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# Alpha-synuclein modulates retinal iron homeostasis by facilitating the uptake of transferrin-bound iron: Implications for visual manifestations of Parkinson's disease

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Running title:  $\alpha$ -synuclein modulates Tf-iron uptake

## Abstract:

Aggregation of  $\alpha$ -synuclein ( $\alpha$ -syn) in neurons of the substantia nigra is diagnostic of Parkinson's disease (PD), a neuro-motor disorder with prominent visual symptoms. Here, we demonstrate that  $\alpha$ -syn, the principal protein involved in the pathogenesis of PD, is expressed widely in the neuroretina, and facilitates the uptake of transferrin-bound iron (Tf-Fe) by retinal pigment epithelial (RPE) cells that form the outer blood-retinal barrier. Absence of  $\alpha$ -syn in knock-out mice ( $\alpha$ -syn<sup>-/-</sup>) resulted in down-regulation of ferritin in the neuroretina, indicating depletion of cellular iron stores. A similar phenotype of iron deficiency was observed in the spleen, femur, and brain tissue of  $\alpha$ -syn<sup>-/-</sup> mice, organs that utilize mainly Tf-Fe for their metabolic needs. The liver and kidney, organs that take up significant amounts of non-Tf-bound iron (NTBI), showed minimal change. Evaluation of the underlying mechanism in the human RPE47 cell line suggested a prominent role of  $\alpha$ -syn in the uptake of Tf-Fe by modulating the endocytosis and recycling of transferrin (Tf)/transferrin-receptor (TfR) complex. Down-regulation of  $\alpha$ -syn in RPE cells by RNAi resulted in the accumulation of Tf/TfR complex in common

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