A novel relationship between β-amyloid precursor protein and tau in neuronal iron trafficking

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Introduction

The life essential element iron is required as a cofactor in metabolic processes throughout the body and specifically in tissues of high oxygen consumption, such as the central nervous system. Iron's ability to freely receive and donate electrons is critical (e.g. oxidative phosphorylation) and a deficiency in iron can lead to metabolic stress. However, the over presence of unbound iron is also detrimental as this may catalyze the production of toxic reactive oxygen species. Since too much or too little iron can compromise cell viability, cellular iron homeostasis is tightly regulated. This can be carried out through a number of ways, including our recently discovered ability for β-amyloid precursor protein (APP) to facilitate the movement of iron within extracellular fluid and maintain intracellular iron homeostasis. The iron homeostatic control of APP is partly through it's ability to bind to the iron exporter ferroportin (FPN) and with iron transporting proteins (e.g. members of the Transferrin family) that require Fe^{3+} loading. Efficiency of APP to assist in the efflux of intracellular iron through FPN requires it to be transported to the cell surface from within.

APP's iron homeostatic role is particularly evident within neurons and failure, either through reduced expression or disrupted localization on the cell surface, associates with age-related increases in brain iron and altered iron-related protein expression. Brain iron content is further increased in patients and animal models of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). This has created significant interest in the possibility that homeostatic disturbances in brain iron may contribute to a common underlying age-related pathogenesis of these diseases.

Results

We have identified a direct interaction with lactoferrin (LF) captured *in vitro* using sedimentation velocity and quenching of tryptophan fluorescence (Figure 1A&B), and *in vivo* using immunoprecipitation. We show this interaction is likely to cause the observed altered location of LF in hepatocytes (that correlates with iron changes) (Figure 1C-E) and decreased presence of LF in plasma from APP-deficient mice (not shown).

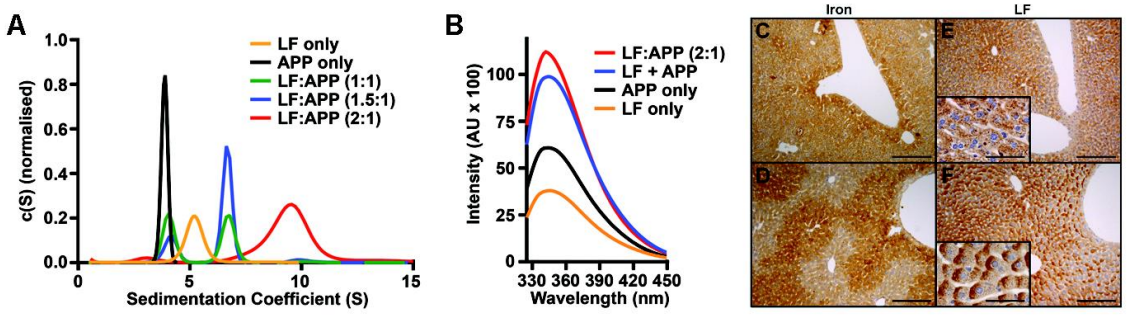

Figure 1: APP has a direct protein-protein interaction with Lactoferrin; a member of the transferrin family. (a) Sedimentation coefficient distributions of holo-Lactoferrin (LF) alone (orange) and APP in the absence (black) and presence of LF (green, blue & red). The c(S) distributions indicate two different complexes which form in a concentration-dependent manner. (**b**) Tryptophan fluorescence spectra (excitation wavelength of 295nm) for APP alone (black), holo-LF alone (orange) and a mixture of APP and holo-LF (red). The total expected intensity of the APP alone and holo-LF alone spectra was also calculated (blue). **(c & d)** Modified Perl's staining of liver detects a higher concentration of iron in $APP^{-/-}$ compared to WT mice. **(e & f)** LF was evenly distributed throughout WT mouse hepatocytes but pooled preferentially towards one side of the cell in $APP^{-/-}$ (see inset)**.**

In addition we have recently established a direct iron-related link between APP and another pathologically relevant protein called tau; whereby tau is required to transport APP to the cell surface, thus allowing it to interact with FPN and facilitate iron efflux. Upon tau's deletion within the mouse knockout model cell surface APP is decreased and intracellular iron accumulates (Figure 2), similar to when APP expression is disrupted (APP knockout mice) or in neurodegenerative diseases such as AD and PD. We are now currently investigating APP's ability to control iron homeostasis via its complex post-translational processing that is required for its correct localization within the cell. While the processing of APP, particularly within the brain, has been extensively studied due to its historic association with AD, it still lacks a conspicuous function until our recent discovery.

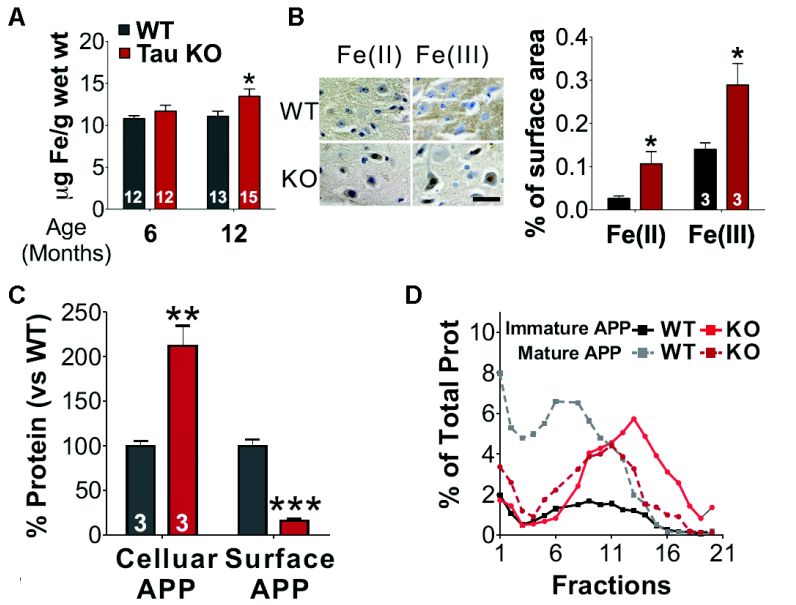

Figure 2: Tau deletion causes iron accumulation by preventing APP trafficking to the cell surface. (**a)** Substantia Nigra iron levels in tau KO mice compared to WT**. (b)** Fe^{2+} and Fe^{3+} histology (brown) and quantification in SN from aged WT and tau KO mice. **(c)** Densitometric quantification of cellular (total) APP and surface (biotinylated) APP in primary neuronal cultures of tau KO compared to WT mice. (**d**) Distribution of immature and mature forms of APP in an iodixanol step gradient of primary neuronal cultures from tau-KO compared to WT.

Publications

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Lei, P., Ayton, S., Finkelstein, D., Spoerri, L., Ciccotosto, G., Wright, D., Wong, B., Adlard, P, Cherny, R., Lam, L., Roberts, B., Volitakis, I., Egan, G., McLean, C., Cappai, R., Duce, J. & Bush, A. (2012) Tau deficiency induces parkinsonism with dementia by impairing APP-mediated iron export. *Nat Med.* **18:**291-95.

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Collaborators

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