In the last few years, there has been a rapid advance in our knowledge of genetic causes for ALS. Furthermore, the relationship between the genetic subtypes and the pathological subtypes as well as clinical phenotype has become more and more clear. In addition to superoxide dismutase 1 (SOD1), mutations in the genes coding for TAR DNA-Binding Protein (TARDBP), fused in sarcoma (FUS), Ubiquilin2 (UBQLN2), C9ORF72 and several others are closely associated with typical clinical phenotype. Figure 1 provides up-to-date findings of genetic defects in ALS and the underlying mechanisms for the cause and pathogenesis of the disease.

Genetics of fALS

The causative genes have been identified in almost 5-10% of all fALS cases to date [4,5]. Among those 20% of fALS cases are caused by the mutation in SOD1 gene, 4-5% of fALS cases are the results of mutations in TARDBP and FUS genes, more than 30% of fALS cases are associated with C9ORF72 mutations and the rest are

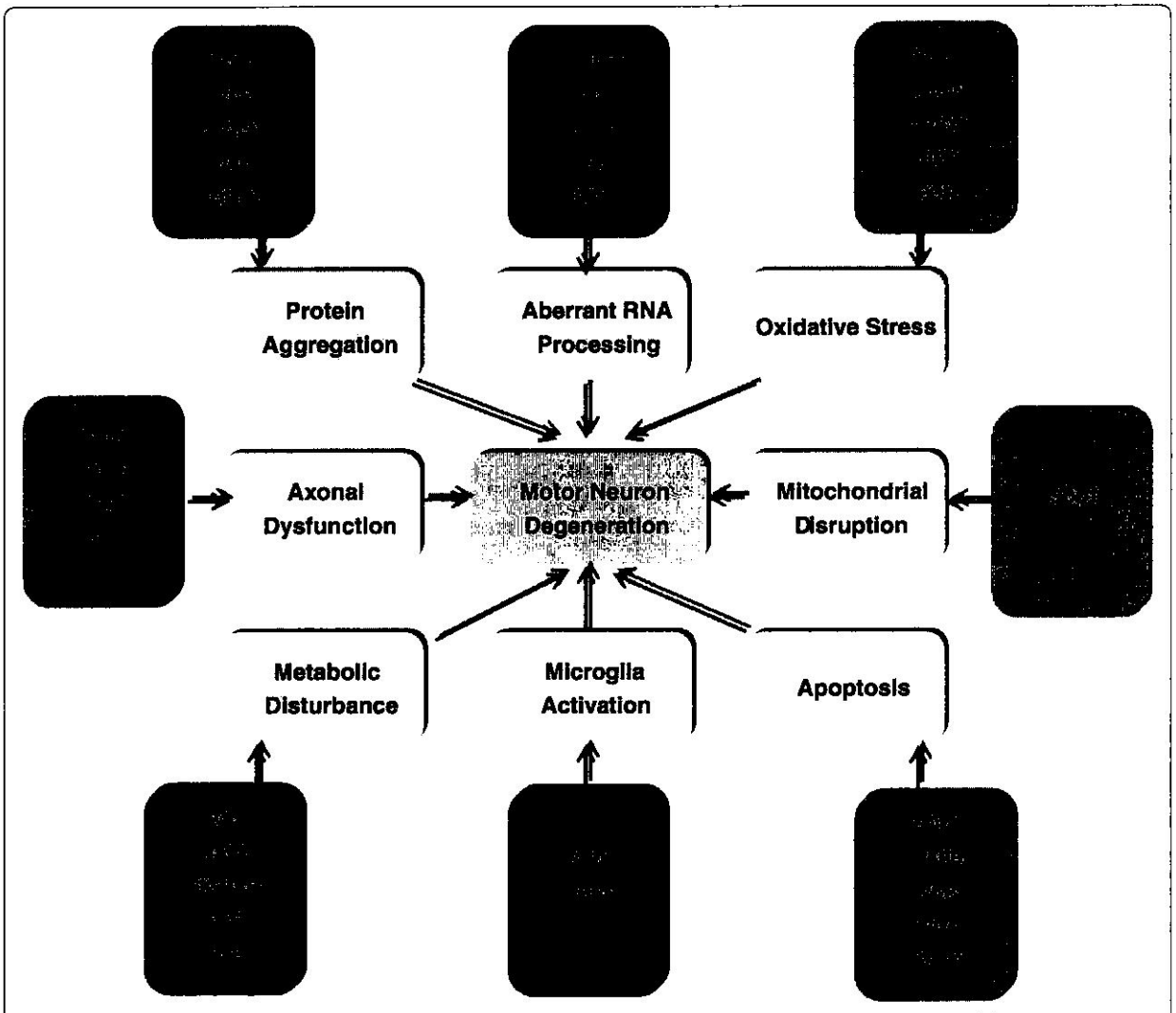

Figure 1 ALS is caused by interplay of various molecular pathways in motor neurons and an interaction with neighbouring non-neuronal cells like microglia and astrocytes. Microglial cells activate an inflammatory cascade via secretion of cytokines. Astrocytes lead to motor neuron injury through release of inflammatory mediators such as nitric oxide and prostaglandin E2. Accumulation of superoxide radicals and oxidative stress, aberrant RNA processing, protein misfolding and insoluble proteins may cause motor neuron degeneration in ALS. Protein aggregation may lead to endoplasmic reticulum stress along with defective endosomal trafficking and mitochondrial damage, which may cause organelle disruption and activates autophagy and apoptotic pathways. Axonal transport abnormalities lead to energy deficiency in the axon along with the defective axonal growth and axonal dysfunction. Axonal dysfunction, defective angiogenesis and metabolic disturbance may contribute to motor neuron degeneration in ALS.