Figure 1

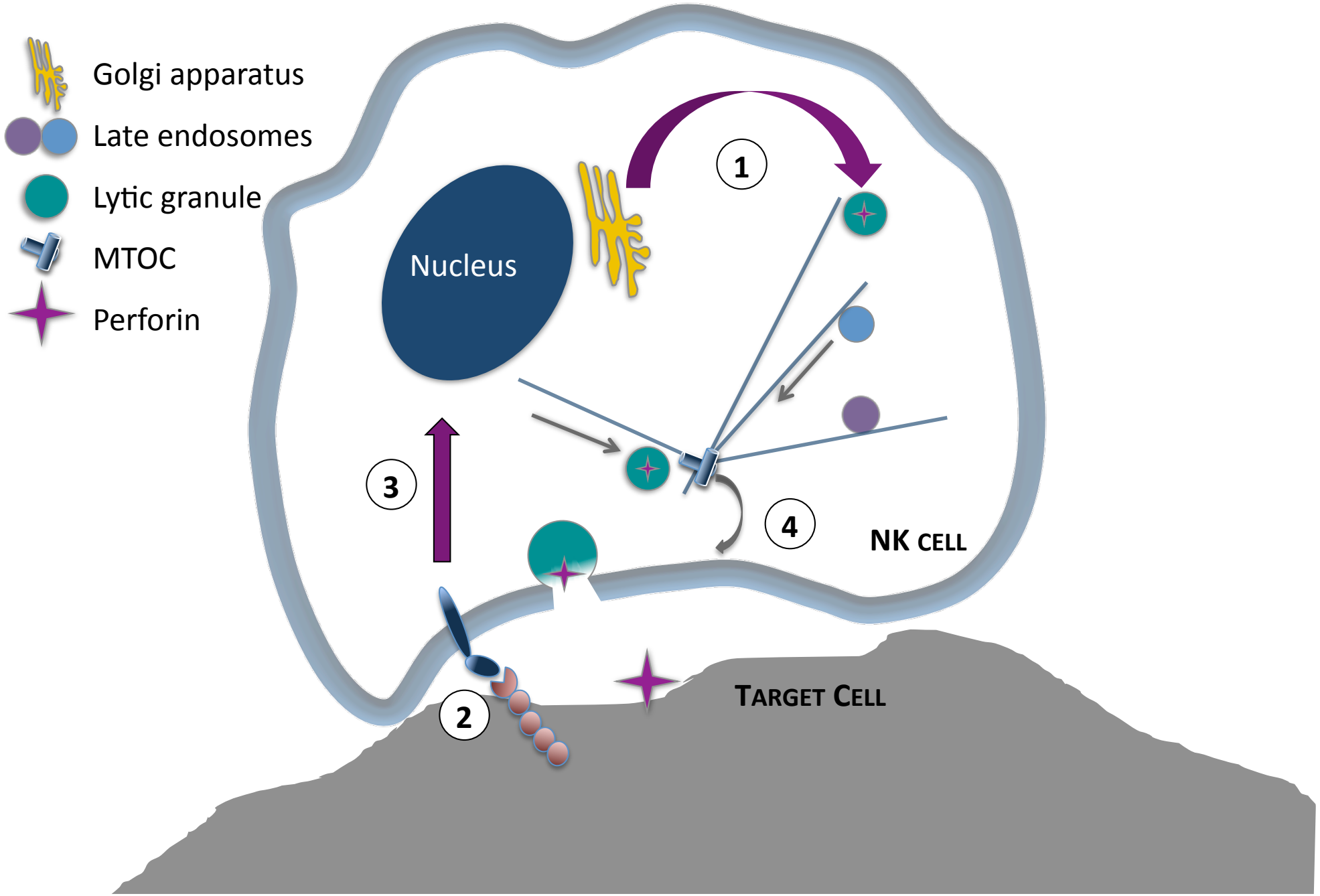
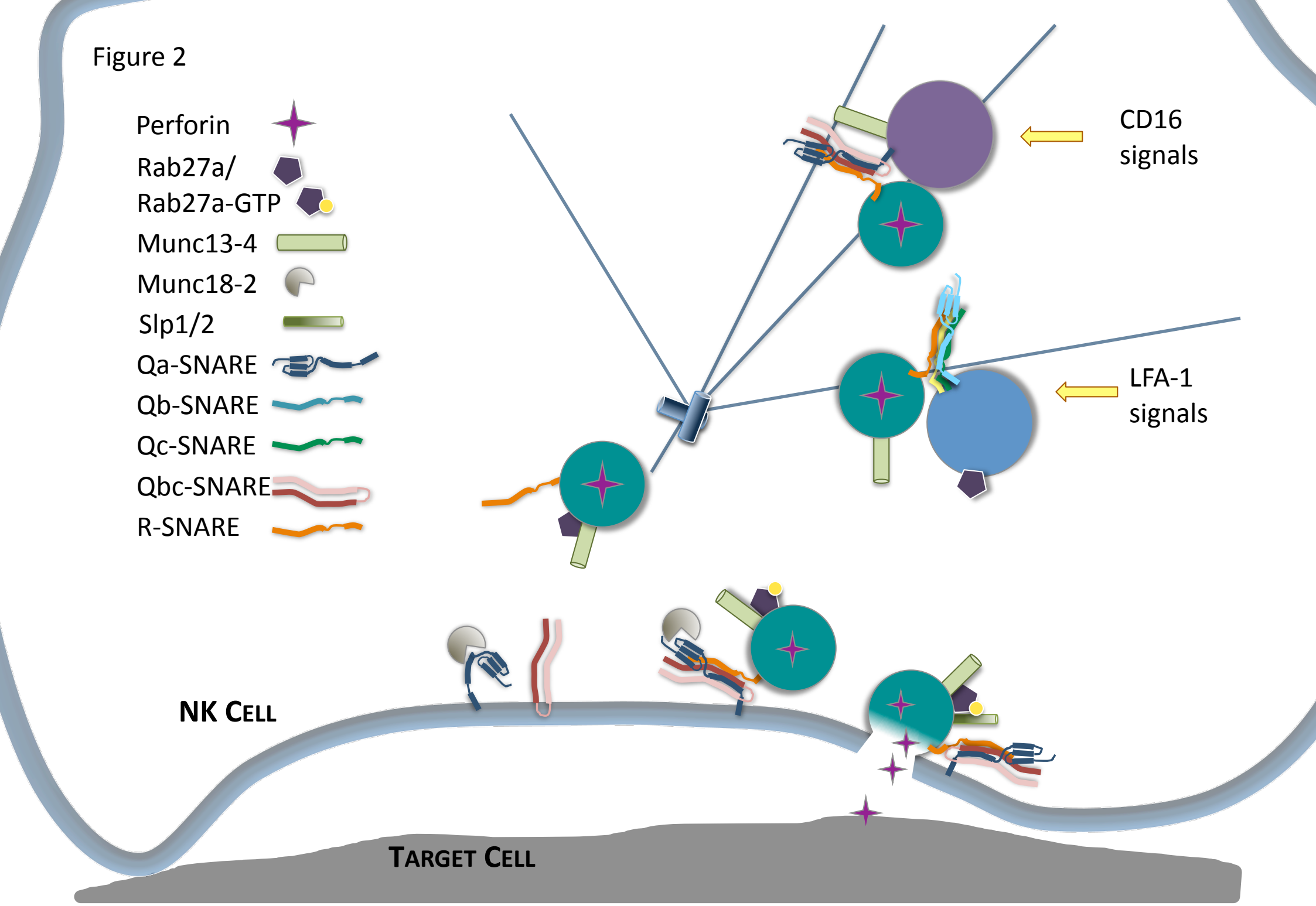

Golgi apparatus
Late endosomes
Lytic granule
MTOC
Perforin
Nucleus
1
2
3
4
NK CELL
TARGET CELL

Figure 1: The four stages of NK cell cytotoxicity affected by disease-causing mutations. 1) Granule biogenesis, which can be affected by mutations to LYST or AP3, or to the granule content proteins Cathepsin C or perforin. Granules are synthesised prior to activation. 2) Target cell recognition CD18, KINDLIN3, CD16, NKG2D, KIR, TAP. NK cells recognise expression of a range of ligands for activating and inhibitory receptors on target cells. 3) NK cell activation, which can be affected by mutations in CD3ζ, DAP12, IKK, WASP, Caspase 8, SAP or XIAP. Signals induce polarization of lytic granules to the MTOC, repolarization of the MTOC and granules to the immune synapse, and fusion of lytic granules with other endosomal compartments. 4) Lytic granule exocytosis, which can be affected by mutations to Rab27a, Munc13-4, Stx11 or Munc18-2.

Figure 2: Regulation of of lytic granule exocytosis. Immature perforin-positive lytic granules fuse with multiple endosomal compartments. CD16 signals for granules to fuse with Munc13-4-positive compartments, while LFA-1 signals induce fusion of Rab27a-positive compartments with granules. Mature granules at the immune synapse are positive for Munc13-4 and Rab27a. Rab27a has multiple effectors during exocytosis, including Munc13-4 and Slp1 and/or Slp2. Unknown SNARE complexes mediate these fusion events, and Stx11 and Munc18-2, which interact directly, are required for exocytosis at an unknown stage.

Figure 2


Perforin
Rab27a/
Rab27a-GTP
Munc13-4
Munc18-2
Slp1/2
Qa-SNARE
Qb-SNARE
Qc-SNARE
Qbc-SNARE
R-SNARE
CD16
signals
LFA-1
signals
NK CELL
TARGET CELL