APPealing for a role in cellular iron efflux

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Dlouhy *et al.* (1) recently refined how β-amyloid precursor protein (APP)[2] participates in iron (Fe) efflux and hinted that APP may be unnecessary for ferroportin-supported Fe efflux. APP and Fe efflux have long been our interest, given recent work on the APP mRNA 5′-UTR and how regulation of APP translation operates through an interleukin-1 acute box, an iron response element (IRE), where iron-responsive protein 1 (IRP1) binds, and a target sequence for microRNA-346 (2). Untangling the roles of IRE, IRP1, interleukin-1, and miR-346 at the APP 5′-UTR is critical in Alzheimer's disease (AD). Fe regulation of APP levels through this site is well-documented (3). For example, that APP knockout alters Fe efflux in model mice (4) argues in favor of APP regulation of Fe efflux. Dlouhy's group (1) reported that cellular APP plays no role in Fe homeostasis, at least with ferroportin, and secreted APP (sAPP) stabilizes ferroportin at the cell membrane (5). In normal cells, APP is processed by α- or β-secretase to generate sAPPα or sAPPβ, respectively. Post-translational secretase modification of APP alters neuronal Fe homeostasis (6). Because the APP they generated used a C-terminal tag that probably prevented secretase processing, it would have eliminated sAPP. They examined the specific form of APP that was not implicated in Fe metabolism in their own previous work (5) and suitably found further lack of implication. Nevertheless, their work of APP on Fe efflux will encourage researchers to examine effects of more AD relevance, such as the sAPPα (nonamyloidogenic pathway) *versus* sAPPβ (amyloidogenic pathway), and cytokines and microRNA regulation of APP in overall Fe metabolism as well as AD pathogenesis, progression, and therapeutics.

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[2] The abbreviations used are: APP, β-amyloid precursor protein; sAPP, secreted APP; IRE, iron response element; AD, Alzheimer's disease.

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