How Does APP Modulate Ferroportin? Developing Strategies to Determine Mechanism

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Research Abstract

? DESCRIPTION (provided by applicant): A connection between trace metals – particularly iron – and amyliodogenic diseases is well-known but poorly understood at the level of mechanism. Certainly, the fact that the transcript for amyloid precursor protein – APP – contains an iron response binding protein stem-loop structure and thus, like ferritin, APP protein synthesis directly correlates with cell iron content, indicates that APP is part of the mammalian “”iron

regulon."" The Why? of this iron regulation of APP remains an unknown with respect to both iron metabolism and amyloidogenesis. A recent finding in our and another lab provides a clue as to the Why? of this connection between APP and iron metabolism. We have identified a unique function exhibited by a 22-amino acid residue peptide element within the E2 domain in human amyloid precursor protein (APP). Using a synthetic version of this sequence, residues 327-348 (based on APP695, the most prevalent brain splice form), we demonstrated that this peptide binds to and stabilizes ferroportin (Fpn) in the plasma membrane, thus stimulating cell iron-efflux. We have designated this species FTP for Ferroportin Targeting Peptide. In binding to Fpn, FTP acts as antagonist of the key regulator of Fpn function, hepcidin (Hepc) and indicates that APP itself is a key regulator of iron efflux from any mammalian cell that expresses this amyliodogenic protein. Although the effect of APP and FTP on Fpn plasma membrane display is well-demonstrated, the molecular basis of this activity remains to be determined. Delineation of this mechanism would be highly significant because of: 1) the key role APP and its products play in Alzheimer's Disease; 2) the implied role that iron plays in this neurodegenerative disorder; and 3) the potential that FTP or its synthetic congeners may have as (a) pharmacologic regulator of iron metabolism. The objective of this RO3 is to generate reagents designed to probe this interaction between APP and Fpn by a combination of structure-function and cell biology approaches. Success towards this objective will: 1) provide novel insight into the mechanism of this interaction and its role in the cell trafficking of the two proteins; 2) testa basis set of FTP congeners as potential therapeutics; and 3) provide a template for future investigation into how this interaction might be manipulated in addressing and/or treating iron-dependent neurologic disorders.

Further information available at:

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