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VABILO NA PREGLOV KOLOKVIJ /
INVITATION TO THE PREGL COLLOQUIUM

Prof. Adriano Aguzzi

Institute of Neuropathology, University Hospital Zurich, Switzerland
adriano.aguzzi@usz.ch

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PrP^C function and prion toxicity

A plethora of functions have been ascribed to PrP^C based on phenotypes of *Prnp*$^{-/-}$ mice. *Prnp-linked* loci polymorphic between 129 and the backcrossing strain led to erroneous conclusions. We used TALEN-mediated genome editing in fertilized mouse oocytes to create the Zurich-3 (ZH3) *Prnp-ablated* allele on a pure C57BL/6J genetic background. Genomic, transcriptional, and phenotypic characterization of *Prnp*$^{ZH3/ZH3}$ mice failed to identify phenotypes previously described in non-coisogenic *Prnp*$^{-/-}$ mice. However, aged *Prnp*$^{ZH3/ZH3}$ mice developed a chronic demyelinating peripheral neuropathy (CDP), confirming the crucial involvement of PrP^C in peripheral myelin maintenance. Neuron-restricted PrP^C expression prevents the CDP, suggesting that it acts in trans through an unidentified Schwann cell receptor. We found that the cAMP concentration in PrP^C-deficient sciatic nerves is reduced, suggesting the involvement of a G protein-coupled receptor (GPCR). The amino-terminal "flexible tail" (FT, residues 23-120) of PrP^C triggered a concentration-dependent cAMP increase in primary Schwann cells and in Hek293T cells overexpressing a specific GPCR. In contrast, naïve Hek293T cells and Hek293T cells expressing several other GPCRs did not react to the FT, and ablation of this GPCR from a Schwann-cell line abolished the FT-induced cAMP response. A 27-mer PrP^C-derived peptide sufficed to induce a cAMP response in cells and mice, and improved myelination in hypomorphic zebrafish mutants lacking the orthologous GCPR receptor.. We conclude that PrP^C promotes myelin homeostasis through FT-mediated GPCR agonism. Antibodies against the prion protein PrP^C can antagonize prion replication and neuroinvasion, and therefore hold promise as possible therapeutics against prion diseases. We have reported that several antibodies against certain epitopes of PrP^C, are profoundly neurotoxic, yet antibody ICSM18 was reported to be innocuous when injected into mouse brains. Both D13 and ICSM18 induced rapid, dose-dependent, on-target neurotoxicity. No such toxicity was found when antibodies against the flexible tail of PrP^C were administered. We posit that any attempt at immunotherapy or immunoprophylaxis of prion diseases should account for these potential untoward effects.

Vljudno vabljeni / Kindly invited

info: Roman Jerala (roman.jerala@ki.si)