Abstract: The overall impact of prion disease on gene expression is not well characterized. We have carried out a large-scale expression analysis of specific cell types commonly employed in studies of prion disease. Neuroblastoma cells (N2a) and hypothalamic neuronal cells (GT1) can be persistently infected with mouse-adapted scrapie prions, the latter demonstrating cytopathologic effects associated with prion neuropathology. Exploiting a mouse DNA microarray containing approximately 21,000 spotted cDNAs, we have identified several hundred differentially expressed sequences in the two cell lines when infected with prion strain RML. ScN2a and ScGT1 cells demonstrate unique changes in RNA profiles and both differ from the reported changes in human microglia and prion-infected brain studies albeit with some overlap. In addition, several of the identified changes are shared in common with other neurodegenerative diseases such as Alzheimer’s disease. The results illustrate that prion infection differs in effect depending on cell type, which could be exploited for diagnostic or therapeutic intervention.