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# Molecule of the month: miRNA and Human Prion brain disease

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Human prion brain disease has been studied intensely since 1920. Examples of such diseases include Creutzfeldt-Jakob disease (CJD), fatal familial insomnia, Gerstmann-Straussler-Scheinker disease, and Kuru. Central in the epidemiology and pathogenesis of prion diseases is the prion protein itself and the gene for this protein resides on chromosome 12, at locus 20pter-p12. The prion protein is termed PRNP, has a monomer molecular weight of 22-36 Kd and is linked to glycosyl-phosphatidyl-inositol (GPI) on cell surfaces. Various mutants of PRNP have roles in disease pathogenesis. Interestingly, the functions of the normal prion protein include synaptic interactions, cell adhesion, and transmembrane signaling **[1].**

Within the human genome, an RNA universe includes non-coding RNA, microRNA (miRNA), which regulates many genes and pathways. Processes influenced and regulated by prion gene-associated miRNAs include cell death, neuronal differentiation, development, synapse function, neurogenesis, as well as neurodegeneration and neuropathogenesis. Studies in mouse brains indicated that prion disease results in deregulation of miRNAs as follows. MiR-342-3p, miR-146a, miR-139-5p, miR-320, miR-128, miR-328, and let-7b miRNAs were up regulated; miR-337-3p and miR-338-3p miRNAs were down regulated. Gene promoters that were cognate to several of these miRNAs included E2F-1 (cell cycle re-entry and neurodegeneration), MAZ (inflammatory response transcription factor), PAX6 (neurogenesis), KROX (transcription factor), and Early Growth Response 1 (EGR1), a Nerve Growth Factor-Induced Protein. Additional work indicated effects on N-methyl-D-aspartic acid (NMDA) receptor glutamate receptor (ionotropic, N-methyl D-aspartate 2A, GRIN2A) as well **[2, 3].**

MiRNAs also participate in neuronal development, dendrite, spine, and synapse, as well as neuron sub-type specificity and they are involved in CNS ischemia, recovery from ischemia, spinal cord injury, and traumatic brain injury **[4].**

Exosomes are released from cells and are 50-130 nm size vesicles. Exosomes from normal and prion-diseased humans and animals contain molecular mixtures including cellular prion protein, PrP(C), and the abnormal infectious form, PrP (Sc). Exosomes released from prion-infected neuronal cells contained miRNAs, other non-coding RNA, messenger RNA fragments, retroviral RNA repeat regions, transfer RNA fragments, small cytoplasmic RNA, small nuclear RNA, and small nucleolar RNA. Compared to uninfected exosomes, infected exosomes contain increased expression of miRNAs miR-424, miR-29b, miR-342-3p, miR-128a, miR-21, let-7b, let-7i, and miR-222 as well as miR-146 at decreased levels **[5].**

In addition to prion diseases, miRNAs are also involved in Parkinson's and Huntington's diseases **[4].** In **(Figures 1A, 1B, 1C & 1D),** it illustrates the gene expression and protein networks involving the proteins that interact with miRNAs in prion-related disease **[3, 4, 5].** The study of miRNAs is a new field and much has been accomplished. In this article, we summarize just a few of the protein interactions of proteins whose expression levels are perturbed in conjunction with miRNAs in prion disease. The identification of the miRNAs involved in the disease process and the subsequent interacting protein networks provide several pivotal junctures that could be attacked in developing treatments and possibly cures for prion-related diseases. It is left as a puzzle for the interested reader to identify the various genes and their functions in the figures **[6, 7, 8].**

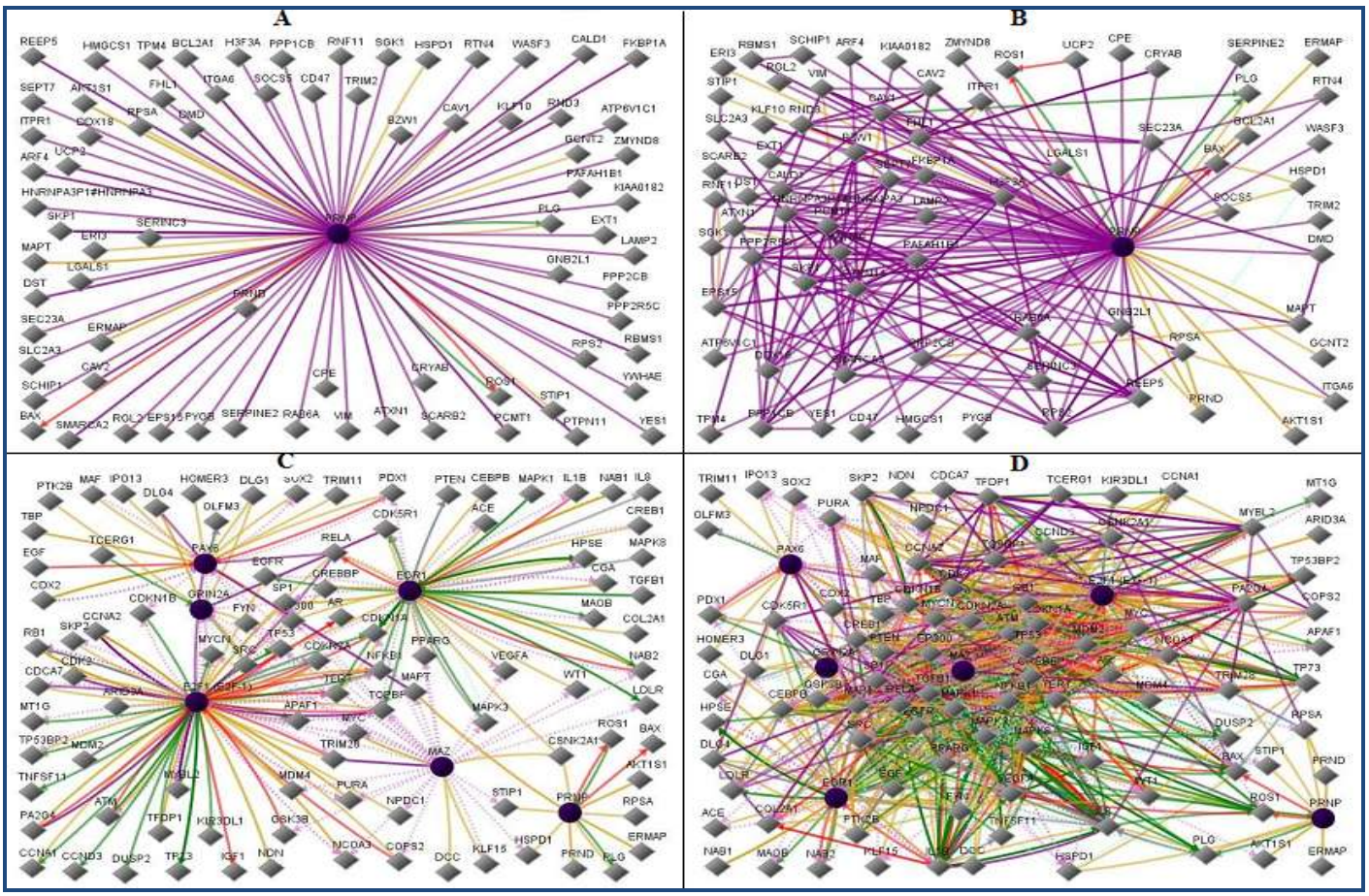


**Figure 1: A) Network of input prion - protein, PRNP with immediate input neighbors.** In this figure, line-colors and various interactions with other genes are red Down-regulation, green Up-regulation, beige Regulation, purple Co-expression, brown Physical Interaction, turquoise dotted Predicted Protein Interaction, and mauve dotted Predicted TFactor Regulation **[6].** The genes shown interacting with the PRNP gene are immediate interactions; **B) Network of input prion - protein, PRNP with additional output neighbors.** In this figure, line-colors and various interactions with other genes are red Down-regulation, green Up-regulation, beige Regulation, purple Co-expression, brown Physical Interaction, turquoise dotted Predicted Protein Interaction, and mauve dotted Predicted TFactor Regulation **[6].** This figure is a continuation of the genes shown in **Figure 1A** and shows additional levels of interactions among the genes; i.e. many of these are downstream from the first level shown in **Figure 1A**. **C) Network of input proteins PRNP, E2F-1, MAZ, PAX6, EGR1, and GRIN2A with immediate input neighbors**. In this figure, line-colors and various interactions with other genes are red Down-regulation, green Up-regulation, beige Regulation, purple Co-expression, brown Physical Interaction, turquoise dotted Predicted Protein Interaction, and mauve dotted Predicted TFactor Regulation. **[6]** The expression of the proteins illustrated PRNP, E2F-1, MAZ, PAX6, EGR1, and GRIN2A are perturbed in conjunction with miRNAs. The gene networks shown are immediate interactions. **D) Network of input proteins PRNP, E2F-1, MAZ, PAX6, EGR1, GRIN2A and additional output neighbors.** In this figure, line-colors and various interactions with other genes are red Down-regulation, green Up-regulation, beige Regulation, purple Co-expression, brown Physical Interaction, turquoise dotted Predicted Protein Interaction, and mauve dotted Predicted TFactor Regulation **[6].** This figure is a continuation of the genes shown in **Figure 1C** and shows additional levels of interactions among the genes; i.e. many of these are downstream from the first level shown in **Figure 1C.**

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