



Commentary

Mice are not Men: ADAM30 Findings Emphasize a Broader Look Towards Murine Alzheimer's Disease Models



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Due to the growing population of people at advanced age, the number of patients affected by Alzheimer's disease (AD) is increasing tremendously. In 2015 about 46.8 million people suffered from AD worldwide which is estimated to increase to 131.5 million by 2050. Brains of AD patients all show a common histopathology; they are marked by an atrophy and degeneration that is caused by a severe loss of neurons and synapses (Braak and Del Tredici, 2012). Moreover, so-called extracellular senile plaques that consist of predominantly amyloid β ($A\beta$) peptides can be detected in the grey matter where they surround neurons. Since generation of $A\beta$ peptides is hypothesized to play a major role in AD pathogenesis, it is essential to decipher the enzymatic cascade leading to the generation of $A\beta$. Most of the $A\beta$ -peptides are initially generated by β -secretase (BACE1) with subsequent γ -secretase cleavage of the amyloid precursor protein (APP). In contrast, ADAM10 as α -secretase cleaves APP within the $A\beta$ sequence and prevents the generation and subsequent accumulation of this neurotoxic peptide. Recently, several studies described the presence of N-terminally truncated $A\beta$ peptides in brain or cerebrospinal fluid (CSF), including $A\beta_{2-42}$, pyroglutamate $A\beta_{3-42}$ ($A\beta_{pE3-42}$) or $A\beta_{4-42}$ (Kummer and Heneka, 2014). However, BACE-1 is incapable in generating these truncated peptides, since it only cleaves APP in amino acid positions p1 or p11 of the $A\beta$ peptide (Vassar et al., 1999). Therefore, it is of utmost importance to identify new players in APP metabolism that might have been overlooked so far, possibly due to low expression, lack of appropriate tools, or other experimental confounds.

A striking challenge in studying Alzheimer's disease is the use of appropriate animal models. Since $A\beta$ peptides derived from murine APP do not lead to neurodegeneration, almost all animal studies are based on humanized mice overexpressing human APP. Moreover, the mutated APP variant inserted in these animals is almost exclusively cleaved N-terminally by BACE-1 lacking the generation of N-terminally truncated $A\beta$ peptides. Although, these animal models are of great value, they may exhibit critical restrictions: potential factors involved in pathological APP processing that are not expressed in normal murine brain are

certainly ignored. Recently, it has been suggested that additional enzymes like meprin β may be involved in the generation of N-terminal truncated $A\beta$ peptides, but the *in vivo* relevance remains unclear due to the lack of mouse models (Schonherr et al., 2016). In this issue of *EBioMedicine*, Lambert and colleagues report on the metalloprotease ADAM30 as a potential regulator of APP processing, which itself is also not expressed under physiological conditions in mice (Letronne et al., 2016).

Most interestingly, ADAM30 was found to be expressed at lower levels in brains of AD patients compared to controls and the authors demonstrate correlation of low expression of ADAM30 with increased $A\beta$ levels. Thus, ADAM30 does not act like the α -secretase ADAM10, but instead ADAM30 was found to induce cathepsin D activity through its maturation, subsequently influencing lysosomal APP metabolism. Remarkably, both enzymes were identified in unbiased screens, ADAM30 in a GWAS study and cathepsin D with the help of modern proteomics techniques for the identification of protease substrates of ADAM30. The activation of cathepsin D by ADAM30 was unexpected, and brings back an old player into the game. More than twenty years ago cathepsin D was implicated in Alzheimer's disease (Cataldo et al., 1995; Ladrör et al., 1994). However, the murine knock-out of the cathepsin D gene had no effect on $A\beta$ formation (Saftig et al., 1996). Interestingly it had been demonstrated that cathepsin D displays BACE 1-like β -secretase specificity at low pH values but shows poor kinetic activity towards the wildtype β -secretase amino acid sequence (Schechter and Ziv, 2008).

Lambert and colleagues demonstrated that overexpression of ADAM30 in transgenic mice led to reduced levels of $A\beta_{42}$ due to increased lysosomal APP cleavage by cathepsin D. Here, one might argue that this is not a direct proof for the correlation of low ADAM30 expression in Alzheimer's disease patients and the onset and/or progression of the disease. This is indeed true. However, it again demonstrates potential pitfalls using mouse models for AD, because ADAM30 is obviously not expressed in the murine brain under physiological conditions, which excludes the use of ADAM30 knock-out mice.

Therefore, it is important to combine different approaches to gain a better understanding of molecular factors involved in the onset and progression of Alzheimer's disease. Murine models have great value but certain drawbacks, which demonstrate the necessity of developing new techniques better resembling the human system. For instance, a recent paper reports on the employment of brain region specific organoid cultures derived from human induced pluripotent stem cells (iPSCs)

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(Qian et al., 2016). This platform was used to model Zika virus exposure but it may also be a suitable approach to study A β mediated neurodegeneration in a human system.

Dementia is a global threat and to date no effective treatment for AD is available more than 100 years after the discovery of the disease by Alois Alzheimer. Hence, the key message from the paper is: Keep one's eyes peeled for yet ambiguous factors potentially involved in Alzheimer's disease. They may one day lead to biomarkers or treatments for this devastating disease.

Conflict of Interest

None.

References

- Braak, H., Del Tredici, K., 2012. Where, when, and in what form does sporadic Alzheimer's disease begin? *Curr. Opin. Neurol.* 25, 708–714.
- Cataldo, A.M., Barnett, J.L., Berman, S.A., Li, J., Quarless, S., Bursztajn, S., Lippa, C., Nixon, R.A., 1995. Gene expression and cellular content of cathepsin D in Alzheimer's disease brain: evidence for early up-regulation of the endosomal-lysosomal system. *Neuron* 14, 671–680.
- Kummer, M.P., Heneka, M.T., 2014. Truncated and modified amyloid-beta species. *Alzheimers Res. Ther.* 6, 28.
- Ladror, U.S., Snyder, S.W., Wang, G.T., Holzman, T.F., Krafft, G.A., 1994. Cleavage at the amino and carboxyl termini of Alzheimer's amyloid-beta by cathepsin D. *J. Biol. Chem.* 269, 18422–18428.
- Letronne, F., et al., 2016. ADAM30 downregulates APP-linked defects through cathepsin D activation in Alzheimer's disease. *EBioMedicine* <http://dx.doi.org/10.1016/j.ebiom.2016.06.002>.
- Qian, X., Nguyen, H.N., Song, M.M., Hadiono, C., Ogden, S.C., Hammack, C., Yao, B., Hamersky, G.R., Jacob, F., Zhong, C., Yoon, K.J., Jeang, W., Lin, L., Li, Y., Thakor, J., Berg, D.A., Zhang, C., Kang, E., Chickering, M., Nauen, D., Ho, C.Y., Wen, Z., Christian, K.M., Shi, P.Y., Maher, B.J., Wu, H., Jin, P., Tang, H., Song, H., Ming, G.L., 2016. Brain-region-specific organoids using mini-bioreactors for modeling ZIKV exposure. *Cell* 165, 1238–1254.
- Saftig, P., Peters, C., von Figura, K., Craessaerts, K., Van Leuven, F., De Strooper, B., 1996. Amyloidogenic processing of human amyloid precursor protein in hippocampal neurons devoid of cathepsin D. *J. Biol. Chem.* 271, 27241–27244.
- Schechter, I., Ziv, E., 2008. Kinetic properties of cathepsin D and BACE 1 indicate the need to search for additional beta-secretase candidate(s). *Biol. Chem.* 389, 313–320.
- Schonherr, C., Bien, J., Isbert, S., Wichert, R., Prox, J., Altmeyen, H., Kumar, S., Walter, J., Lichtenthaler, S.F., Weggen, S., Glatzel, M., Becker-Pauly, C., Pietrzik, C.U., 2016. Generation of aggregation prone N-terminally truncated amyloid beta peptides by meprin beta depends on the sequence specificity at the cleavage site. *Mol. Neurodegener.* 11, 19.
- Vassar, R., Bennett, B.D., Babu-Khan, S., Kahn, S., Mendiaz, E.A., Denis, P., Teplow, D.B., Ross, S., Amarante, P., Loeloff, R., Luo, Y., Fisher, S., Fuller, J., Edenson, S., Lile, J., Jarosinski, M.A., Biere, A.L., Curran, E., Burgess, T., Louis, J.C., Collins, F., Treanor, J., Rogers, G., Citron, M., 1999. Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science* 286, 735–741.