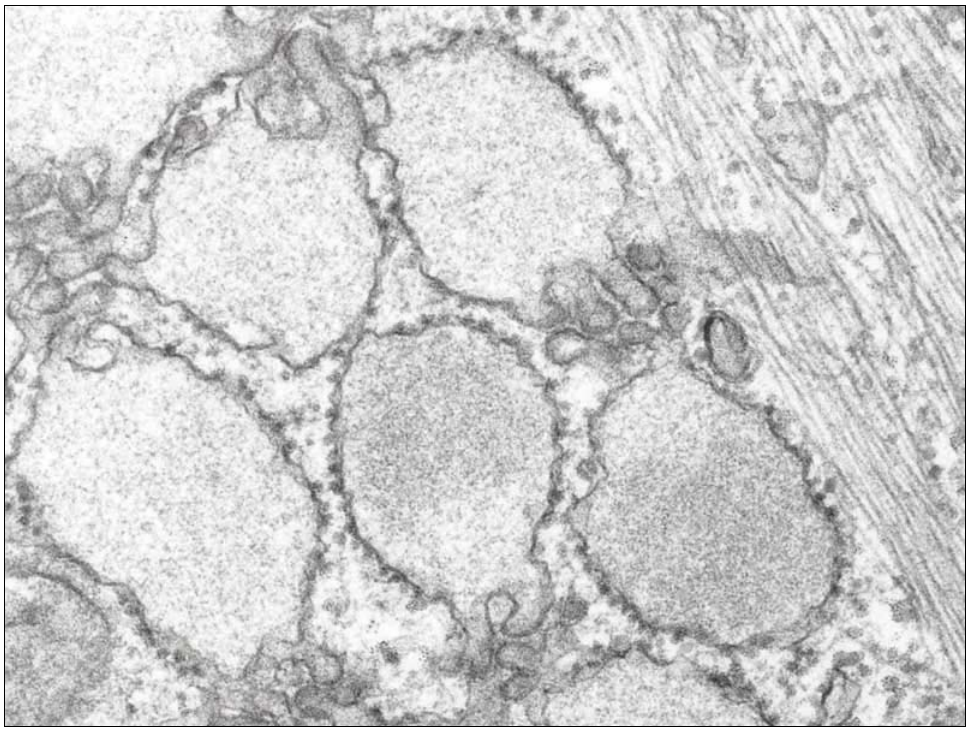

a SEC23A+/+ PDI
b SEC23A+/+ COL1A1
c MERGE
5μm
d SEC23A-/- PDI
e SEC23A-/- COL1A1
f MERGE
5μm



Membrane surface view of Sec31 in proximity to the F382 residue of SEC23A

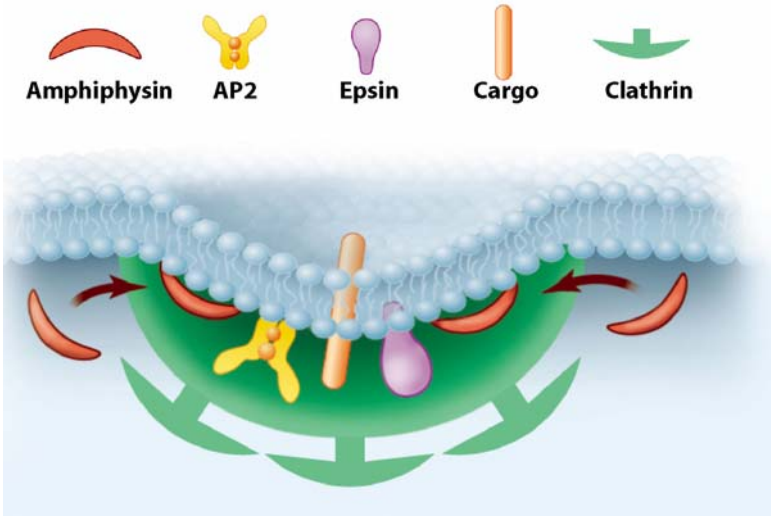


Lateral view

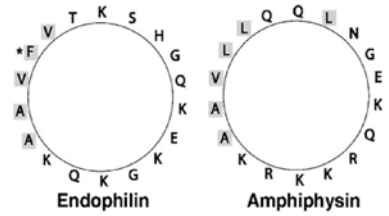


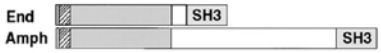
ER exit sites in mut. 23A, #2

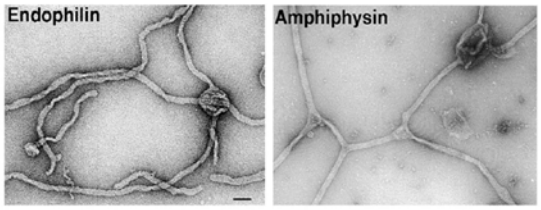
Endocytosis



Amphipathic helices promote membrane curvature

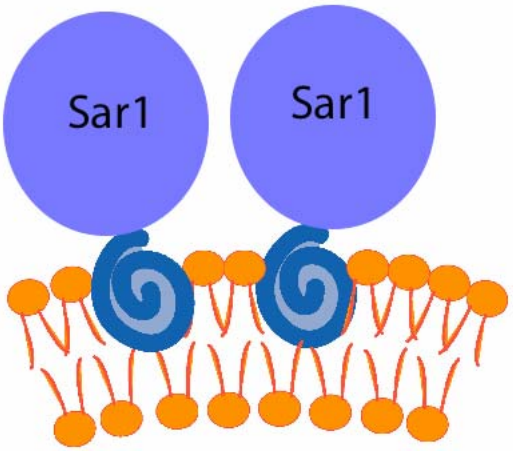


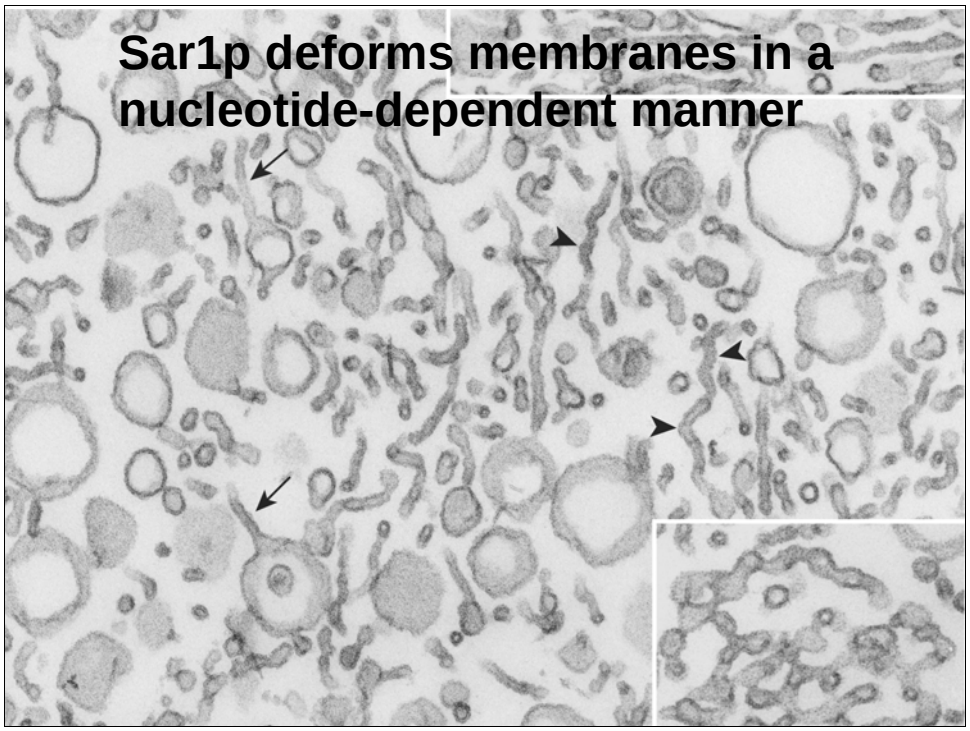




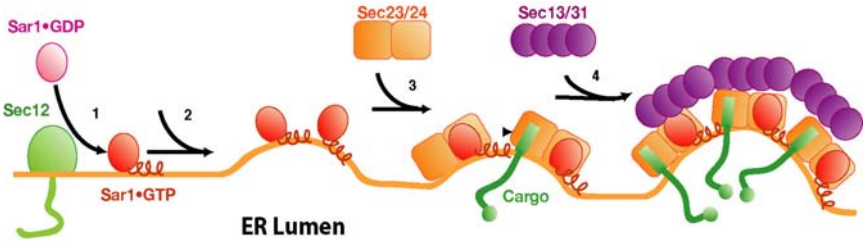
Farsad, K. et al, J Cell Biol (2001)

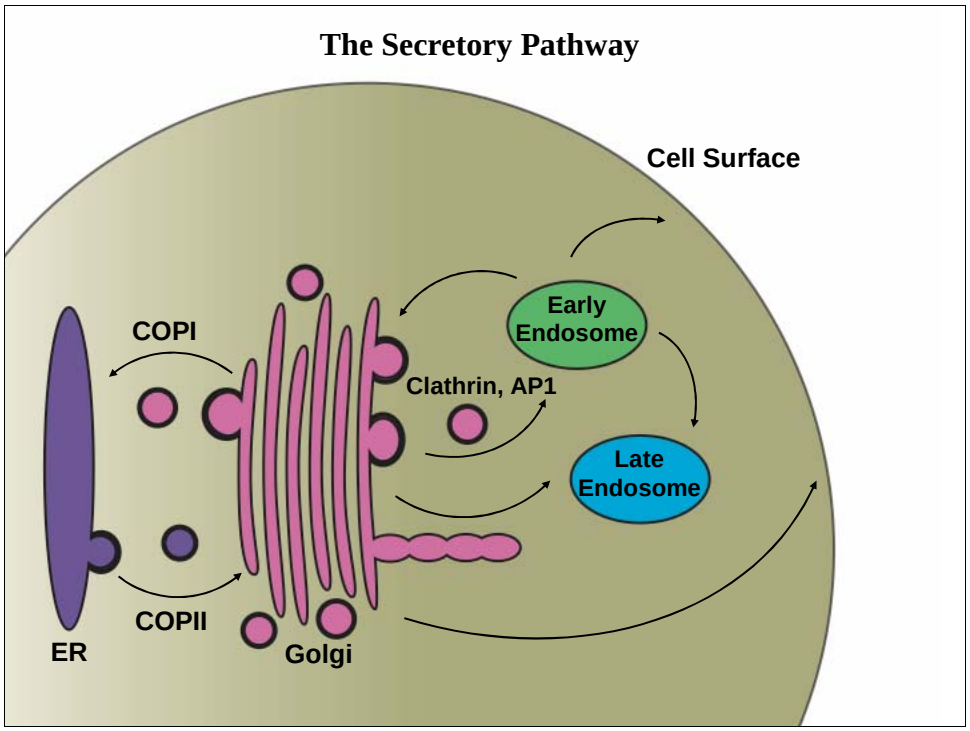
Membrane curvature generated by asymmetric expansion of outer leaflet




Sar1p deforms membranes in a nucleotide-dependent manner

Revised model of how COPII - Sar1p initiates budding




The Secretory Pathway
Cell Surface
Early Endosome
COPI
Clathrin, AP1
Late Endosome
COPII
ER
Golgi