Targeting membrane lipids to modulate amyloid precursor protein processing

B. Garner, Illawarra Health and Medical Research Institute, University of Wollongong, Wollongong, NSW 2522, Australia and School of Biological Sciences, University of Wollongong, Wollongong, NSW 2522, Australia.
(Introduced by Peter Thorn)

Inhibition of cerebral amyloid-β (Aβ) deposition represents a therapeutic target for Alzheimer's disease (AD). Aβ is derived from the amyloid precursor protein (APP) *via* two sequential cleavages that are mediated by β-secretase and the γ-secretase complex. Such amyloidogenic APP processing occurs in lipid raft microdomains of cell membranes (Vetrivel *et al.*, 2005) and it is known that modulating the distribution of cholesterol in lipid rafts can regulate APP processing and Aβ production (Simons *et al.*, 1998). Certain ATP-binding cassette (ABC) transporters regulate lipid transport across cell membranes and, as recent studies reveal, within membrane microdomains (Glaros *et al.*, 2005). We therefore examined the role that ABCA1, A2, A7 and G1 may play in regulating neuronal lipid homeostasis and APP processing. In addition, we directly modulated raft lipid composition using glycosphingolipid (GSL) synthesis inhibitors as another means to assess the impact membrane lipid composition has on APP processing. Our studies revealed that ABCA1, A2 and G1 were expressed in human neurons as was ABCA7, albeit at much lower levels. The same transporters were also expressed in human brain (Kim *et al.*, 2008). Cellular cholesterol efflux to apolipoprotein acceptors was accelerated by over-expressing ABCA1, A7 or G1 (but not A2) in HEK293 cells (Kim *et al.*, 2007, Chan *et al.*, 2008). Extracellular Aβ levels were reduced when CHO cells stably expressing human APP (CHO-APP) were transfected with ABCA1, A7 or G1 (but not A2); implying regulation of APP processing by ABC transporters was correlated with lipid efflux activity (Kim *et al.*, 2007). In very recent studies, we assessed the capacity of three ABCA1 mutants (that do not promote cholesterol efflux) to modulate APP processing and, unexpectedly, these also reduced Aβ production. Co-immunoprecipitation experiments indicated ABCA1 and APP physically interact which suggests a novel pathway by which ABCA1 may regulate APP processing. Using a different approach to modulate cellular lipid homeostasis, we reduced membrane GSL levels using synthetic ceramide analogues based on the D-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP) structure that are established glucosylceramide synthase inhibitors. PDMP and related compounds PPMP and EtDO-P4 inhibited Aβ secretion from CHO-APP cells with approximate IC50 values of 15, 5 and 1 μM, respectively (Li *et al.*, 2010). In addition, EtDO-P4 inhibited endogenous Aβ production by human neurons. In conclusion, ABC transporter mediated modulation of APP processing may involve lipid–dependent and –independent processes. Our studies also provide novel information regarding the regulation of APP processing by synthetic ceramide analogues that could offer a novel therapeutic avenue to explore as a treatment for AD.

Chan SL, Kim WS, Kwok JB, Hill AF, Cappai R, Rye KA & Garner B (2008) *Journal of Neurochemistry* **106:** 793-804.

Glaros EN, Kim WS, Quinn CM, Wong J, Gelissen I, Jessup W & Garner B (2005) *Journal of Biological Chemistry* **280:** 24515-23.

Kim WS, Suryo Rahmanto A, Kamili A, Rye KA, Guillemin GJ, Gelissen IC, Jessup W, Hill AF & Garner B (2007) *Journal of Biological Chemistry* **282:** 2851-61.

Kim WS, Weickert CS & Garner B (2008) *Journal of Neurochemistry* **104:** 1145-66.

Li H, Kim WS, Guilemin GJ, Hill AF, Evin G & Garner B (2010) *Biochimica et Biophysica Acta*, **1801:** 887-895.

Simons M, Keller P, De Strooper B, Beyreuther K, Dotti CG & Simons K (1998) *Proceedings of the National Academy of Sciences of the United States of America* **95:** 6460-4.

Vetrivel KS, Cheng H, Kim SH, Chen Y, Barnes NY, Parent AT, Sisodia SS & Thinakaran G (2005) *Journal of Biological Chemistry* **280:** 25892-900.