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Review

Redundancy and divergence in the amyloid precursor protein family

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ABSTRACT

Gene duplication provides genetic material required for functional diversification. An interesting example is the amyloid precursor protein (APP) protein family. The APP gene family has experienced both expansion and contraction during evolution. The three mammalian members have been studied quite extensively in combined knock out models. The underlying assumption is that APP, amyloid precursor like protein 1 and 2 (APLP1, APLP2) are functionally redundant. This assumption is primarily supported by the similarities in biochemical processing of APP and APLPs and on the fact that the different APP genes appear to genetically interact at the level of the phenotype in combined knockout mice. However, unique features in each member of the APP family possibly contribute to specification of their function. In the current review, we discuss the evolution and the biology of the APP protein family with special attention to the distinct properties of each homologue. We propose that the functions of APP, APLP1 and APLP2 have diverged after duplication to contribute distinctly to different neuronal events. Our analysis reveals that APLP2 is significantly diverged from APP and APLP1.

1. Introduction

Amyloid β peptide is the main constituent of the amyloid plaques in Alzheimer patients. Amyloid precursor protein (APP) is the precursor protein from which the Aβ peptide is generated. This peptide is produced by endoproteolytic cleavages of APP, which in addition shed a larger soluble ectodomain in the extracellular environment and an intracellular domain into the cytoplasm [1,2]. The proteolytic processing of APP is a constitutive process, and explains in part the relative short half life (less than an hour) of full length APP [3]. Unbalanced proteolytic cleavage of APP or mutations in the Aβ sequence can result in increased production, and mainly in alterations of the biophysical properties of Aβ. Consequently, oligomerization and aggregation of Aβ can contribute to the brain pathology and neurodegeneration in familial and sporadic Alzheimer Disease [2]. In contrast, our knowledge of the physiological function of APP remains surprisingly incomplete. Although the loss of APP and its homologues were studied in several model organisms, no clear picture has yet emerged. Sometimes, the protein is called "All Purpose Protein" to indicate the many different signaling pathways and protein interactions in which APP has been implicated. The different proposed functions for APP are not always consistent. For instance both enhancement and inhibition of dendritic spine formation [4–6] or neuronal cell migration [7,8] have been proposed to be mediated by APP.

Next to APP, APP-like proteins are present in different species. Similar to APP, APP-like proteins (APLP) undergo proteolytic processing [9]. Furthermore, mutant mice lacking *Aplp2* combined with *App* or *Aplp1* display a lethal phenotype, with mice dying around birth [10]. The genetic interactions of the *App* and *App-like* genes and the similarity in proteolytic processing have been taken as evidence for functional redundancy of the three *App* paralogues. Therefore, experiments to deduce the biological function of APP are mainly based on the "redundancy model" which assumes that the *App* paralogues are functionally interchangeable. Such an approach pays too little attention to the unique properties of each *App* paralogue and might disregard the possibility that they are operating in different and independent pathways. In such a view, their combined mutations lead to a "synthetic phenotype" (lethality) by

Abbreviations: APP, amyloid precursor protein; APLP, amyloid precursor like protein; APBA1, precursor protein binding, family A; Arc, member 1, activity-regulated cytoskeleton-associated protein; ApoeR2, apolipoprotein E receptor 2; CR, Cajal-Retzius; CASK, calcium/calmodulin-dependent serine protein kinase; CP, cortical plate; DAB1, Disabled-1; dko, double knockout; GFAP, glial fibrillary acidic protein; FOS, FBJ murine osteosarcoma viral oncogene homolog; ko, Knockout; LTP, long term potentiation; MAP2, Microtubule-associated protein 2; PCP, planar polarity pathway; KCNH6, member 6; SVZ, Subventricular zone; VZ, ventricular zone; Vldlr, very low density lipoprotein receptor; WNT5A, Wingless-type MMTV integration site family, member 5A

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Table 1
The species and protein sequences used for functional divergence analysis.

Organism	Accession number	Gene name
Homo sapiens (Human)	NP_000475.1	APP
	NP_001019978.1	APLP1
	NP_001135748.1	APLP2
Pan troglodytes (Chimps)	NP_001013036.1	APP
	XP_003316372.1	APLP1
	XP_001155401.1	APLP2
Canis lupus familiaris (Dog)	NP_001006601.1	APP
	XP_533688.4	APLP1
	XP_536530.2	APLP2
Mus musculus (Mouse)	NP_001185752.1	APP
	NP_031493.2	APLP1
	NP_001095925.1	APLP2
Gallus gallus (Chicken)	NP_989639.1	APP
	NP_001006317.2	APLP2
Danio rerio (Fish)	NP_571639.1	APPa
	NP_690842.1	APPb
	XP_001342921.4	APLP
	NP_690842.1	APLP2
Xenopus laevis (Frog)	NP_001082098.1	APP
	NP_001089419.1	APLP1
	NP_001094408.2	APLP2a
	NP_001094407.1	APLP2b
Drosophila melanogaster (Fly)	NP_001245451.1	APPL
Caenorhabditis elegans (Worm)	NP_508871.1	APL1

affecting distinct pathways. This also implies that *App* paralogues are not simply extra copies but have evolved to perform specialized function.

We structure our review on the divergence of APP function by asking following questions: What are the possible evolutionary fates of duplicated APP homologues? What does the loss of function studies tell us about the specialization of APP family proteins? What are the similarities and differences in processing of APP and APLPs? How does transcriptional and interaction network divergences contribute to the evolution of the APP family? Finally, we provide support for the "divergence" idea by using a computational method to predict critical amino acid and sub-domains that potentially contribute to the divergence of the APP protein family. Based on this comparison, it will become clear that the different APP genes do not simply encode duplicated proteins with interchangeable function. This should bring the focus back on the unique properties of each member of the APP family and might help to explain some of the discrepancies in the field.

2. The APP family

Genes encoding for the APP protein family have experienced several twists and turns during evolution (Table 1 lists all the species and proteins discussed in this review). APP-like proteins have not been identified in prokaryotes, yeasts and plants (Fig. 1). The simplest and earliest branches of the evolutionary tree in which *APP*-like genes have been identified contain insects such as the fruit fly (*Drosophila melanogaster*) and roundworms (*Caenorhabditis elegans*) each carrying one gene encoding for an APP-like protein. It is intriguing that APP-like proteins first emerge in *Bilaterians* with an early nervous system with functional synapses [11,12]. Indeed, the extracellular domains of APP molecules have cell adhesion properties and can promote cell-cell adhesion [13]. Such intercellular interaction is important in early evolution for the generation of the synaptic junction [12,14]. Strikingly, when overexpressed in HEK cells, APP can potently induce synaptogenesis in the contacting axon and this activity requires the extracellular domain as well as the intracellular part of APP. The later associates with presynaptic molecules such as APP binding family A (APBA1) and Calcium/calmodulin-dependent serine protein kinase (CASK) [15]. Interestingly, APP is required both at pre- and postsynaptic compartments to induce synaptogenesis [15] which suggests that ancestral APP indeed might be a transmembrane protein responsible for homophilic interactions at the synaptic junction early in evolution.

Five nodes of duplications are observed in the phylogenetic tree of the APP protein family when using Ensemble comparative genomics tools (schematically represented in Fig. 1). For example, fishes (*Danio rerio*) have in total four genes encoding APP proteins: two homologues for the human *APP* gene (*appa* and *appb*) plus *aplp1* and *aplp2* (Fig. 1). Similar to fishes, amphibians (*Xenopus laevis*) carry four *app* genes in their genome but they have two homologues for the human *APLP2* gene: *aplp2a*, *aplp2b* plus *app* and *aplp1* (Fig. 1). Instead, birds (*Gallus gallus*) have lost the *APLP1* gene leaving them with *APP* and *APLP2* genes (Fig. 1). The paradoxical expansion and contraction of the APP family suggest that the duplications of the encoding genes have been the subject of highly selective evolutionary forces. The complicated trajectory of the evolution of the APP protein family ends with the three best-studied members in mammals: *APP*, *APLP1* and *APLP2* (Fig. 1) [16].

The evolutionary maintenance of a duplicated gene in the genome is influenced by the accumulation of genetic mutations affecting the function of the descendant duplicates. Three possible

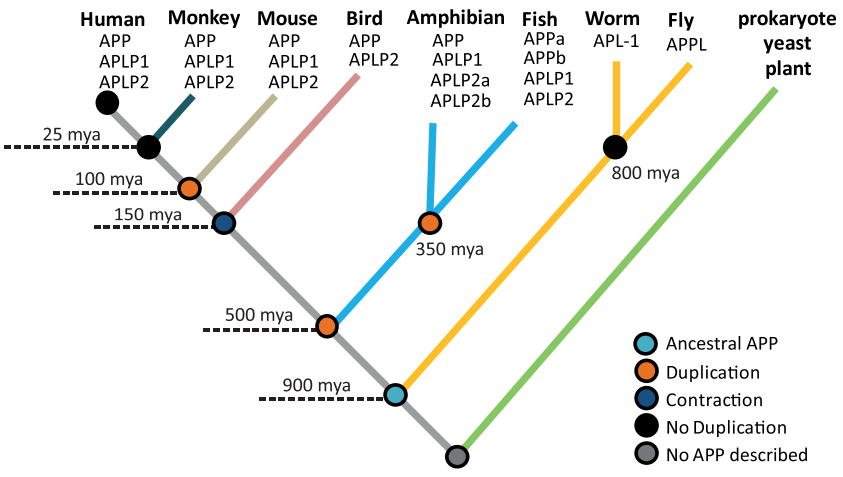

Fig. 1. A simplified dendrogram based on APP protein family tree of Ensemble illustrates the important events in the evolution of APP gene family. The duplication and contraction nodes are color coded. The lengths of the lines are not proportional to the evolutionary distance of species. The scientific names of species are listed in the Table 1. For details of APP protein family evolution see the text. Mya: million years ago.