Why it's hard to make a bunny mad: Examining prion disease resistance in rabbits

6 August 2015

Rabbits have long been considered immune to prion disease, but recently scientists have shown that they can—under certain circumstances—get transmissible spongiform encephalopathy (or TSE, the scientific term for the fatal brain disease caused by prions). Two studies published on August 6th in *PLOS Pathogens* address what makes rabbits hard to infect with prions and how their resistance can be overcome.

Prions are misfolded versions of a protein that, in its normal form (called PrPC, encoded by the PRNP gene), is found mainly in nerve cells of all mammals. The misfolded prions can trigger a domino effect by causing folding changes in their normal cellular counterparts, which turns them into toxic prions as well. Accumulation of toxic prions triggers the death of nerve cells and literally leaves holes in the brain, causing a spongiform (or sponge-like) appearance.

In one study, Joaquín Castilla, from CIC bioGUNE in Derio, Spain, and colleagues tested prion preparations from different species to see which ones could cause TSE in rabbits. To model the transmission barrier between rabbits and other species, they generated a transgenic mouse model that expressed the rabbit PRNP gene instead of the corresponding mouse gene.

The researchers then exposed these transgenic mice to prion isolates collected from sick animals, including classical and atypical strains of Bovine Spongiform Encephalopathy (i.e., mad cow disease), sheep Scrapie, and deer Chronic Wasting Disease. They found that the transgenic mice were susceptible to classical and atypical Bovine Spongiform Encephalopathy prions, and also to mouse-derived Scrapie prions.

These results provide further evidence that rabbits are susceptible to TSE following exposure to prions from several other species, and the researchers urge that "this information must be taken into account when assessing the risk of using ruminant derived protein as a protein source to feed rabbits."

Vincent Beringue, from INRA Virologie Immunologie Moléculaires in Jouy-en-Josas, France, and colleagues designed the second study to address what makes rabbits relatively resistant to prions. To clarify the respective roles of rabbit PrPC and non-PrP host factors in the rabbits' pronounced but not absolute resistance to TSE, they created transgenic rabbits that have both sheep and rabbit PRNP genes and tested their susceptibility to TSE. The sheep transgene they introduced into the rabbits coded for a version of sheep PrPC that is thought to be easily convertible to its toxic prion form.

Following exposure to sheep prions, all rabbits with the sheep PRNP transgene in addition to the full complement of rabbit genes (including rabbit PRNP) developed typical TSE after 6-8 months, whereas rabbits without the sheep PRNP transgene remained healthy more than 700 days after inoculation. Despite the presence of normal rabbit PrPC in the nerve cells, only sheep prions (i.e. the toxic misfolded form) were detectable in the brains of the diseased rabbits.

Beringue and colleagues conclude that their collective data demonstrate "that rabbits do not bear non-PrP factors that make them intrinsically resistant to prions." However, as the study by Castilla and colleagues suggests that the rabbit PRNP gene and its normal PrPC protein product do not act as absolute barriers to TSE development after exposure to prions from other species, they also acknowledge that "what exactly makes the rabbit species comparatively resistant to prion

disease remains to be clarified."

More information: Transgenic Rabbits Expressing Ovine PrP Are Susceptible to Scrapie, *PLoS Pathog* 11(8): e1005077. DOI: 10.1371/journal.ppat.1005077

Transgenic Mouse Bioassay: Evidence That Rabbits Are Susceptible to a Variety of Prion Isolates, *PLoS Pathog* 11(8): e1004977. DOI: 10.1371/journal. ppat.1004977

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