ABSTRACT

How do glia become toxic to neurons under neurodegenerative conditions?

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Although the pathological contributions of reactive astrocytes have been implicated in Alzheimer's disease (AD), their *in vivo* functions remain elusive due to the lack of appropriate experimental models and precise molecular mechanisms. Here, we show the importance of astrocytic reactivity on the pathogenesis of AD using GiD, a newly developed animal model of reactive astrocytes, where the reactivity of astrocytes can be manipulated as mild (GiDm) or severe (GiDs). Mechanistically, excessive hydrogen peroxide (H_2O_2) originated from monoamine oxidase B in severe reactive astrocytes causes glial activation, tauopathy, neuronal death, brain atrophy, cognitive impairment and eventual death, which are significantly prevented by AAD-2004, a potent H_2O_2 scavenger. These $H_2O_2^-$-induced pathological features of AD in GiDs are consistently recapitulated in a three-dimensional culture AD model, virus-infected APP/PS1 mice and the brains of patients with AD. Our study identifies H_2O_2 from severe but not mild reactive astrocytes as a key determinant of neurodegeneration in AD.

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