Protein folding activity of ribosomal RNA is a selective target of two unrelated antiprion drugs active from yeast to mammals

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Prion-based diseases are neurodegenerative disorders affecting several mammalian species and that belong to the class of chaperonopathies. According to the protein-only hypothesis, the infecting unit responsible for prions-based diseases is supposed to be mainly if not solely constituted of PrP^{Sc}, an alternatively folded form of PrP^{C}, a protein largely conserved in mammals. The infectivity of PrP^{Sc} is generally admitted to be due to its unique ability to catalyze transformation of PrP^{C} into PrP^{Sc}, therefore propagating the formation of amyloid fibres of PrP that are linked to the progression of the disease. Several popular biological models like the budding yeast *Saccharomyces cerevisiae* also contain proteins behaving like prions. Based on the high degree of conservation of most if not all the main basic cellular mechanisms from yeast to human and on the fact that yeast prions are toxic neither for yeast nor for human, we recently developed a yeast-based assay to isolate drugs active against prions. The initial assumption was that at least some prion-controlling mechanisms may be conserved from yeast to mammals. Most of the active compounds that we isolated turned also to be active against mammalian prion, not only *ex vivo* in various cell-based assays, but also *in vivo* in a mouse model for prion-based diseases, thus confirming that common mechanism(s) involved in prion propagation exist(s). Using as baits 6AP and GA, two of the most active antiprion compounds isolated, the targeted cellular mechanisms were identified by reverse-screening strategies. We found that RPFA (Ribosome-borne Protein Folding Activity), a protein chaperone activity borne by the large rRNA (28S in mammals) of the large subunit of the ribosome was specifically inhibited by the antiprion compounds suggesting the intriguing possibility that this activity of the ribosome could be involved in prion propagation. This represents the first potential biological role for RPFA.

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