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Evaluating sequential processing of Aβ by γ-secretase in cell culture models

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Understanding how different species of Aβ are generated and how β-secretase can be modulated has broad therapeutic implications for AD, as shifts in β-secretase processing increasing the relative production of Aβ42 can cause Alzheimer's disease (AD). We further explored the tri-peptide cleavage model proposed by Ihara and colleagues using BRI2-Aβ fusion proteins. We generated BRI2-Aβ proteins spanning from Aβ1-37 to Aβ1-55 and C99. Each of these 21 constructs were tranfected into cells and Aβ production assessed. Both secreted Aβ and cell associated Aβ were detected using ELISA and IP/MS. In addition effects of β-secretase inhibitors (GSIs) on Aβ production was examined. BRI2 fusion proteins expressing Aβ47 or smaller Aβs were not significantly processed by β-secretase, though Aβ peptides were readily detected in the cells and media. Aβ48 was processed by β-secretase but almost exclusively produced species other than Aβ40 or 42. Aβ peptides longer then Aβ48 were efficiently cleaved by β-secretase and produced varying ratios of Aβ40:42. Most notably Aβ51 produced the greatest shift towards Aβ42 production. IP/MS studies are underway to define the profiles of Aβ produced from these constructs, including those delivered to the mouse brain using rAAV vectors. Truncated substrates dramatically increased the IC50s of multiple GSIs relative to APP in some cases from sub nanomolar to micromolar levels. A wealth of observations regarding fate and properties of these longer Aβ peptides will provide crucial information regarding their biological and disease relevance.

Biography

Dr. Yong Ran got his Ph.D from Huazhong University of Science and Technology, China, in 2004. His postdoctoral studies at the University of Florida (2006-2010) were focused on lipid transfer proteins. Currently he is and Assistant Scientist of the Center for Translational Research in Neurodegenerative Disease at University of Florida.

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