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| **Supplementary Figure 1** |
| 321AMMAAA326 and 333SWGMMGMLASQ343 form anti-parallel steric-zipper structures. |
| Views perpendicular to the fibril axis (vertical) are shown for three steric-zipper structures of Fig. 1. 321AMMAAA326 and 333SWGMMGMLASQ343 are two zippers that adopt anti-parallel packing, as shown by the alternating orientation of arrows representing the direction of strands. 328AALOSS333 is shown as an example of the zippers which adopt parallel packing, as shown by the same orientation of arrows in each sheet. |
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| **Supplementary Figure 2** |
| Validation of TDP-CTF and TDP-LCD constructs. |
| The SUMO tagged TDP-CTF and TDP-LCD were analyzed by SDS-PAGE and stained with coomassie blue and anti-TDP-43 antibody. For TDP-CTF, notice that 1 hour after (1h) ULP1 cleavage, it generates SUMO protein and tag-free TDP-CTF, and both SUMO-tagged and tag-free TDP-CTF can be recognized by anti-TDP-43 antibody. SUMO tagged TDP-LCD also can be recognized by anti-TDP-43 antibody, and generates SUMO protein and tag-free TDP-LCD after cleavage. The molecular weight of SUMO and tag-free TDP-LCD are so close to each other that the two bands are indistinguishable on SDS-PAGE when stained by coomassie blue. However, the existence of tag-free TDP-LCD can be detected by anti-TDP-43 antibody, forming a band (although very dim) at its expected position. Tag-free TDP-LCD can also be detected by SDS-PAGE of the TDP-LCD pellet, showing a band at its expected position, and SUMO protein remains soluble as shown in Fig. 2A. |
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| **Supplementary Figure 3** |
| Positive control of denaturing conditions shown in Fig. 3B, and structural details of 312NFGEFS317 and 312NFGpTFS317. |
| (A) Negative stain EM images of Aβ1-42 fibrils, typical amyloid fibrils, before and after treatment with 2% SDS and 70 °C for 15 mins. Notice that Aβ1-42 fibrils are stable and maintain their morphology after treatment in denaturing conditions. Scale bar = 200 nm. (B) Omit map of phosphate in 312NFGpTFS317 structure viewed from two angles. Green mesh shows the electron density of the Fo-Fc map with sigma > 4.5. Notice that the electron density of the same map with sigma <-4.5 is also computed as red mesh, however there is no observable negative density. TPO: phosphorylated threonine. (C) Hydrogen bond networks that stabilizes the packing of 312NFGEFS317 and 312NFGpTFS317. In each structure, three Glu/pThr residues from three adjacent strands of same sheet are shown, as well as the residues hydrogen-bonded to them. The hydrogen bonds formed by all Glu and the central pThr are shown as yellow dash lines, with distances between 2.3 and 3.2 Å. |