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1

Bridging the age spectrum of neurodegenerative storage diseases

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For over a century, researchers have observed similar neurodegenerative hallmarks in brains of people affected by rare early-onset lysosomal storage diseases and late-onset neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Increasing evidence suggests these apparently disparate diseases share a common underlying feature, namely, a dysfunctional clearance of cellular cargo through the secretory-endosomal-autophagic-lysosomal-exocytic (SEALE) network. By providing examples of rare and common neurodegenerative diseases known to have pathologically altered cargo flux through the SEALE network, we explore the unifying hypothesis that impaired catabolism or exocytosis of SEALE cargo, places a burden of stress on neurons that initiates pathogenesis. We also describe how a growing understanding of genetic, epigenetic and age-related modifications of the SEALE network, has inspired a number of novel disease-modifying therapeutic approaches aimed at alleviating SEALE storage and providing therapeutic benefit to people affected by these devastating diseases across the age spectrum.

Cellular storage diseases

The term “lysosomal storage disease” has traditionally been used to describe congenital diseases caused by mutations in genes that encode lysosomal enzymes. Substrates for deficient enzymes

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accumulate within late endosomes and lysosomes, forming "storage" material, which triggers a complex cascade of pathogenic events. Lysosomal storage diseases are also used to describe a broad range of cellular storage diseases that originate from mutations in non-lysosomal enzymes found throughout the secretory-endosomal-autophagic-lysosomal-exocytic (SEALE) network (Fig. 1). Today, over seventy diseases are known to involve lysosomal storage as an integral part of their cellular phenotype, and considering the large number of SEALE component proteins whose loss of function can produce a storage phenotype, the overall number of cellular storage diseases is likely to be in the hundreds (Source: Online Mendelian Inheritance in Man (OMIM), http://www.omim.org/). Storage diseases are typically inherited as autosomal recessive traits and occur at a combined frequency of 1:5000–1:7000 live births depending on the human population studied [1,2]. Approximately seventy percent of these diseases involve neurodegenerative symptoms, which typically present early in life and result in premature death. Outlined below are three categories of storage disease that differ in their pathogenesis, but all share the overlapping hallmark of having a phenotype that involves impaired cargo flux through the SEALE network. Although the three categories of storage diseases described here aim to highlight pathogenic differences between storage diseases, their phenotypic classification is more complex, as considerable overlap in storage phenotypes occur during disease progression.

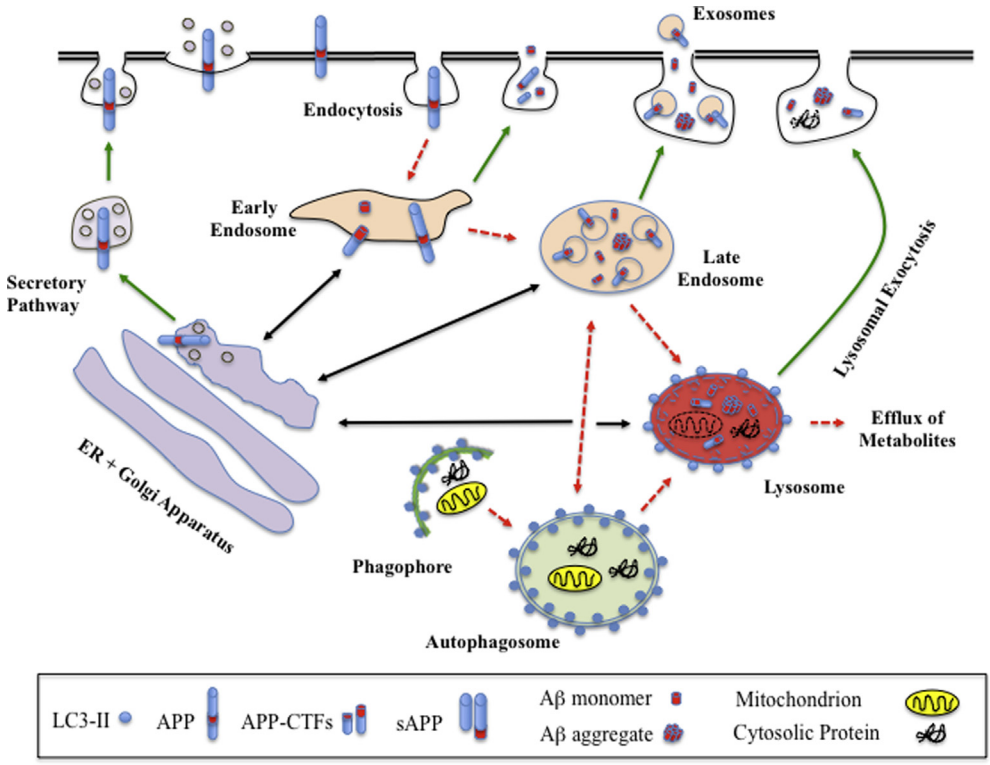

Fig. 1. Cargo transport through the secretory-endosomal-autophagic-lysosomal-exocytic (SEALE) network. The kinetic flux of cargo through the secretory-endosomal-autophagic-lysosomal-exocytic (SEALE) network is broadly defined as (i) processes that regulate cargo exocytosis (green arrows) and (ii) processes that regulate cargo catabolism (red dotted arrows). Within the SEALE network, bi-directional cargo trafficking also occurs (black arrows), particularly between endosomal/lysosomal organelles and the ER/Golgi. Macroautophagy can occur through *de novo* synthesis within the cytosol or from membranes originating from the ER/Golgi (ERphagy). Proteins involved in common neurodegenerative diseases, such as amyloid precursor protein (APP), are metabolised within the SEALE network, and their metabolites can become "cargo toxins" (e.g. amyloid-β-protein (Aβ) aggregates) when catabolic flux is impaired. Note: the lysosome depicted here represents an active lysosome receiving cargo from autophagic and endocytic routes. LC3-II is present on autolysosomal but not lysosomal membranes. Abbreviations: APP-CTFs: APP C-terminal fragments, sAPP: secreted APP.

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