NEURODEGENERATIVE DISEASE

Directing amyloid- β deposition

In Alzheimer's disease, the deposition of amyloid- β in the brain as insoluble extracellular amyloid plaques follows a region-specific pattern, but why certain regions are vulnerable to plaque development is unclear. Now, Holtzman and colleagues show that variation in basal neuronal activity across different brain regions might regulate the distribution of amyloid- β pathology.

The authors focused their study on Tg2576 mice, which express a mutant form of the amyloid precursor protein — from which amyloid- β is derived — and develop plaques. They first showed that the plaque distribution in aged mice resembled that observed in Alzheimer's disease, thereby validating this model for further investigation.

A previous study showed that elevated levels of amyloid- β in the brain's interstitial fluid (ISF) were closely linked to plaque development in a mouse model

of Alzheimer's disease. Here, the authors showed that in young Tg2576 mice, which do not have plaques, regional variation in the steady-state ISF amyloid- β concentration — as detected by microdialysis — predicted the distribution of amyloid- β pathology that was observed in aged animals.

In Alzheimer's disease, brain regions that comprise the default mode network are particularly vulnerable to amyloid- β deposition. As this network exhibits high levels of metabolism during resting conditions, the authors explored the link between metabolic activity and ISF amyloid- β levels before plaque formation. Strikingly, they found that in young Tg2576 mice, regional levels of ISF lactate — a marker of neuronal activity — correlated with regional ISF amyloid- β levels, indicating that area-specific vulnerability to amyloid- β deposition is associated with local levels of brain metabolism.

To examine whether neuronal activity directly affected ISF amyloid- β levels in young mice, the authors focused their attention on the barrel cortex, which shows some amyloid- β pathology in aged Tg2576 animals. In rodents, whisker stimulation causes an increase in barrel cortex activity, whereas whisker trimming reduces such activity. Young Tg2576 mice showed increased ISF

amyloid- β levels with stimulation but decreased levels of this peptide with trimming, suggesting that physiological neuronal activity regulates the ISF amyloid- β concentration.

Using *in vivo* multiphoton microscopy and a fluorescent marker of plaques, the authors examined the effect of hemisphere-specific long-term (28-day) whisker shortening on amyloid- β deposition in a double transgenic mouse model of Alzheimer's disease that shows plaque pathology at a younger age than in the Tg2576 model. Compared with the control hemisphere of the barrel cortex, the whisker-deprived hemisphere showed marked decreases in the growth of existing plaques and the formation of new plaques, suggesting that a long-term decrease in physiological activity inhibits amyloid- β deposition.

Together, these results indicate that regional basal neuronal activity in the brain is a key determinant of regional amyloid plaque load. Factors that affect such activity might, therefore, alter an individual's risk of Alzheimer's disease.

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