Transmissibility of SOD1 prion strains between mice expressing different mutant human SOD1s

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Background. Two structurally different human (h) SOD1 aggregate strains, A and B, can arise in CNS of transgenic (Tg) mice expressing hSOD1 variants (Bergh et al. 2015). When inoculated into spinal cords of Tg mice both strains transmit exponentially growing templated hSOD1 aggregation and premature paralysis (Bidhendi et al. 2016, 2018).
It is known from the prion protein field that there are species barriers for prion transmission and that mutations/polymorphisms in a given species can determine susceptibility to prion transmission. Here we investigate if such transmission barriers exist for hSOD1 aggregate/prion strains when prepared from, and inoculated into Tg mouse expressing different hSOD1 variants.

Methods. hSOD1 A and B seeds were prepared from mouse spinal cords by ultracentrifugation through a density gradient (Bidhendi et al. 2016). Seeds were microinoculated into lumbar spinal cord of adult recipient Tg mice.

Results. We have shown that A-prions prepared from hSOD1G85R, hSOD1G127X Tg mice and B-prions from hSOD1D90A mice efficiently seed aggregation and motor neuron disease in hSOD1G85R mice (Bidhendi et al. 2016, 2018).
We have also found that strain A seeds from hSOD1G85R mice efficiently seed aggregation and disease in both hemi and homozygous hSOD1D90A mice. Likewise strain B seeds from hSOD1D90A mice transmit disease to hemi and homozygous hSOD1D90A mice. A second passage strain B seed from hSOD1G85R mice transmitted disease to hSOD1G85R mice, but without any enhanced efficiency compared with such seeds from hSOD1D90A mice. Finally, strain A-like seeds from hSOD1G127X mice efficiently transmitted disease to both hemi and homozygous hSOD1G127X mice (unpublished data).

However, strain A seeds from hSOD1G93A Tg mice did transmit strain A aggregation and disease to hSOD1G85R mice, but apparently with low efficiency. The lifespans of recipient mice were longer than expected from the dose of hSOD1G93A aggregates that was inoculated. Finally, strain A seeds prepared from paralytic hSOD1WT mice (Graffmo et al. 2013) have so far failed to transmit disease to hSOD1G85R mice.

Conclusions. Our experience suggests that hSOD1 A and B prions on different hSOD1 mutation backgrounds in most cases freely transmit disease to Tg mice expressing other mutant hSOD1s. However, strain A seeds on hSOD1G93A background apparently showed reduced efficiency in hSOD1G85R mice, and we have so far failed to transmit ALS with strain A seeds from hSOD1WT Tg mice.