stem cell research&therapy

COMMENTARY

Amyloid precursor protein: more than just neurodegeneration

Sanjay W Pimplikar* and Kaushik Ghosal

See related research by Demars et al., http://stemcellres.com/content/2/4/36

Abstract

Amyloid precursor protein (APP) fascinates cell biologists because it is proteolytically processed to generate multiple peptides, including amyloid-β, which is implicated in Alzheimer's disease. However, a large body of data also shows that the extracellular soluble fragment of APP produced by α-secretase (sAPPα) is neuroprotective and promotes neuronal outgrowth. A study by Demars and colleagues appearing in the previous issue provides data showing that sAPPα is a general growth factor for stem cells of multiple lineages. Thus, APP seems to play complex and disparate roles in neurodegeneration and neuroprotection.

Amyloid precursor protein (APP) is a ubiquitously expressed membrane protein with a domain structure that resembles a typical membrane receptor protein. Unlike most receptor proteins, however, it is constitutively cleaved into smaller fragments. APP has attracted a lot of attention due to its pathological role in Alzheimer's disease, yet the biological necessity of APP processing, which results in the secretion of large extracellular fragments (soluble fragments sAPPα or sAPPβ) together with smaller peptides (beta-amyloid (Aβ), p3 and APP intracellular domain (AICD)), remains uncertain. A study by Demars and colleagues [1] that appears in the previous issue of *Stem Cell Research & Therapy* sheds some light on why APP is processed. Using stem cell populations from three different origins, this study provides clear evidence that the sAPPα fragment released by α-secretase cleavage of APP stimulates proliferation of adult neural progenitor cells, mesenchymal stem cells and human placental stem cells.

*Correspondence: pimplis@ccf.org
Department of Neurosciences, Lerner Research Institute, Cleveland Clinic, NC-30, Cleveland, OH 44195, USA

One of the intriguing features of APP processing is that APP can be cleaved at two sites in very close proximity (separated by only 16 residues) by α-secretase or β-secretase, generating either sAPPα or the slightly smaller sAPPβ, respectively. α-Secretase cleavage is the major pathway of APP processing, which is mediated by a disintegrin and metalloproteinase ADAM10 or ADAM17. Demars and colleagues found that treatment of cells with GM6001, a broad-spectrum inhibitor of matrix-metalloproteinases and ADAMs, significantly reduced proliferation of stem cells of all three origins. Importantly, they were able to rescue cell proliferation by adding purified sAPPα in a dose-dependent manner. The stimulatory action of sAPPα on stem cell proliferation was independent of epidermal growth factor and basic epidermal growth factor, which are the known stimulators of stem cell proliferation [2]. Using specific inhibitors of kinase pathways, Demars and colleagues demonstrated that ERK signaling is involved downstream of the proliferating effects of sAPPα.

This study by Demars and colleagues adds to previous studies demonstrating the neuroprotective and neuroproliferative effects of sAPPα on adult neurons [2,3]. Indeed, mice lacking APP (APP-KO) show smaller brain size and reduced body growth [4] and studies show that expression of sAPPα alone can rescue the growth and brain weight deficits [5]. Thus, there is now overwhelming evidence that sAPPα exerts a positive, growth-promoting effect on both neuronal precursor stem cells as well as adult neurons. The novel conclusion of this study is that sAPPα is a general proliferation factor for stem cells of multiple lineages since APP is ubiquitously expressed and since sAPPα stimulates proliferation of diverse stem cell populations.

What remains unknown is whether sAPPβ, the fragment 16 residues shorter than sAPPα, also exerts similar effects. Since sAPPα and sAPPβ are generated in a roughly 9:1 ratio, the biological effects of sAPPβ, unless dramatically different from those of sAPPα, are likely to be marginal on neuronal stem cells. A recent study from the Allinquant group [6] shows that both sAPPα and sAPPβ stimulated axon growth via ERK activation and

the LaFerla group [7] reported that amino-terminally secreted products of APP, and in particular sAPPβ, caused a rapid and robust differentiation of pluripotent human embryonic stem cells toward a neural fate. Together, these studies suggest that APP processing has a stimulating effect on both neural stem cell proliferation and differentiation. However, the overall effects of APP processing on neural stem cell proliferation and differentiation are likely to be more complex since APP processing also generates Aβ and AICD fragments, which have been shown to exert a negative influence on neurogenesis [8,9].

The identity of the membrane protein that binds sAPPα and acts as a receptor to activate the intracellular ERK signaling pathway remains unknown. One intriguing possibility is that sAPPα binds uncleaved, membrane-bound APP since APP has been shown to form homodimers in *cis* and in *trans* through its extracellular portion. Moreover, APP has been known to activate the ERK pathway through its intracellular domain [10]. Future studies will be needed to test this hypothesis.

Although the biological consequences of APP-processing on neural stem cell proliferation and differentiation are likely to be complex, these studies of Demars and colleagues and Freude and colleagues indicate that sAPPα/sAPPβ can be harnessed to generate large numbers of neural precursor cells and neurons from human embryonic stem cells. This has the potential for new approaches to study the physiological as well as pathological roles of APP.

Abbreviations

Aβ, beta-amyloid; ADAM, a disintegrin and metalloproteinase; AICD, APP intracellular domain; APP, amyloid precursor protein; sAPP, soluble amyloid precursor.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

We thank Dr Chris Nelson for his comments on the manuscript. SWP acknowledges funding support from the NIH, Alzheimer's Association and CART-Rotary Funds.

Published: 14 October 2011

References

1. Demars MP, Bartholomew A, Strakova Z, Lazarov O: **Soluble amyloid precursor protein: a novel proliferation factor of adult progenitor cells of ectodermal and mesodermal origin.** *Stem Cell Res Ther* 2011, **2:**36.
2. Caille I, Allinquant B, Dupont E, Bouillot C, Langer A, Muller U, Prochiantz A: **Soulble form of amyloid precursor protein regulates proliferation of progenitors in the adult subventricular zone.** *Development* 2004, **131:**2173-2181.
3. Gakhar-Koppole N, Hundeshagen P, Mandl C, Weyer SW, Allinquant B, Muller U, Ciccolini F: **Activity requires soluble amyloid precursor protein alpha to promote neurite outgrowth in neural stem cell-derived neurons via activation of the MAPK pathway.** *Eur J Neurosci* 2008, **28:**871-882.
4. Zheng H, Jiang M, Trumbauer ME, Sirinathsinghji DJ, Hopkins R, Smith DW, Heavens RP, Dawson GR, Boyce S, Conner MW, Stevens KA, Slunt HH, Sisoda SS, Chen HY, Van der Ploeg LH: **beta-Amyloid precursor protein-deficient mice show reactive gliosis and decreased locomotor activity.** *Cell* 1995, **81:**525-531.
5. Ring S, Weyer SW, Kilian SB, Waldron E, Pietrzik CU, Filippov MA, Herms J, Buchholz C, Eckman CB, Korte M, Wolfer DP, Müller UC: **The secreted beta-amyloid precursor protein ectodomain APPs alpha is sufficient to rescue the anatomical, behavioral, and electrophysiological abnormalities of APP-deficient mice.** *J Neurosci* 2007, **27:**7817-7826.
6. Chasseigneaux S, Dinc L, Rose C, Chabret C, Coulpier F, Topilko P, Mauger G, Allinquant B: **Secreted amyloid precursor protein β and secreted amyloid precursor protein α induce axon outgrowth *in vitro* through Egr1 signaling pathway.** *PLoS One* 2011, **6:**e16301.
7. Freude KK, Penjwini M, Davis JL, LaFerla FM, Blurton-Jones M: **Soluble amyloid precursor protein induces rapid neural differentiation of human embryonic stem cells.** *J Biol Chem* 2011, **286:**24264-24274.
8. Lazarov O, Mattson MP, Peterson DA, Pimplikar SW, van Praag H: **When neurogenesis encounters aging and disease.** *Trends Neurosci* 2010, **33:**569-579.
9. Ghosal K, Stathopoulos A, Pimplikar SW: **APP intracellular domain impairs adult neurogenesis in transgenic mice by inducing neuroinflammation.** *PLoS One* 2010, **5:**e11866.
10. Nizzari M, Venezia V, Repetto E, Caorsi V, Magrassi R, Gagliani MC, Carlo P, Florio T, Schettini G, Tacchetti C, Russo T, Diaspro A, Russo C: **Amyloid precursor protein and Presenilin1 interact with the adaptor GRB2 and modulate ERK 1,2 signaling.** *J Biol Chem* 2007, **282:**13833-13844.

doi:10.1186/scrt80
Cite this article as: Pimplikar SW, Ghosal K: **Amyloid precursor protein: more than just neurodegeneration.** *Stem Cell Research & Therapy* 2011, **2:**39.