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component of the antiviral immune response, type I interferon, promotes FUS protein accumulation by increasing its mRNA stability. Our data suggest that antiviral immune response can expedite the onset and progression of FUS proteinopathy by promoting FUS protein accumulation and its coalescence into persistent cytoplasmic aggregates.

1915: **A novel pathogenic mechanism of ALS-associated VCP-mutant.**

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease caused by motorneuron death. ALS is classified as a proteinopathy in fact, the alteration of proteinostasis is one of main pathogenic mechanism that is associated to the ALS. All ALS forms are characterized by the presence of insoluble protein aggregates in the brain tissue of effected patient. Moreover, there are many genes involved in protein regulation that are found mutated. One of these genes associated to ALS encodes for Valosin Containing Protein (VCP), an AAA+ ATPase. VCP has many roles in the regulation of proteinostasis. Recent studies demonstrate that VCP is also involved in the removal of altered organelles like lysosomes. The alteration of lysosomes is deleterious for cell; firstly, for its key role in proteinostasis and secondly lysosome-damage leads to massive lysosomal leakage that causes cell toxicity and death. There are different mechanisms that can be activated to maintain the lysosomal activity. The most studied is lysophagy where VCP has been found involved.
We have found that the overexpression of VCP wild type (WT) and fALS mutations (VCP R155H; VCP R191Q) decrease the levels of insoluble species of a SOD1-mutant (SOD1 G93A). In addition, we study lysosomal-damage response in presence of overexpressed VCP WT and its mutants in NSC-34 cell line. To study VCP contribute in the clearance of damaged lysosomes we used trehalose treatment that induces lysosome damage and in addition we found that the overexpression of SOD1 G93A causes lysosome damage. We observed that overexpressed VCP WT reduces lysosomal damage when it is induced by trehalose or by SOD1 G93A overxpression. On the contrary, VCP R155H induces lysosomal damage in basal conditions and prevents the clearance of damaged lysosomes when the damage is induced by trehalose. VCP R191Q also induces lysosome damage in basal conditions, but to lower rate compared to VCP R155H. When the damage is induced, we observed that VCP R191Q can partially reduce lysosomal damage, but it significantly loses its functionality compared to overexpressed VCP WT. Moreover, the overexpression of the VCP-mutants leads to the conversion of LC3-I into LC3-II that significantly increases when cells are treated with NH_4Cl, a inhibitior of autophagy. This suggests an activation of autophagy in the presence of VCP-mutants. The activation of the autophagic could explain the decrease of insoluble aggregates when VCP-mutants are overexpressed.

1923: **Single cell transcriptomics of degenerating human motor neurons identifies master regulators of synaptic dysfunction in SOD1 ALS.**

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