Supplement Figure Legends:

Supplemental Figure 1: Tau partially colocalizes with LC3 in N2a cells.

N2a cells overexpressing $Tau_{RD}\Delta K$ were induced to express Tau for 2 days. **A.** Distribution of $Tau_{RD}\Delta K$ in different Subcellular fractions from the transfected cells. AV15 autophagosomes; AV20: autophagolysosomes; Lyso: lysosomes. The distribution of LC3 I and II in these fractions is shown at the bottom. **B.** Colocalization of Tau and the autophagosome marker LC3. *Left*, LC3 monitored by immunolabeling with anti-LC3 antibody and Cy5 secondary antibody. *Middle*, Tau expression monitored by immunolabeling with anti-Tau antibody (KBTR4) and TRITC secondary antibody. *Right,* merged image. Note that a part of Tau colocalizes with LC3.

Supplemental Figure 2: Effects of Tau on lysosomal stability in vitro.

Tau or Tau fragments were incubated with freshly isolated lysosomes. Lysosomal integrity after interaction with Tau proteins was verified by measuring the activity of ß-hexosaminidase in the incubation medium at 0, 10 and 30 minutes of incubation in an isotonic buffer at 37°C. Values are expressed as percentage of total activity in the lysosomal fraction at time 0. Note that none of the Tau proteins cause an increase in leakiness, compared to control without Tau.

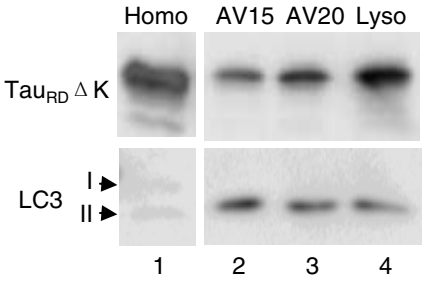
Supplemental Figure 3: Effect of CMA substrate on oligomerization of F1 at the lysosomal membrane. F1 (2µg) was incubated with intact rat liver lysosomes alone (lane 2) or in the presence of the indicated increasing concentrations of GAPDH (lanes 3-5) or ovalbumin (Oval; lane6). Lane 1 shows 1/10 of the input (i) and inset shows the amount of GAPDH associated with the lysosomal membranes. Monomeric F1 is indicated with an arrow and multimeric forms of F1 with a line. Note that the CMA-mediated binding of F1 monomer is inhibited by GAPDH, but F1 oligomers are not affected.

Supplemental Figure 4: A detailed model of fragmentation and degradation of $Tau_{RD}\Delta K$ by autophagy-lysosomal system.

$Tau_{RD}\Delta K$ can be degraded via the proteasome or lysosome, but some of it is cleaved in the cytosol by a thrombin-like activity to generate F1 (Step 1) (Wang et al., 2007). A fraction of F1 is delivered to lysosomes

via CMA (Step 2). As the c-terminus of the protein reaches the lysosomal lumen it is cleaved by cathepsin L to generate F2 and F3 (Step 3). These fragments remain bound to the lysosomal membrane with high affinity acting as a seed for aggregate formation (Step 4). The presence of the oligomeric forms of F2 and F3 on the cytosolic side of the lysosomal membrane eventually promotes partial rupture of the lysosomal membrane with the subsequent release of lysosome hydrolases into the cytosol and the deinsertion of the F2 and F3 fragments from the membrane into the cytosol (Step 5). These fragments are highly amyloidogenic and then induce the aggregation of intact $Tau_{RD}\Delta K$ (or full-length Tau) in the cytosol (Step 6). The aggregates are then degraded through the macroautophagy pathway (Step 7).

A



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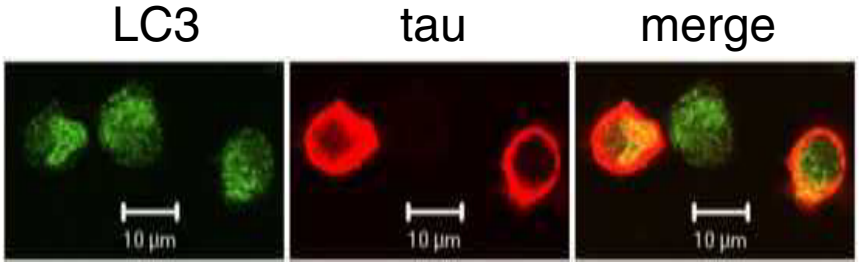
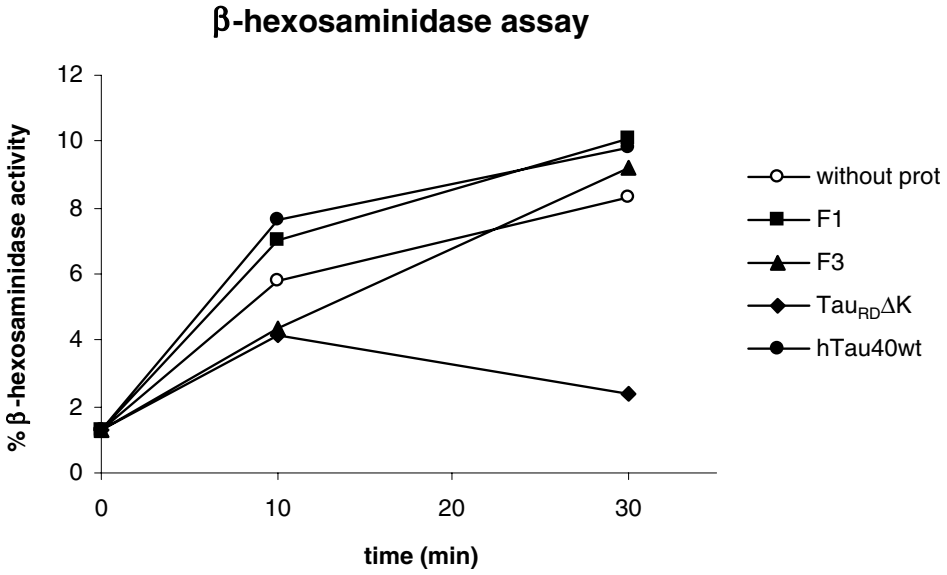
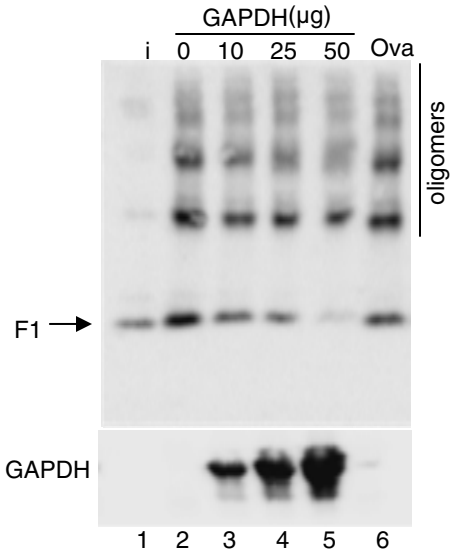


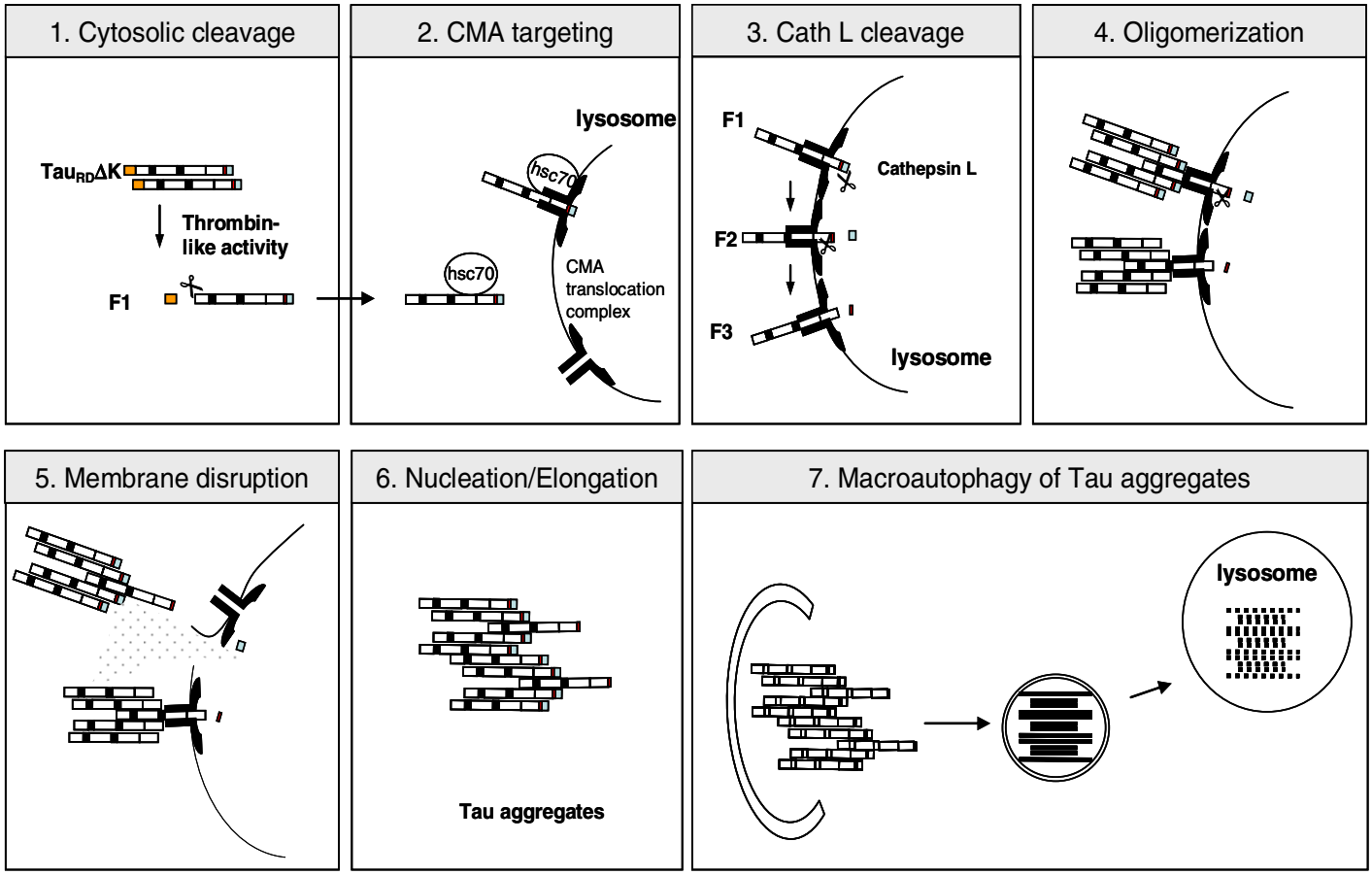
Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3



Supplemetal Figure 4