Amyotrophic Lateral Sclerosis (ALS) is a devastating disease of the human motor neuron system. Mutations in genes encoding for several RNA-binding proteins can cause the disease and suggest that regulation at the level of RNA may be involved in ALS pathogenesis. Our program investigates miRNA malfunction in ALS using human materials, mouse genetics and bioinformatics. I will discuss a few discoveries: (i) miRNA expression is broadly downregulated in human ALS and that accordingly, (ii) miRNAs are essential for motor neuron survival, in vivo. (iii) The underlying mechanism for miRNA insufficiency in ALS involves failure of Dicer activity due to gained toxic interactions with membraneless organelles (macromolecular assemblies), such as stress granules. We now use proximity labeling omics approaches to characterize membraneless organelles in disease. (iv) Specific miRNAs that reside downstream of Dicer are critical for neuronal function. For example, the expression of the motor-neuron specific miRNA, miR-218, is reduced in ALS because of Dicer inhibition or because of novel mutations in the miR-218-2 gene sequence. Loss of miR-218 de-represses voltage-gated potassium channels, thus impairing neuronal excitability. Taken together, neurodegeneration serves as intriguing model for RNA biologist and encourage further investigations of neuro-protective RNA mechanisms and their failure in disease states.