Journal of Neurochemistry
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JNC Highlights December 2020

Latest Research and Reviews

The following articles are part of Volume 155, Issue 3 – Pages 225-338

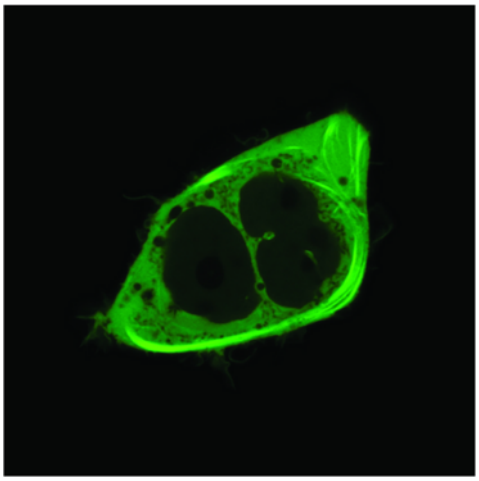
Cover Image

Tau protein phosphorylation at Thr175 initiates fibril formation via accessibility of the N-terminal phosphatase-activating domain

Matthew A. Hintermayer, Kathryn Volkening, Alexander J. Moszczynski, Neil Donison, Michael J. Strong

Front cover: The aberrant phosphorylation of tau protein at threonine Thr175 is a pathologic event that promotes the formation of tau fibrils both in vitro and in vivo. Previous research has shown that this fibril formation is dependant upon the activation of glycogen synthase kinase 3β (GSK3β) via a previously unknown mechanism. The phosphorylation of tau at Thr175 occurs acutely following traumatic brain injury in rats and results in the aberrant exposure of the tau N-terminal phosphatase-activating domain (PAD). This event activates protein phosphatase 1 (PP1), which then removes an inhibitory phosphate from the Ser9 residue of GSK3β, leading to its activation. This research contributes to our understanding of how initial aberrant modifications to tau protein in neuronal injury can contribute to further propagation of tauopathy in a variety of neurodegenerative conditions.

Image content: Live cell imaging of HEK293T cell expressing pseudophosphorylated (Thr175Asp) eGFP-tagged tau protein. Dense curvilinear fibrils are visible within the cell.



Read the full article *'Tau protein phosphorylation at Thr^{175} initiates fibril formation via accessibility of the N-terminal phosphatase-activating domain'* by M. A. Hintermayer, K. Volkening, A. J. Moszczynski, N. Donison, M. J. Strong, (*J. Neurochem.* 2020, vol. 155 (3), pp. 313–326) on doi:10.1111/jnc.14942

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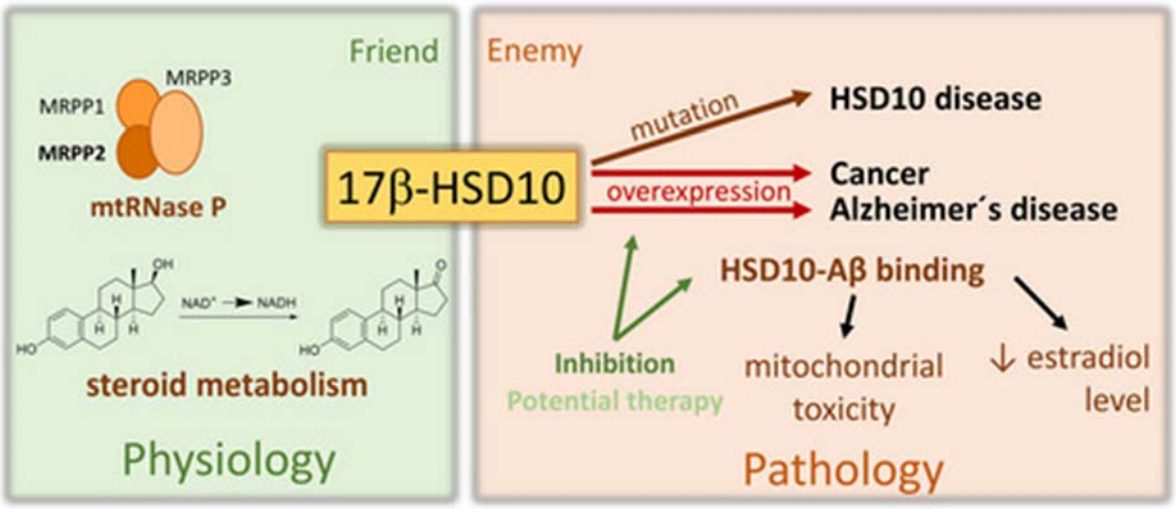
Review articles

Friend or enemy? Review of 17β-HSD10 and its role in human health or disease

Free Access

Lucie Vinklarova, Monika Schmidt, Ondrej Benek, Kamil Kuca, Frank Gunn- Moore, Kamil Musilek

17β-hydroxysteroid dehydrogenase (17β-HSD10) is a multifunctional human enzyme with important roles both as a structural component but also as a catalyst of many metabolic pathways. This mitochondrial enzyme has important functions in the metabolism, development and aging of the neural system, where it is involved in the homeostasis of neurosteroids, especially in regard to estradiol, changes in which make it an essential part of neurodegenerative pathology. In this review, 17β-HSD10 role as a possible druggable target for neurodegenerative diseases including Alzheimer's disease is indicated, but it also has become apparent that it may have a role in hormone dependent cancer.



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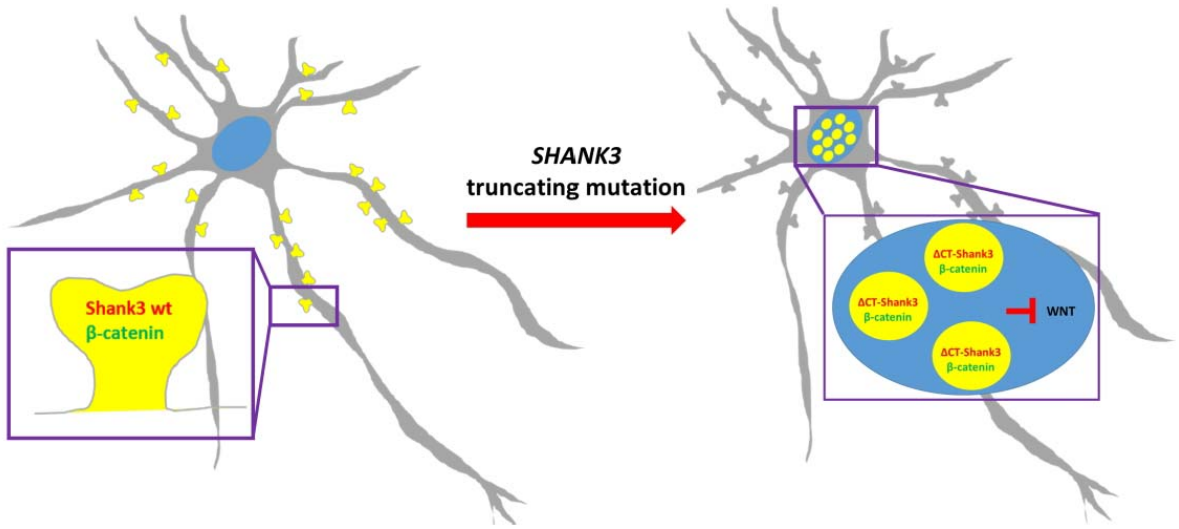
Original articles

Truncating mutations in SHANK3 associated with global developmental delay interfere with nuclear β-catenin signaling

Fatemeh Hassani Nia, Daniel Woike, Katja Kloth, Fanny Kortüm, Hans- Jürgen Kreienkamp

Full-length Shank3 interacts with β-catenin at postsynaptic sites. Mutations in the SHANK3 gene found in patients with autism and intellectual disability lead to expression of a truncated Shank3 protein. The lack of Shank3 synaptic targeting elements leads to recruitment of Shank3 and β-catenin to nuclear bodies, where activation of the Wnt signaling pathway by β-catenin is blocked by the truncated Shank3 fragment.



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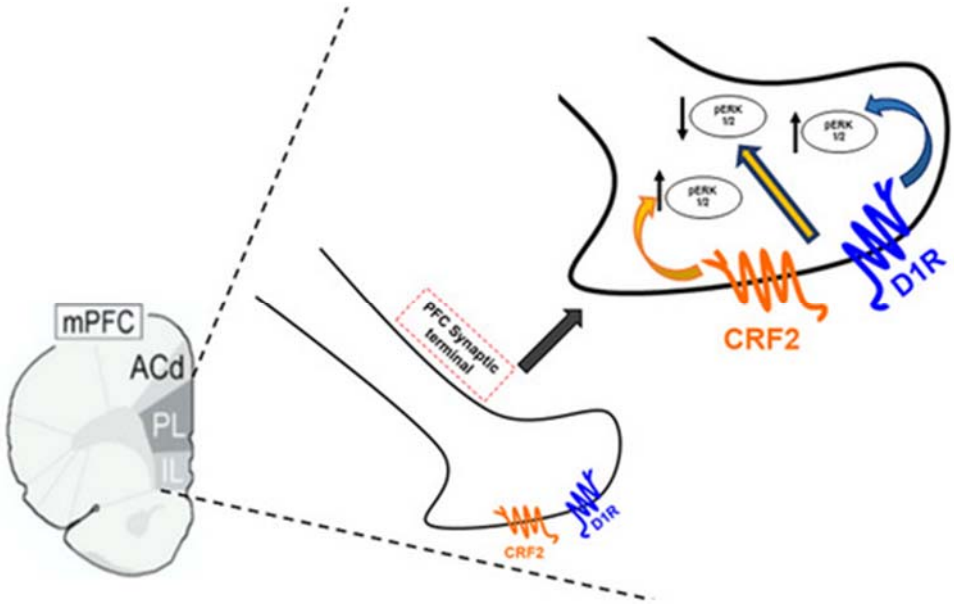
Cross-talk between dopamine D1 and corticotropin releasing factor type 2 receptors leads to occlusion of their ERK1/2 signaling

Hector E. Yarur, Marcela P. González, Daniel Verbel-Vergara, María E. Andrés, Katia Gysling

We are studying the mechanisms determining the strong interaction between stress and addiction. Thus we studied the signaling of corticotropin-releasing factor receptor type-2α (CRF2α) and dopamine D1 receptor (D1R) receptors that colocalize in synaptic terminals of the rat medial prefrontal cortex (PFC) originated in the basolateral amygdala (BLA). We observed that the activation of either CRF2α or D1R induces an increase in ERK phosphorylation. However, the coactivation of both receptors occludes the phosphorylation of ERK. This new evidence strengthens the idea that the CRF2a-D1R heteromer is a functional entity that differs from each receptor alone. Further studies should address the contribution of CRF2a-D1R heteromer to the strong interaction between stress and addiction.



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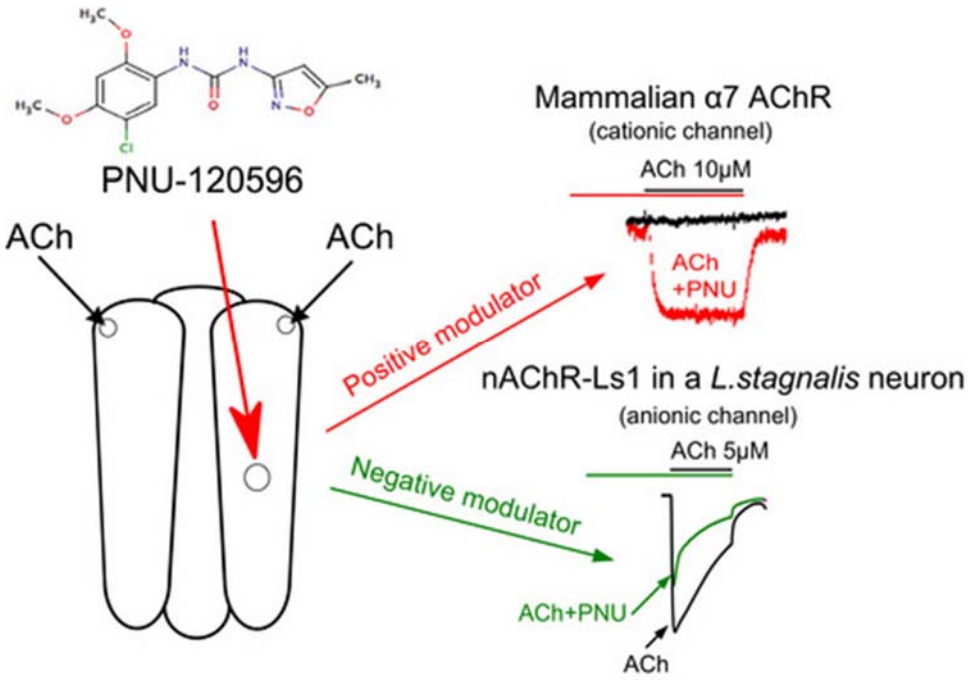
PNU-120596, a positive allosteric modulator of mammalian α7 nicotinic acetylcholine receptor, is a negative modulator of ligand-gated chloride-selective channels of the gastropod Lymnaea stagnalis

Catherine A. Vulfius, Dmitrii S. Lebedev, Elena V. Kryukova, Denis S. Kudryavtsev, Sergey N. Kolbaev, Yuri N. Utkin, Victor I. Tsetlin

Our aim was probing the effects of PNU-120596, a positive allosteric modulator (PAM) of α7 nicotinic acetylcholine receptors (nAChR), on the anion-conducting channels. Experiments were performed on *Lymnaea stagnalis* and rat Purkinje neurons and mammalian receptors expressed in *Xenopus* oocytes or PC12 cells. In *Lymnaea* neurons, PNU-120596, contrary to α7 nAChR, inhibited chloride currents mediated by two nAChR subtypes, GABA and glutamate receptors; one nAChR subtype demonstrated a strong acceleration of desensitization. With the mammalian glycine and $GABA_A$ receptors, PNU-120596 was a weak PAM. Thus, our results provide new information about the dependence of PAM action on the receptor structure.



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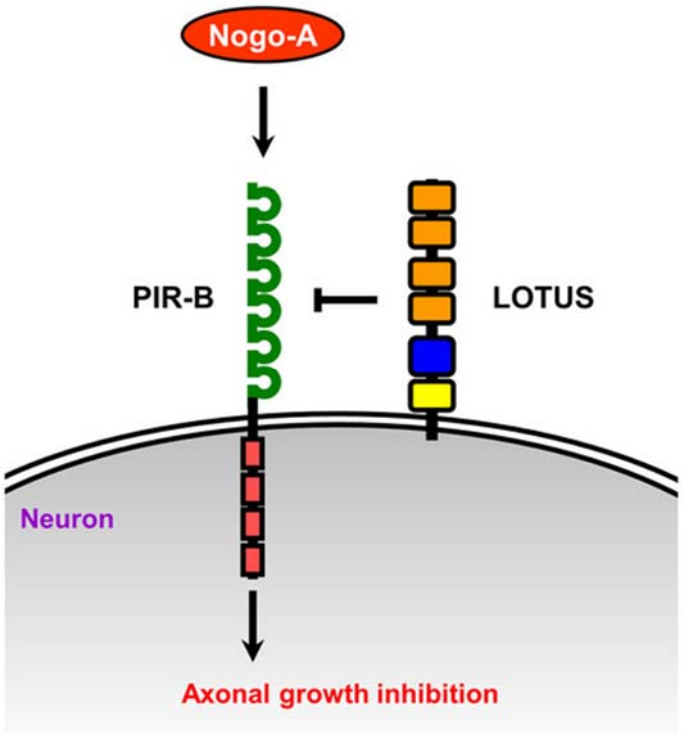
Nogo receptor antagonist LOTUS exerts suppression on axonal growth-inhibiting receptor PIR-B

Yuji Kurihara, Toshiyuki Takai, Kohtaro Takei

Myelin-associated axonal growth inhibitors such as Nogo protein bind to both receptors of Nogo receptor-1 (NgR1) and paired immunoglobulin-like receptor (PIR)-B, leading to a regenerative failure of damaged axons in the adult mammalian central nervous system. We previously reported that lateral olfactory tract usher substance (LOTUS) suppresses NgR1-mediated axonal growth inhibition. In this study, we found that LOTUS interacts with PIR-B, inhibits Nogo-binding to PIR-B, and thereby suppresses PIR-B-mediated axonal growth inhibition. These findings show that LOTUS exerts an antagonistic activity on PIR-B, suggesting that LOTUS may enhance the regenerative capacity of injured axons.



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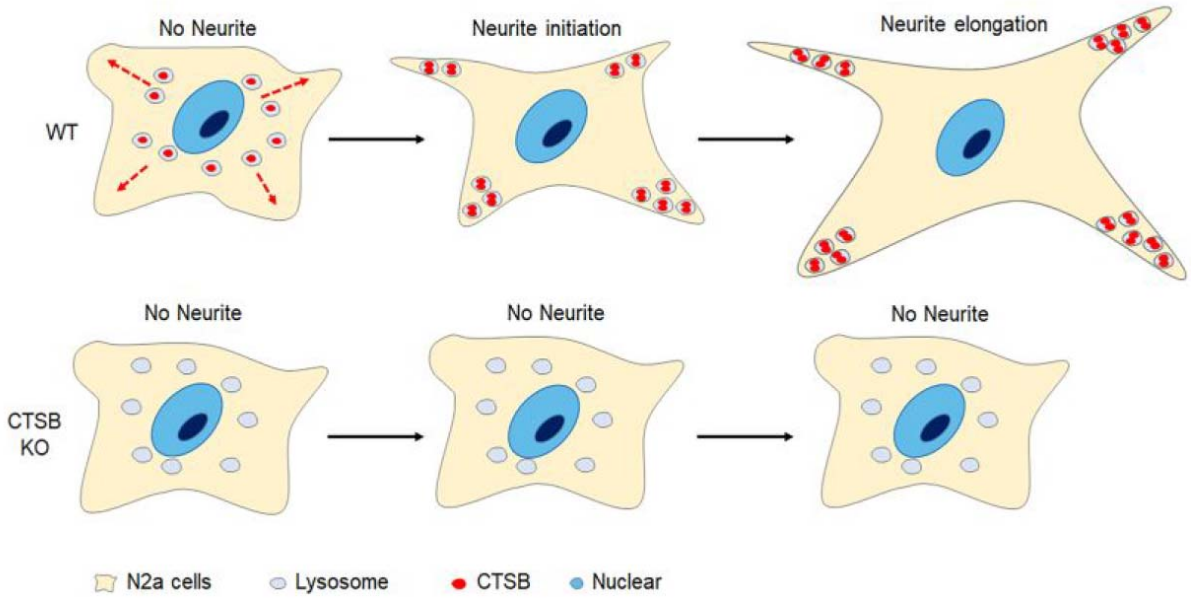
Cathepsin B inhibition blocks neurite outgrowth in cultured neurons by regulating lysosomal trafficking and remodeling

Muzhou Jiang, Jie Meng, Fan Zeng, Hong Qing, Gregory Hook, Vivian Hook, Zhou Wu, Junjun Ni

Lysosomes were trafficked to the cell membrane in N_2a cells during neurite outgrowth initiation; however, Cathepsin B (CTSB) inhibition induced a cytosol distribution of lysosomes and neurite outgrowth blockage. We proposed that intracellular CTSB controls neurite outgrowth and that it does so through regulation of lysosomal trafficking and remodeling in neurons.



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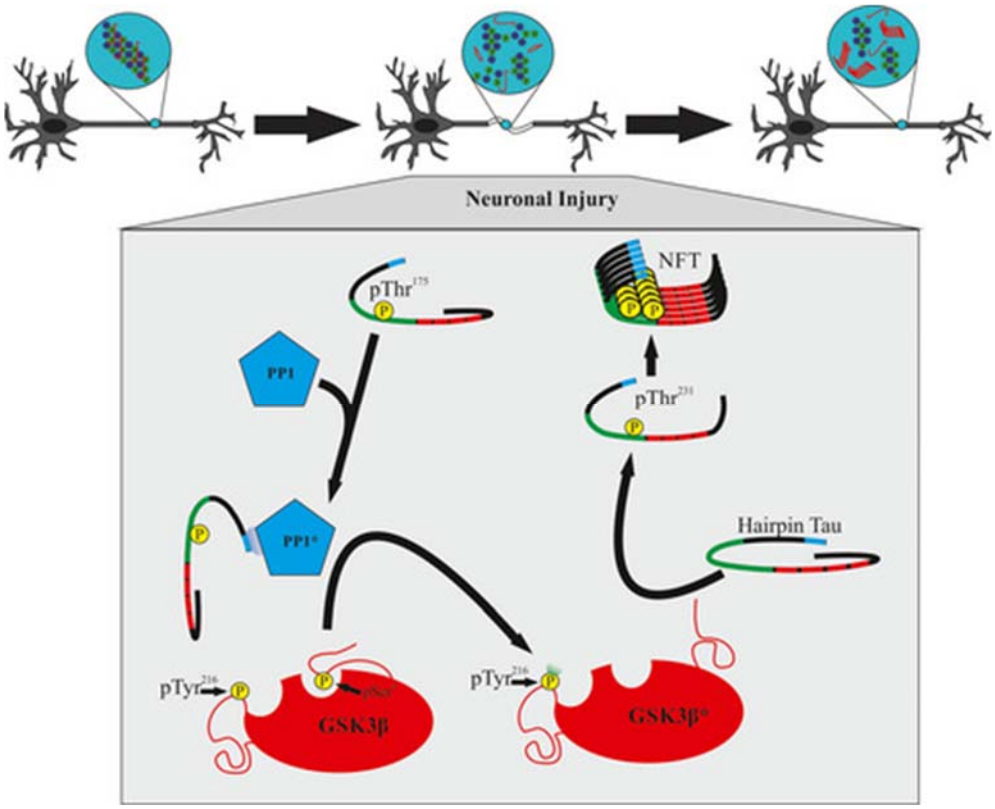
Tau protein phosphorylation at Thr175 initiates fibril formation via accessibility of the N-terminal phosphatase-activating domain

Matthew A. Hintermayer, Kathryn Volkening, Alexander J. Moszczynski, Neil Donison, Michael J. Strong

In response to neuronal injury or stress, tau protein is phosphorylated at the Thr175 residue. Phosphorylation at this residue is associated with changes in the accessibility of the N-terminal phosphatase-activating domain (PAD) of tau protein, which interacts with and activates (*) protein phosphatase 1 (PP1). This activation results in the dephosphorylation of glycogen synthase kinase 3β (GSK3β) at the Ser9 residue, leading to its activation (GSK3β*). Once activated GSK3β phosphorylates tau protein at other residues (for example, Thr231), leading to the formation of tau protein neurofibrillary tangles (NFT) and fibrils associated with injury. Understanding this mechanism contributes to our understanding of how fibril formation is initiated and propagated in individuals with tauopathies.



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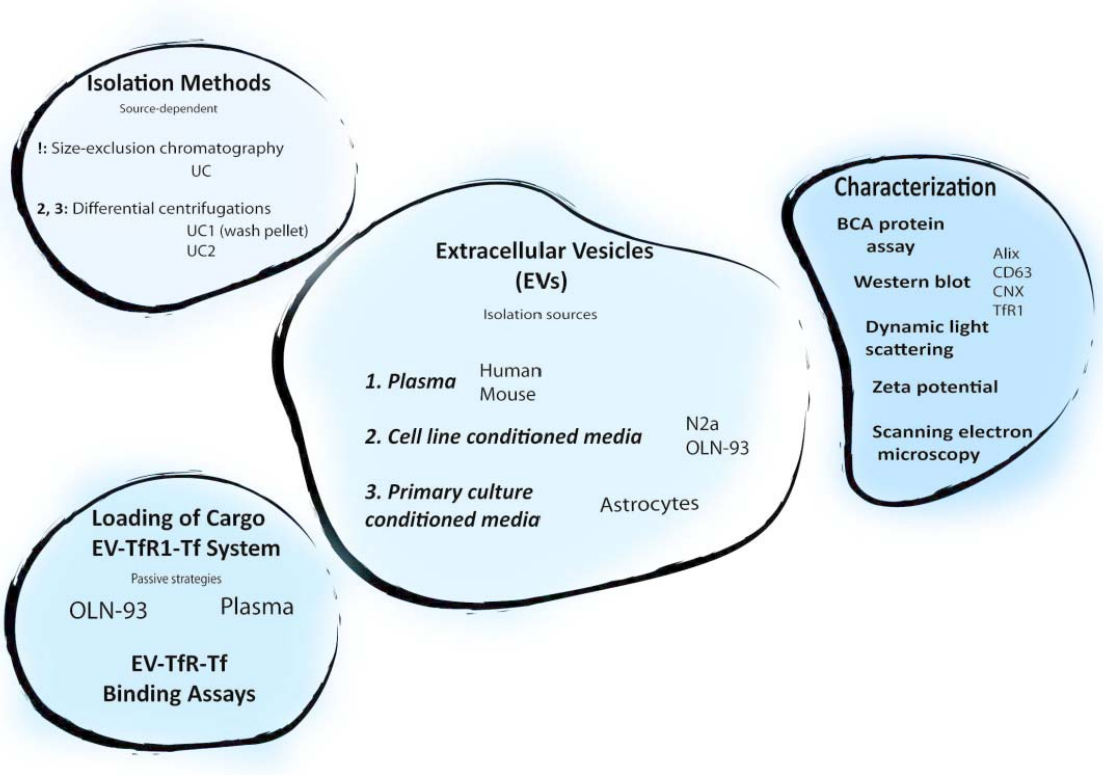
Extracellular vesicles containing the transferrin receptor as nanocarriers of apotransferrin

Vanesa S. Mattera, Pehuén Pereyra Gerber, Romina Glisoni, Matias Ostrowski, Sandra V. Verstraeten, Juana M. Pasquini, Jorge D. Correale

In this work, we isolated extracellular vesicles (EVs) by two methods from plasma and conditioned media with the objective of using them as nanocarriers of apotransferrin (aTf), a protein involved in remyelination processes. We analyzed EVs in terms of stability, quality, quantity, identity and structural integrity and, furthermore, we detected the presence of Tf receptor 1 (TfR1) on the EV membrane. Using two passive strategies, EVs were successfully loaded with aTf through its binding to TfR1. These results unveil EVs as potential nanovehicles of aTf to be delivered into the CNS parenchyma.



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The following articles are part of Volume 155, Issue 4 – Pages 339-461

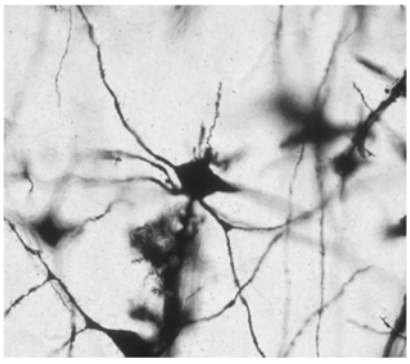
Cover Image

Up-regulation of astrocyte excitatory amino acid transporter 2 alleviates central sensitization in a rat model of chronic migraine

Xue Zhou, Jie Liang, Jiang Wang, Zhaoyang Fei, Guangcheng Qin, Dunke Zhang, Jiying Zhou, Lixue Chen

Front cover: Central sensitization is the potential pathogenesis of chronic migraine (CM) and is related to persistent neuronal hyperexcitability. Dysfunction of excitatory amino acid transporter 2 (EAAT2) leads to the accumulation of glutamate in the synaptic cleft, which may contribute to central sensitization by overactivating the glutamate N-methyl-D-aspartate (NMDA) receptors and enhancing synaptic plasticity. The current study investigated the role of EAAT2 in central sensitization. Upregulation of EAAT2 expression had a protective effect in CM rats, and the study revealed therapeutical potential of EAAT2 expression enhancer LDN-212320.

Image content: Dendritic spines of the pyramidal neurons in the trigeminal nucleus caudalis (TNC) region were observed under a 40 × objective after Golgi-Cox staining.



Read the full article *'Up-regulation of astrocyte excitatory amino acid transporter 2 alleviates central sensitization in a rat model of chronic migraine'* by X. Zhou, J. Liang, J. Wang, Z. Fei, G. Qin, D. Zhang, J. Zhou, L. Chen, (*J. Neurochem.* 2020, vol. 155 (4), pp. 370–389) on doi:10.1111/jnc.14944

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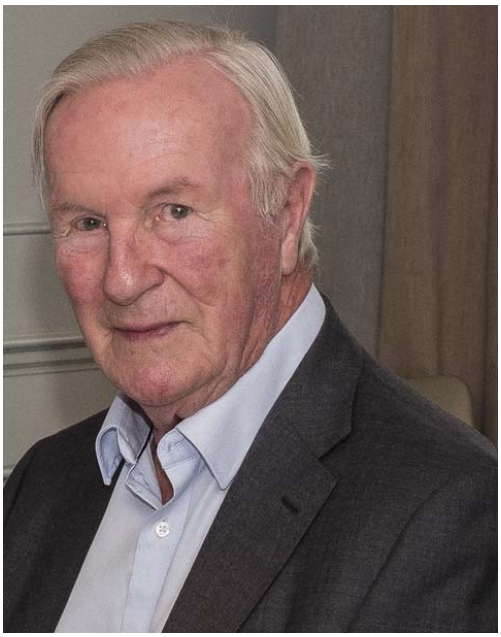
Obituary

Leslie Iversen (1937–2020)

Free Access

Solomon H. Snyder, Bevyn Jarrott, Anthony J. Turner, Philip M. Beart

This is an Obituary for Leslie Iversen (1937–2020). Les Iversen was an internationally renowned neuroscientist and pharmacologist, a substantial contributor to university life, learned societies, the pharmaceutical industry and society at large. He died on July 30th 2020.



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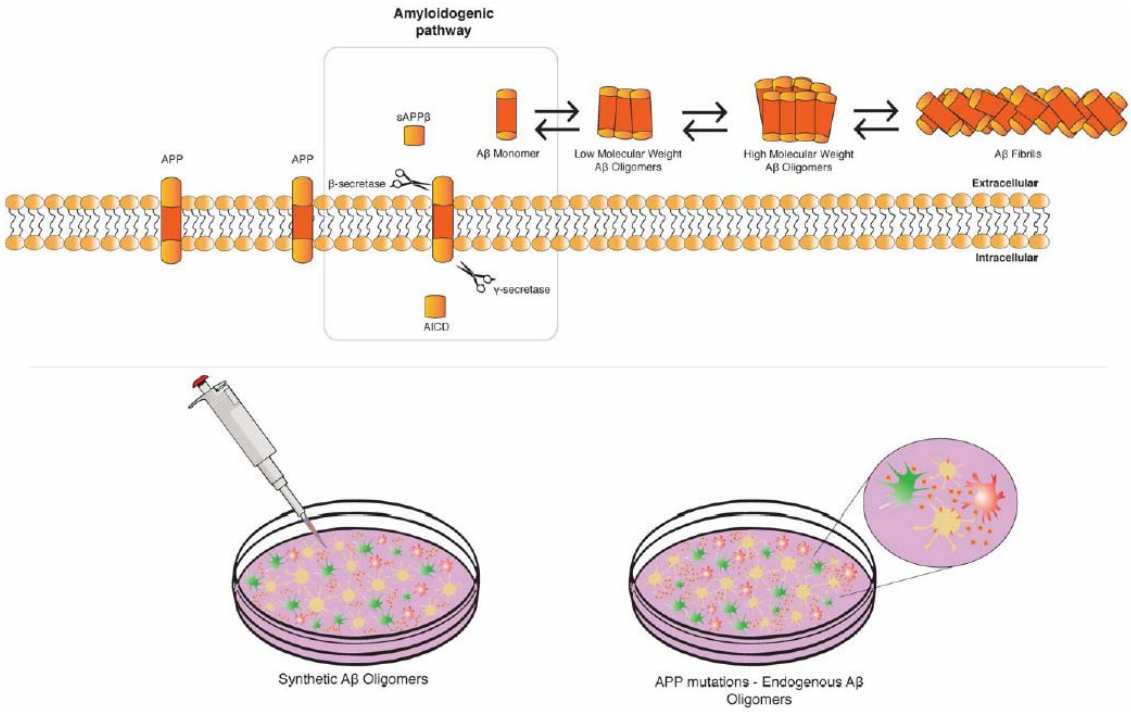
Review articles

Amyloid-β oligomers in cellular models of Alzheimer's disease

Free Access

Igor C. Fontana, Aline R. Zimmer, Andreia S. Rocha, Grace Gosmann, Diogo O. Souza, Mychael V. Lourenco, Sergio T. Ferreira, Eduardo R. Zimmer

Amyloid-beta oligomers (AβOs) are synaptotoxins in Alzheimer's disease (AD) and have been firstly characterized in the 90s. Since mechanisms are not fully elucidated, cell culture may hold the key for better understanding AβOs toxic roles in AD pathophysiology. In this review, we briefly revisit AβOs physicochemical properties and toxic mechanism by discussing three decades of research in AβOs cellular models.



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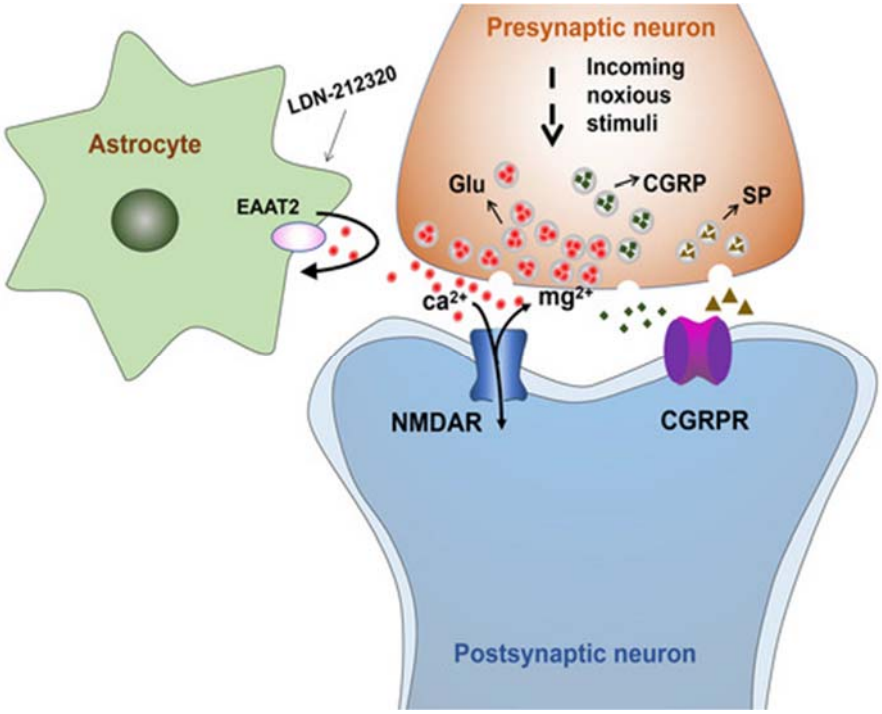
Original articles

Up-regulation of astrocyte excitatory amino acid transporter 2 alleviates central sensitization in a rat model of chronic migraine

Xue Zhou, Jie Liang, Jiang Wang, Zhaoyang Fei, Guangcheng Qin, Dunke Zhang, Jiying Zhou, Lixue Chen

Schematic diagram of the astrocyte excitatory amino acid transporter 2 (EAAT2) participating in central sensitization process through modulating synaptic plasticity. Central sensitization is the potential pathogenesis of chronic migraine (CM) and is related to the persistent neuronal hyperexcitability. In our study, down-regulated EAAT2 was found in CM rats, which may contribute to central sensitization by leading the accumulation of extracellular glutamate and enhancing the synaptic plasticity. The novel compound LDN-212320 greatly up-regulated the protein expression of EAAT2, alleviated hyperalgesia, decreased the glutamate concentration and provided a neuroprotective effect in CM rats, indicating that the recovery of EAAT2 expression may be a new strategy for the treatment of CM, and LDN-212320 could be a potential therapeutic drug.



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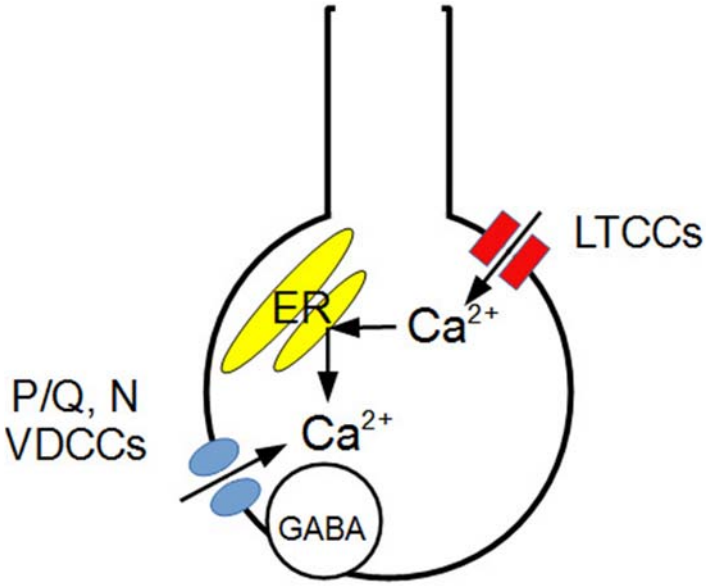
Physiological involvement of presynaptic L-type voltage-dependent calcium channels in GABA release of cerebellar molecular layer interneurons

Stéphanie Rey, Gilliane Maton, Shin'Ichiro Satake, Isabel Llano, Soosung Kang, Dalton James Surmeier, Richard B. Silverman, Thibault Collin

N- and P/Q-type high threshold voltage-dependent Ca^{2+}channels (VDCCs) are known to trigger GABA release in cerebellar molecular layer interneurons. Here, we show that the frequency of miniature and evoked IPSCs is increased in the presence of BayK8644 (BayK) and reduced in the presence of L-type Ca^{2+} channels (LTCC)-specific inhibitors (isradipine, Cp8) or dantrolene. BayK also enhances presynaptic AP-evoked calcium Ca^{2+} transients and increases the frequency of spontaneous axonal Ca^{2+} transients. We propose that aside from N- and P/Q-type VDCCs, LTCCs together with Ca^{2+} stores participate to GABA release by molecular layer interneurons. ER, endoplasmic reticulum.



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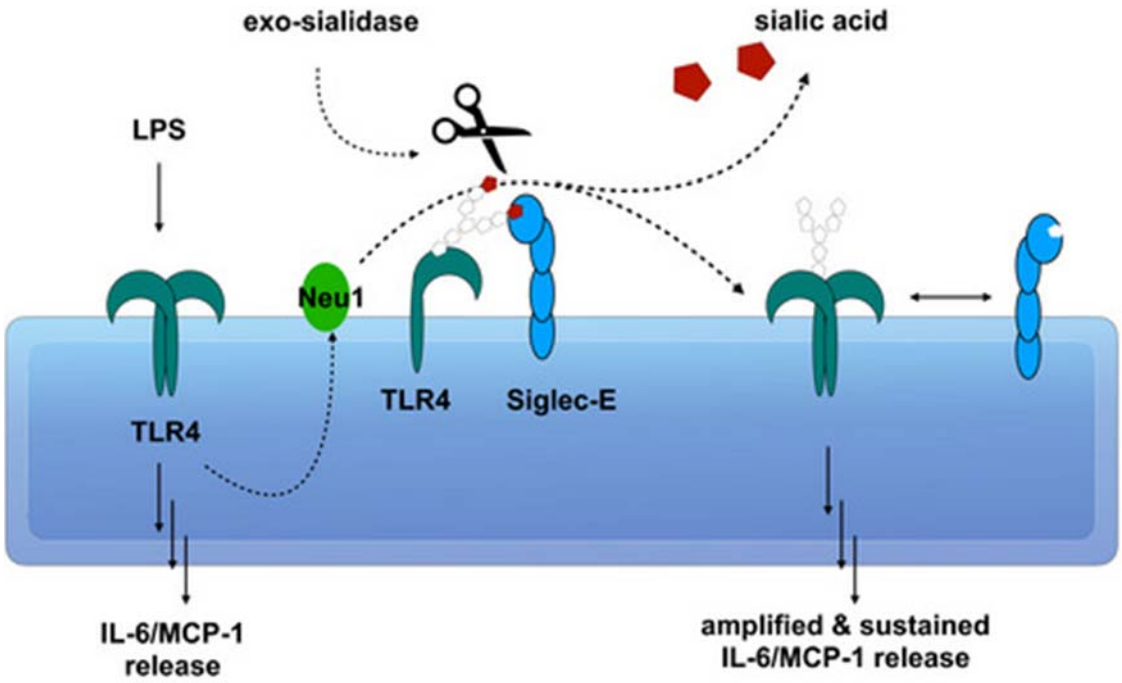
Lipopolysaccharide activates microglia via neuraminidase 1 desialylation of Toll-like Receptor 4

Open Access

David Hans Allendorf, Elske Helena Franssen, Guy Charles Brown

We investigated the mechanisms by which microglial activation is regulated, using murine BV-2 and primary rat microglia. We find that lipopolysaccharide (LPS) causes neuraminidase 1 (Neu1) translocation to the cell surface, where it desialylates toll-like receptor 4 (TLR4), causing dissociation of sialic acid-binding immunoglobulin-like lectin E (Siglec-E), promoting activation of TLR4, resulting in amplified and sustained microglial activation, measured as release of interleukin 6 (IL-6) and macrophage-stimulating factor 1 (MCP-1). Thus, cell surface Neu1 is a potential drug-target to reduce neuroinflammation, which may be relevant in a variety of pathologies.



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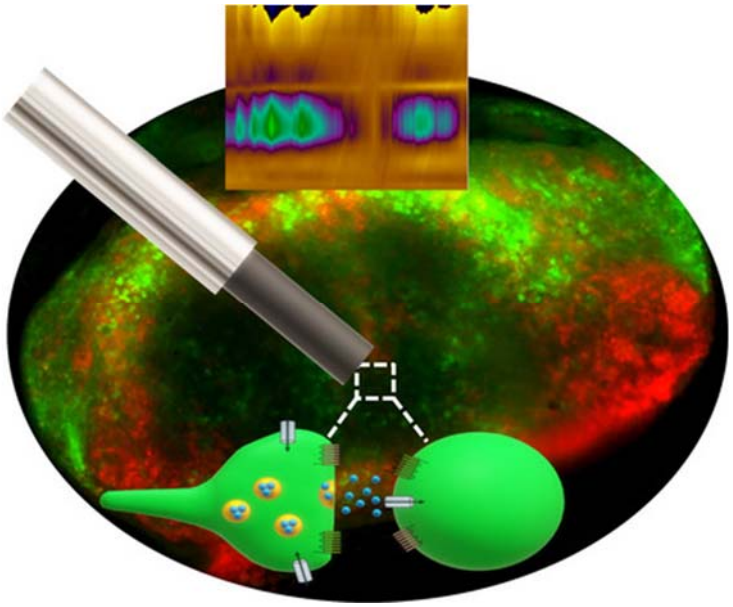
Subsecond spontaneous catecholamine release in mesenteric lymph node ex vivo

Gary N. Lim, Samantha L. Regan, Ashley E. Ross

Sympathetic nerves innervate the mesenteric lymph node in the gut to provide a direct communication pathway between the nervous system and the immune system. To date, measurements of neurochemical signaling in real-time within intact immune tissue have not been possible. Here, we have used fast-scan cyclic voltammetry at carbon-fiber microelectrodes to measure rapid catecholamine transients within ex vivo slices of the mesenteric lymph node. This work provides critical information into the dynamics of neuroimmune communication and will enable the mechanisms and function of neurochemical-regulated immunity to be probed with exquisite spatiotemporal control in the future.



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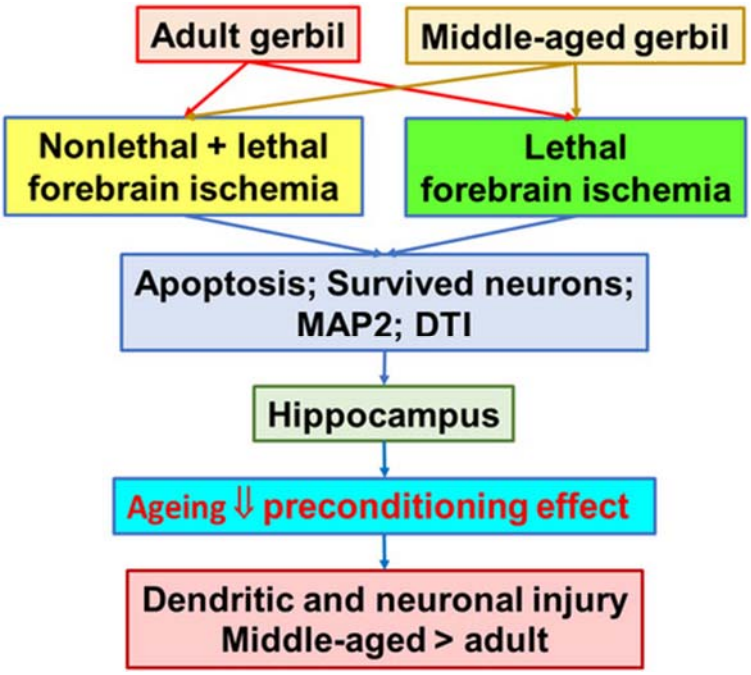
Protective effects of ischemic preconditioning against neuronal apoptosis and dendritic injury in the hippocampus are age-dependent

Tsong-Hai Lee, Jen-Tsung Yang, Jr-Rung Lin, Chaur-Jong Hu, Wen-Hai Chou, Ching-Po Lin, Nai-Fang Chi

Ischemic preconditioning with nonlethal ischemia can be protective against lethal forebrain ischemia eventually in an age-dependent manner. Magnetic resonance diffusion tensor imaging (DTI) is a sensitive tool to detect brain integrity and white matter architecture. The present study found delayed neuronal apoptosis and early dendritic injury evidenced by microtubule-associated protein 2 (MAP2) and diffusion tensor imaging (DTI) indices after lethal forebrain ischemia is more severe in middle-aged gerbils than adult gerbils. In the same way, preconditioning leads to better improvement in adult gerbils than middle-aged gerbils. Our present study suggested an age-dependent protective effect of ischemic preconditioning against both neuronal apoptosis and dendritic injury in hippocampus after forebrain ischemia.



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Gut microbiota regulate cognitive deficits and amyloid deposition in a model of Alzheimer's disease

Zhuo Li, Hua Zhu, Yaxi Guo, Xiaopeng Du, Chuan Qin

This study showed that signals from gut microbes were required for the neuroinflammatory responses and cognitive deficits in a mouse model of Alzheimer's disease. A clear association was established between changes in intestinal microbiota in APPswe/PS1ΔE9 transgenic mice and amyloid deposition via the activation of the MAPK signalling pathway, confirmed by 16S rRNA sequencing and transcriptome analysis. We believe that these findings will have direct implications in the development of methods that can exploit gut microbiota to control amyloid deposition, and thus alleviate neuroinflammation and provide clinical benefits in patients with Alzheimer's disease.