SUPPORTING INFORMATION

Supplementary Experimental Procedures

Preparation of seed-free Aβ peptide. $A\beta_{1-40}$ was synthesized using a standard Fmoc-chemistry strategy for solid-phase peptide synthesis (*1*). The resulting peptides were purified by liquid chromatography and characterized by MALDI-MS. The $A\beta_{1-40}$ peptide was pretreated as described previously (*2*) to monomerize it. Briefly, lyophilized Aβ powder was dissolved in aqueous NaOH (2 mM) and the pH adjusted to 10.5 with aqueous NaOH (100 mM). The solution was sonicated (20 min, 25°C), then filtered sequentially through 0.2 μm and 10-kDa cutoff filters. The concentration of protein was determined by UV absorption at 280 nm (1,280 $M^{-1}cm^{-1}$). The final peptide solution was seed free according to atomic force microscopy (AFM) and dynamic light scattering analysis.

Mice strains and genotyping. An AD mouse model expressing both a mutant chimeric mouse/human APP_{swe} and a mutant human presenilin 1 (Delta E9), both driven by the prion protein promoter, was purchased from Jackson Laboratory (Strain B6C3-Tg, (APP_{swe} PSEN1dE9) 85Dbo/J, Stock number 004462). Long-lived male mice harboring only one *Igf1r* copy (*3*) were obtained from Dr. Jeffery Friedman (TSRI, La Jolla, CA). Males of both strains were crossed for 3 generations with "wild-type" 129 females (Jackson Laboratory, strain 129Xi/SvJ, Stock number 000691), to setup two separate colonies. Mice of each colony were backcrossed for additional two generations. Next, *Igf1r*+/- males were crossed with AD females for three generations to generate the experimental mice. Mice were tail clipped at 8-10 weeks of age and DNA was purified and subjected to PCR analysis. APP_{swe}, and PS1ΔE9 were amplified according to Jackson Laboratory's instructions. *Igf1r* was amplified using the primers: forward: GTATAGTCCTAGAGGCCC reverse: GTTCTGGCAGAAAACATGG

APP-overexpressing cell lines. Genes encoding the 695-amino-acid isomers of human wild type APP (APP_{wt}) and mutated APP carrying the Swedish mutations (APP_{swe}) were isolated and modified to incorporate HindIII and NotI restriction sites using the primers: forward: GGCGCTAAGCTTACCATGCTGCCCGGTTTGGCACTGC reverse: GGCGCTGCGGCCGCCTAGTTCTGCATCTGCTCAAAGAAC. These genes were cloned into the tetracycline-inducible mammalian expression vector pcDNA4/TO (Invitrogen) using standard techniques. T-REx-293 cells (Invitrogen) were stably transfected with empty pcDNA4/TO (EV), pcDNA4/TO/APP_{wt}, or pcDNA4/TO/APP_{swe} vectors according to the Lipofectamine 2000 (Invitrogen) and the T-REx-293 manufacturers' protocols. Following transfection, clones were selected and subcloned to ensure genetic homogeneity. The T-REx-293 cell lines were maintained in Dulbecco's Modified Eagle Medium with high glucose (Gibco), 10% heat-inactivated fetal bovine serum, 1% glutamine Pen-Strep, and 10mM HEPES at 37 °C in 5% CO_2. For expression, $3x10^6$ cells were adhered to 10 cm plates overnight, after which 100 ng/mL tetracycline (Sigma-Aldrich) was added to the culture media to induce over expression. Conditioned culture media were aspirated from individual culture plates over the course of 4 days following tetracycline induction and stored at -20 ºC. The total protein concentration in culture media was measured using the Pierce BCA Assay.

Western blot. Worm PDS or mouse brain homogenate samples (20 μL) spiked with added $A\beta_{1-40}$ amyloid were boiled with SDS loading buffer for 10 min, and then were loaded onto SDS-PAGE gels and blotted onto nitrocellulose paper. The blots were incubated with primary antibody 6E10 (Covance, San Diego, CA) at a 1:10,000 dilution overnight, and then were incubated with secondary goat anti-mouse HRP-conjugated antibody (Pierce, Rockford, IL) at a 1:10,000 dilution. Blots were visualized by enhanced chemiluminescence using SuperSignal West Pico Substrate (Pierce).

Atomic Force Microscopy (AFM). An aliquot of the aggregated $A\beta_{1-40}$ solution (20 μL of 50 μM solution) was adsorbed onto the surface of freshly cleaved mica (5×5 mm) for 1 min. The liquid was wicked off by absorption into filter paper. Salt and unbound materials were removed by three washes with 30 μL of water. AFM images were recorded in tapping mode utilizing a Digital Instruments multimode scanning probe microscope with FESP tips and a Nanoscope IIIa controller (Veeco, Woodbury, NY).

Ultracentrifugation. Following the kinetic aggregation assay, the 96-well plate was sonicated for 45 min in a Fisher Scientific FS60 Sonic Cleaner. Samples were removed from wells and spun at 150,000 × g for 1 h at 4 ºC. Supernatants were separated from pellets, and guanidine hydrochloride was added to all samples to a final concentration of 8 M. Samples were then sonicated for 1 h in a Fisher Scientific FS60 Sonic Cleaner.

RP-HPLC. Samples denatured in 8 M guanidine hydrochloride with sonication (1 h) in a Fisher Scientific FS60 Sonic Cleaner were injected in 100% H_2O, 0.03% NH_4OH on a Phenomenex Gemini-NX C18 column and eluted with a linear gradient to 100% acetonitrile, 0.03% NH_4OH over 40 min. Resulting $A\beta_{1-40}$ peak areas (220 nm absorbance) were quantified and normalized to a known mass of $A\beta_{1-40}$ (Figure S2) or to undigested control (Figure S4). For PK digestion analysis (Figure S4), samples eluting at 16-18 min were collected and identified as full-length $A\beta_{1-40}$ (m/z = 4331) or oxidized full-length $A\beta_{1-40}$ (m/z = 4347) by MALDI-TOF mass spectrometry. Resulting $A\beta_{1-40}$ peak areas (220 nm absorbance) were quantified and normalized to undigested control.

Supplemental References

1. Wellings, D. A., and Atherton, E. (1997) Standard Fmoc protocols, *Methods Enzymol. 289*, 44-67.
2. Zhang, Q., Powers, E. T., Nieva, J., Huff, M. E., Dendle, M. A., Bieschke, J., Glabe, C. G., Eschenmoser, A., Wentworth, P., Jr., Lerner, R. A., and Kelly, J. W. (2004) Metabolite-initiated protein misfolding may trigger Alzheimer's disease, *Proc. Natl. Acad. Sci. U. S. A. 101*, 4752-4757.
3. Holzenberger, M., Dupont, J., Ducos, B., Leneuve, P., Geloen, A., Even, P. C., Cervera, P., and Le Bouc, Y. (2003) IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice, *Nature 421*, 182-187.

Supporting Figure Legends

Supporting Figure 1. (**a**) AFM image of $A\beta_{1-40}$ amyloid prepared *in vitro* according to the procedure in the Methods section. (**b**) AFM image of $A\beta_{1-40}$ amyloid prepared *in vitro* after sonication for 40 min.

Supporting Figure 2. Selectivity of the kinetic aggregation assay. (Quantification is reported as mean ± SD of triplicate results; * denotes $P < 0.01$, and n.s. denotes $P > 0.05$.) **(a)** Amyloidogenesis from the $A\beta_{1-40}$ kinetic aggregation assay (pH 7.4, 37 °C) without or with preformed α-synuclein or $A\beta_{1-40}$ fibrils added. The quantity of the preformed fibrils is equivalent to 1 μM (*blue*, 4.3 μg/mL) or 1 nM (*green*, 4.3 ng/mL) of the monomeric Aβ species, or 1 μM of the monomeric α-synuclein species (*orange*, 14.5 μg/mL). **(b)** Amyloidogenesis from the $A\beta_{1-40}$ kinetic aggregation assay (pH 7.4, 37 °C) without or with preformed 8 kDa gelsolin or $A\beta_{1-40}$ fibrils added. The quantity of the preformed fibrils is equivalent to 1 μM (*blue*, 4.3 μg/mL) or 10 nM (*gray*, 43 ng/mL) of the monomeric Aβ species, or 1 μM of the monomeric 8 kDa gelsolin species (*purple*, 7.9 μg/mL). **(c)** RP-HPLC traces and quantification of $A\beta_{1-40}$ peak areas of supernatants and pellets of 5 μg monomerized $A\beta_{1-40}$ (*red*) and 5 μg $A\beta_{1-40}$ fibrils (*blue*)

following ultracentrifugation of samples for 1 h at 150,000 × g. Quantities are normalized to the peak area of a 5 μg $A\beta_{1-40}$ standard (*black*). **(d)** Quantification of RP HPLC $A\beta_{1-40}$ peak areas of 150,000 × g ultracentrifugation from **(a)**. **(e)** Quantification of RP HPLC $A\beta_{1-40}$ peak areas of 150,000 × g ultracentrifugation from **(b)**.

Supporting Figure 3. Proteinase K (PK) digestion of wild type mouse brain homogenate. Mouse brain homogenate was incubated with PK (w/w ratio of PK to total protein in mouse brain = 0.002:1 or 0.01:1) for 2 h at 25 °C. The samples were boiled with SDS loading buffer, loaded onto an SDS-PAGE gel and visualized with silver staining. The left lane is wild type mouse sample without PK treatment, and the middle and right lanes result from PK treatment.

Supporting Figure 4. PK treatment of preformed $A\beta_{1-40}$ amyloid fibrils in pH 7.4 phosphate buffer, conditions under which $A\beta_{1-40}$ amyloid is resistant to digestion. $A\beta_{1-40}$ amyloid was incubated with different concentrations of PK (w/w ratio of PK to $A\beta_{1-40}$ amyloid = 0.002:1 or 0.01:1) for 2 h at 25 °C. Guanidine hydrochloride powder was added to samples to a final concentration of 8 M, and samples were sonicated for 1 h, after which they were subjected to RP-HPLC. **(a)** RP-HPLC traces of $A\beta_{1-40}$ amyloid without (blue) or with (red, green) PK treatment. **(b)** Quantification of $A\beta_{1-40}$ peak area (16 – 18 minutes) shows that the majority of $A\beta_{1-40}$ amyloid is resistant to PK digestion.

Supporting Figure 5. $A\beta_{1-40}$ kinetic aggregation assay (pH 7.4, 37 °C) in the presence of added preformed $A\beta_{1-40}$ amyloid seeds that were unboiled (open triangles) versus boiled (filled diamonds). The seeds were sonicated for 40 min and diluted to concentrations ranging from

0.043 ng/mL to 4,300 ng/mL. Boiled samples were incubated in a boiling water bath for 10 min, while unboiled samples were incubated at room temperature. All samples were then sonicated for an additional 20 min before being added to the $A\beta_{1-40}$ kinetic aggregation assay.

Supporting Figure 6. $A\beta_{1-40}$ kinetic aggregation traces (pH 7.4, 37 °C) with added wild type (N_2) or Aβ worm PDS. Triplicate results are shown in each figure. (**a**) The worm PDS was sonicated for 20 min, treated with PK for 2h (w/w ratio of PK to total protein in PDS sample is 1:500), boiled for 10 min, sonicated for an additional 20 min, and then added to the $A\beta_{1-40}$ kinetic aggregation assay. The total protein concentration from the worm PDS before PK treatment was 10 μg/mL in the final kinetic aggregation assay. (**b**) The worm PDS was sonicated for 20 min, incubated with PK for 2 h (w/w ratio of PK to total protein in PDS sample is 1:500), and sonicated for another 20 min after adding Roche complete protease inhibitor cocktail at four times the recommended concentration to inhibit PK activity, and then added to the $A\beta_{1-40}$ kinetic aggregation assay. The toal protein concentration from the worm PDS before PK treatment was 10 μg/mL in the final kinetic aggregation assay. Insets: statistical analysis of results obtained in (**a**) ($p < 0.002$) and in (**b**) ($p < 0.01$) (analyzed using a two-tailed student's t-test). Data are reported as mean ± SD of triplicate results.

Supporting Figure 7. (**a**) Western blot analysis of cell culture media samples from EV, APP_{wt} and APP_{swe} cells. Conditioned media samples were collected as a function of incubation time in days following the induction of expression via addition of tetracycline to the culture media. Media samples (50 μL) were boiled with SDS loading buffer for 5 min and were loaded onto a 12% SDS-PAGE gel that was visualized by Western blot analysis using the 6E10 antibody (1:10,000 dilution) and secondary goat anti-mouse HRP-conjugated antibody (1:5,000 dilution).

(**b**) $A\beta_{1\text{-}40}$ kinetic aggregation assay (pH 7.4, 37 °C) with added conditioned cell culture media samples without PK and PI pretreatment. Triplicate results were shown in each figure. The cell media samples were sonicated for 20 min before being added to the $A\beta_{1\text{-}40}$ kinetic aggregation assay. The total protein concentration from the cell media samples was 25 μg/mL in the final kinetic aggregation assay.

Supporting Figure 8. $A\beta_{1\text{-}40}$ kinetic aggregation traces (pH 7.4, 37 °C) with added 5 μL, 8 μL, or 10 μL CM bead slurry (solid curves). In the dotted curve assays, CM beads (5 μL, 8 μL, or 10 μL CM bead slurry) were incubated with additional $A\beta_{1\text{-}40}$ amyloid seeds (13 ng) at 4 °C with shaking overnight, and then washed with H_2O before being added to the $A\beta_{1\text{-}40}$ kinetic aggregation assay (total final volume 300 μL).