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Review Article

Amyloid-β precursor protein: Multiple fragments, numerous transport routes and mechanisms

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ABSTRACT

This review provides insight into the intraneuronal transport of the Amyloid-β Precursor Protein (APP), the prototype of an extensively posttranslationally modified and proteolytically cleaved transmembrane protein. Uncovering the intricacies of APP transport proves to be a challenging endeavor of cell biology research, deserving increased priority, since APP is at the core of the pathogenic process in Alzheimer's disease. After being synthesized in the endoplasmic reticulum in the neuronal soma, APP enters the intracellular transport along the secretory, endocytic, and recycling routes. Along these routes, APP undergoes cleavage into defined sets of fragments, which themselves are transported - mostly independently - to distinct sites in neurons, where they exert their functions. We review the currently known routes and mechanisms of transport of full-length APP, and of APP fragments, commenting largely on the experimental challenges posed by studying transport of extensively cleaved proteins. The review emphasizes the interrelationships between the proteolytic and posttranslational modifications, the intracellular transport, and the functions of the APP species. A goal remaining to be addressed in the future is the incorporation of the various views on APP transport into a coherent picture. In this review, the disease context is only marginally addressed; the focus is on the basic biology of APP transport under normal conditions. As shown, the studies of APP transport uncovered numerous mechanisms of transport, some of them conventional, and others, novel, awaiting exploration.

Contents

Abbreviations: APP, Amyloid-β Precursor Protein; AD, Alzheimer's disease; Aβ, Amyloid-β; ER, endoplasmic reticulum; ERGIC, ER-Golgi Intermediate Compartment; TGN, trans-Golgi network; AICD, APP Intracellular Domain; PTB, phosphotyrosine binding; JIP-1, JNK-interacting protein-1; APP_C and APP_N, APP C- and N-terminal epitopes; NTF and CTF, N- and C-terminal fragment; RTN4, Reticulon 4

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Introduction, or why should we care about APP transport

It is not uncommon for today's biomedical research that the function of a protein at the center of a major disease is poorly understood. Amyloid-β Precursor Protein (APP), the protein viewed at the core of the pathogenesis of Alzheimer's disease (AD) makes one good example. APP was discovered more than 25 years ago [1], and became one of the most studied proteins as soon as it was associated with AD. Multiple functions have been proposed for APP [2], but none of them is clearly demonstrated (Sam Sisodia of the University of Chicago once referred to APP as the All Purpose Protein - seminar delivered ~10 years ago to an audience at Case Western Reserve University). There are several explanations for this situation: (1) In mammals, APP is one of three related proteins, which may have overlapping functions; (2) Mice deficient in the *APP* gene, show a plethora of phenotypic changes – none essential for survival - that remain mechanistically unexplained [2]; (3) APP has complex biology, and is the precursor protein for Amyloid-β (Aβ), and several other polypeptides, which are generated from APP by successive cleavages operated by numerous proteases [3]. These polypeptides could have their own functions, independent of the parent protein, thus increasing the complexity of APP functions. Moreover, APP is extensively posttrans-lationally modified by glycosylation – both in the ecto- and endo-domain - and by phos-phorylation at several residues within its short, cytoplasmic domain [4]. This domain interacts with multiple cytoplasmic proteins, including molecular motors that carry APP to different destinations [5]. In neurons, APP is transported along secretory, endocytic, and recycling routes that are currently being elucidated [6]. The cleavage of APP into fragments occurs along these routes, certainly at more than one cellular location.

APP is subjected to successive proteolytic cleavages by two of three endoproteases, called secretases, which operate along two mutually exclusive pathways [3]. Depending on its intracellular location, APP is cleaved by either α- and γ–secretase (non-amyloidogenic pathway) or β- and γ–secretase (amyloidogenic pathway) (Fig. 1A). Although the first and second cleavages may occur in the same subcellular compartment, they usually are temporarily and spatially separated. These two proteolytic pathways produce mostly distinct, but topologically similar, sets of protein fragments (Fig. 1A). It is the amyloidogenic pathway, which generates the potentially toxic Aβ peptide that is most relevant to AD. Other proteases, including caspases, also cleave APP, but these proteolytic pathways are less investigated. Obviously, the transport and cleavage of APP are intimately related processes, essential for both the physiology and pathology of the neuron, and cannot be dissociated from each other.

This short review provides a glimpse into the transport of APP in relation to its processing; due to space limitations, it is not a comprehensive list of all identified APP transport routes, and their regulation. We aim to reveal the complexity of APP transport, which comprises the transport of the full-length APP, and of its derived fragments; we will also discuss the experimental challenges encountered when trying to track down what is, in fact, transported: full-length APP, or APP fragments. We will limit our analysis to a few examples, focusing on neurons. For the most part, we will avoid the beaten path, and stress on novelty.

Where does APP localize in neurons? short answer: almost everywhere

APP, a type I transmembrane protein, is synthesized at the endoplasmic reticulum, and enters the intracellular transport along the secretory, endocytic, and recycling routes, in the soma and neuronal processes. With immunocytochemistry at light or electron microscopy level, APP was detected at the ER, the ER-Golgi Intermediate Compartment (ERGIC), in all subcompartments of the Golgi apparatus, the trans-Golgi network (TGN), post-Golgi secretory vesicles, the plasma membrane, in the early, sorting/recycling, and late endosomes, lysosomes, and autophagosomes. APP is transported to both axons and dendrites, but the fates of axonally- and dendritically-localized APP likely differ [7]. APP – full length and/or fragments - was also found in unexpected places, such as mitochondria [8], the nucleus [9], the ciliary rootlet of the retinal photoreceptor cells [10], and even - apparently free - in the cytoplasm [11]. In some of these locations, cleaved fragments were predominant. Still, some anomalies are obvious: the detection of Aβ epitope in the cytoplasm is not explainable, unless intracellular degradation of membrane-bounded compartments, retrotranslocation from the membrane-bounded organelles, or some other - yet to be explained – phenomenon, reverses the topology of the polypeptide. Also, the extent of APP localization to mitochondria needs to be carefully assessed, because ER-localized APP is enriched at ER-mitochondria contact sites [12]. The localization to the nucleus of APP represents the nuclear targeting of the cytoplasmic fragment of APP (the APP Intracellular Domain, AICD), presumed to enter the nucleus alone, or in association with the APP binding protein, Fe65 [9].

Exogenously expressed APP, usually C-terminally tagged with YFP [13], also localizes to many intraneuronal compartments. While the resolution of detection of the tag varies among reports, expressed, tagged APP usually shows fewer details, being often localized throughout the neuronal soma and processes, unless the expression levels are kept low [14]. Little justification is found in expressing APP-derived polypeptides with incorrect topology, such as

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