

Superoxide Dismutase 1 in Amyotrophic Lateral Sclerosis

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Amyotrophic Lateral Sclerosis (ALS) is a progressive motor neurodegenerative disease. Cell damage in ALS is the result of many different, largely unknown, pathogenetic mechanisms. Superoxide Dismutase 1 (SOD1) physiologically mediates intracellular peroxide generation. About 10% of ALS subjects show a familial disease associated with different gain-of-function SOD1 mutations. The occurrence of sporadic ALS, not clearly associated with SOD1 defects, has been also described. SOD1-dependent pathways have been involved in neuron functional network as well as in immune-response regulation.

Amyotrophic Lateral Sclerosis (ALS)

Superoxide Dismutase 1 (SOD1)

intracellular signaling

1. Pathogenic Mechanisms of Mutant SOD1 in ALS

J.D. Atkin ^[1] demonstrated that mutated SOD1 (mSOD1) can inhibit secretory protein transport from the endoplasmic reticulum (ER) to Golgi apparatus, due to ER stress, Golgi fragmentation and altered axonal transport. The toxic effect carried out by SOD mutations in fALS has been attributed to its gain-of-function activity, in some cases associated with the occurrence of copper-dependent oxidative stress, largely demonstrated in patients affected by this condition. This “copper-dependent” oxidative hypothesis is challenged by the observation that the removal of copper chaperon from both wild-type SOD1 and mSOD1 is not effective in preventing motoneuron degeneration in transgenic mouse models of fALS ^[2]. In addition, it should be highlighted that SOD1 could itself be strongly oxidized, which may not only compromise the antioxidation function, but also acquire new binding and toxic properties ^{[2][3]}.

Toxic effects of mSOD1 have also been related to its ability to produce insoluble intracellular aggregates, likely caused by the altered folding of the mutated protein, able to generate amyloid-like fibrillary structures, as proposed by the ‘aggregation hypothesis’ ^{[4][5][6][7][8]}. This hypothesis is particularly interesting because protein aggregation is frequently observed in ALS ^{[9][10][11]}. In addition, a zinc-deficient SOD1 has also been described to increase its aggregation ability upon oxidation ^[4], thus promoting the peroxynitrite-dependent protein tyrosine nitration, inducing motoneuron apoptosis ^[12]. Moreover, other studies, using transgenic rat/mouse models ^[13] as well as bone marrow transplants or chimeric animals, demonstrated that mSOD1 expression, in microglia cells, can also induce direct neuronal toxicity ^[14].

Between the several SOD1 mutations, the SOD1^{G93A} represents the mSOD1 molecule mostly used for in vitro and in vivo studies regarding human fALS [15][16]. In the transgenic SOD1^{G93A} ALS rodent model, unfolded protein response and ER stress-induced apoptosis have been observed [17].

Autophagy and mitophagy are conserved degradation mechanisms finalized to maintain cellular homeostasis and to respond to cellular stress conditions. These processes have been described to be specifically tuned in highly differentiated cells, like neurons [18]. Several genes implicated in control of autophagy and mitophagy have been observed to be associated with ALS. Thus, their involvement in the impairment of the protein clearance and in the formation of aggregates, severely damaging motor neurons of ALS patients, may be hypothesized [19]. Data on SOD1^{G93A} expressing neurons reveal in vitro a limited ability of such cells to respond to proteotoxic stress [20]. Moreover, in transgenic SOD1^{G93A} mouse models, the presence of a protein complex positive for p62, a product of the ALS-associated gene SQSTM1 that is linked with protein aggregates formation and to the presence of damaged mitochondria, has been observed [21].

2. Microglia Activation, NADPH Oxidase and SOD1 in ALS

Activated microglia represents a key element in Alzheimer's disease as well as in the pathogenesis of ALS and other neurodegenerative conditions [22][23][24]. Microglia activation can be observed in transgenic mice expressing human SOD1 mutants, before neuron loss [25]; thus, dysregulated microglia functions, together with astrocyte activation, carry out an important role in ALS pathogenesis/progression [22][23][24][26].

ROS generated from NADPH oxidases play a role in signaling events leading to microglia activation [27]. Seven structural homologues of the phagocyte NOX enzyme (NOX2) have been identified, such as NOX1-5, DUOX1 and DUOX2 [28]. On the other hand, activated microglia produces ROS, primarily by NADPH oxidase 2 (NOX2), that result in enhanced microglia activation. It has also been shown that redox distress, caused by NOX1 and NOX2, significantly influences the progression of motor neuron disease, in mutant SOD1^{G93A} ALS mice [29]. Generation of ROS represents a general phenomenon in human cells. However, the excess of ROS production or an imbalance between ROS production and antioxidant defense are thought to represent important factors of disease progression in ALS [30][31].

Recent studies have shown that SOD1^{G93A} ALS transgenic mice generate high levels of gp91PHOX (NOX2) and superoxide in spinal cord microglia [32]. Moreover, it has been proposed that SOD1 interacts directly with Rac1, a cytosolic regulator of NOX2 [33], resulting in overproduction of ROS. In addition, ROS generated by Rac-dependent NADPH oxidases have been observed to be involved in cell signaling as well as in microbial killing.

Harraz [34] hypothesized that Rac-GTP-mediated activation of the NADPH oxidase complex might lead to production of O₂^{•-} and H₂O₂, which were able to mediate Nox complex autoregulation by reducing Rac-GTP levels. Interestingly, Marden [29] showed that female ALS mice, lacking a copy of the X-chromosomal Nox1 or Nox2 genes, exhibited significantly increased survival rates, thus suggesting that a 50% reduction in NOX1/NOX2 expression levels might be associated with a substantial improvement of ALS outcome in mice. Moreover, the observation that

multiple Nox genes might contribute to ALS progression clearly expands the potential therapeutic targets for this disease.

3. SOD1, Immunity and Neuroinflammation Processes in ALS

Chronic inflammation has been considered an important element in the pathogenesis/progression of different diseases, as well as in neurodegenerative processes. [35]. In this context, multiple immune dysfunctions, represented by extensive, dysregulated inflammatory processes, auto immunity phenomena, and deranged immune responses have been described in ALS. In addition, mutations in several genes, directly involved in immune response, have recently been reported in ALS patients [36][37][38][39].

Neuroinflammation, in particular, behaves as a key modulator of ALS progression potentially representing a prospective therapeutic target for this disease. In ALS, inflammatory responses are not restricted to the proximity of motoneurons but have been detected in muscles, peripheral axons, skin, liver and blood [40][41][42][43][44][45].

Multiple immune cell subsets have been described to participate in ALS pathogenetic mechanisms. Indeed, T cells, monocytes and other immune effectors have been observed to directly or indirectly access the CNS through the choroid plexus [46], thus mediating neuron damaging as well as neuroprotective processes.

E. Coque et al. [47] showed that ablation of CD8⁺ T cells in ALS mice increased the number of surviving motoneurons. Moreover, CD8⁺ T cells expressing the ALS-causing mSOD protein have been described to recognize and selectively kill motoneurons in vitro. To exert their cytotoxic function, CD8⁺ T cells carrying mSOD1 must be able to recognize neuron antigens inside MHC-I complex at the surface of the motoneurons. Moreover, analysis of the T cell receptor (TCR) diversity supports the evidence that self-reactive CD8⁺ T lymphocytes infiltrate the CNS of ALS mice and exert cytotoxic functions.

Fine-tuning of immune response is usually obtained by multiple regulatory processes, all belonging to the immune tolerance network, that are in place to prevent potentially deleterious immune responses against self-tissues. Regulatory T cells (Treg) are CD4 T lymphocytes characterized by the expression of the Foxp3 transcription factor. This T cell subset controls the immune effector response in terms of clonal expansion, differentiation, cytokine profile and tissue migration and is indispensable for the maintenance of immune self-tolerance [48]. Clinical studies in humans and in transgenic mouse models pointed out the role of Tregs in ALS pathophysiology. In humans and in mouse ALS models, Tregs infiltrating the Central Nervous System have been observed to suppress neuroinflammatory processes and promote the activation of neuroprotective microglia. Thus, immune-modulation strategies aimed at increasing Treg number and enhancing its functional effectiveness might be considered relevant to promote neuroprotective activity in ALS [49].

mTOR is an evolutionarily conserved serine/threonine protein kinase that directly influences T cell differentiation and proliferation by integrating environmental cues (nutrients, energy stores and growth factors) with immunity functions [50]. mTOR activity exerts opposite effects on effector T lymphocytes and on Treg. Indeed, mTOR

inhibition strongly favors Treg differentiation and expansion while modulating T cell effector functions [51]. Compelling evidence indicate that progressive metabolic conversions, usually mediated by mTOR-dependent pathways, underlie the generation of proper effector functions during T cell response. Recent evidence indicates that SOD1 represents one of the major targets of the mTOR enzyme. Indeed, reversible mTOR-dependent SOD1 phosphorylation has been described to mediate SOD1 inhibition [51][52]. These observations propose a complex scenario in which SOD1/mTOR intracellular interplay may finely tune T cell activity [53][54]; instead, no data are available on the role of SOD1 in regulating mTOR dependent pathways. In this context, the recent correlation of increasing SOD1 intracellular levels in T cells with the presence of circulating Tregs in a cohort of subjects affected by Multiple Sclerosis undergoing effective immune-modulating treatment [55], strongly supports the idea that a SOD1-mTOR regulatory network [53][54] may participate in the complex mechanisms regulating immune-modulation processes.

Hydrogen peroxide and superoxide anion are involved in TCR-dependent signaling and adaptive immune response activation [56]. Indeed, antigen-dependent stimulation of human T lymphocytes can modify SOD1 intracellular localization in T cells, mediating a clear SOD1 recruitment by TCR clusters. In addition, increased SOD1 mRNA production and microvesicle secretion of the enzyme, by activated human T lymphocytes, has been observed [56].

In vitro administration of recombinant human SOD1 to activated human T cells increases their IL17 production, a key cytokine in induction/maintenance of chronic inflammatory processes [57][58]. This effect is mediated by SOD1-dependent enzymatic activity, since SOD1 molecule lacking dismutase activity (Apo SOD1), it is unable to affect T cell cytokine production. Furthermore, hydrogen peroxide addition to activated T-cells mimics the SOD1 effect [55]. These data indicate, as summarized in **Figure 1**, that SOD1 effects on inflammatory process may be, at least partially, linked to its hydrogen peroxide production; this molecule is more stable than other ROS and can freely migrate outside cells and between different cell compartments [55].

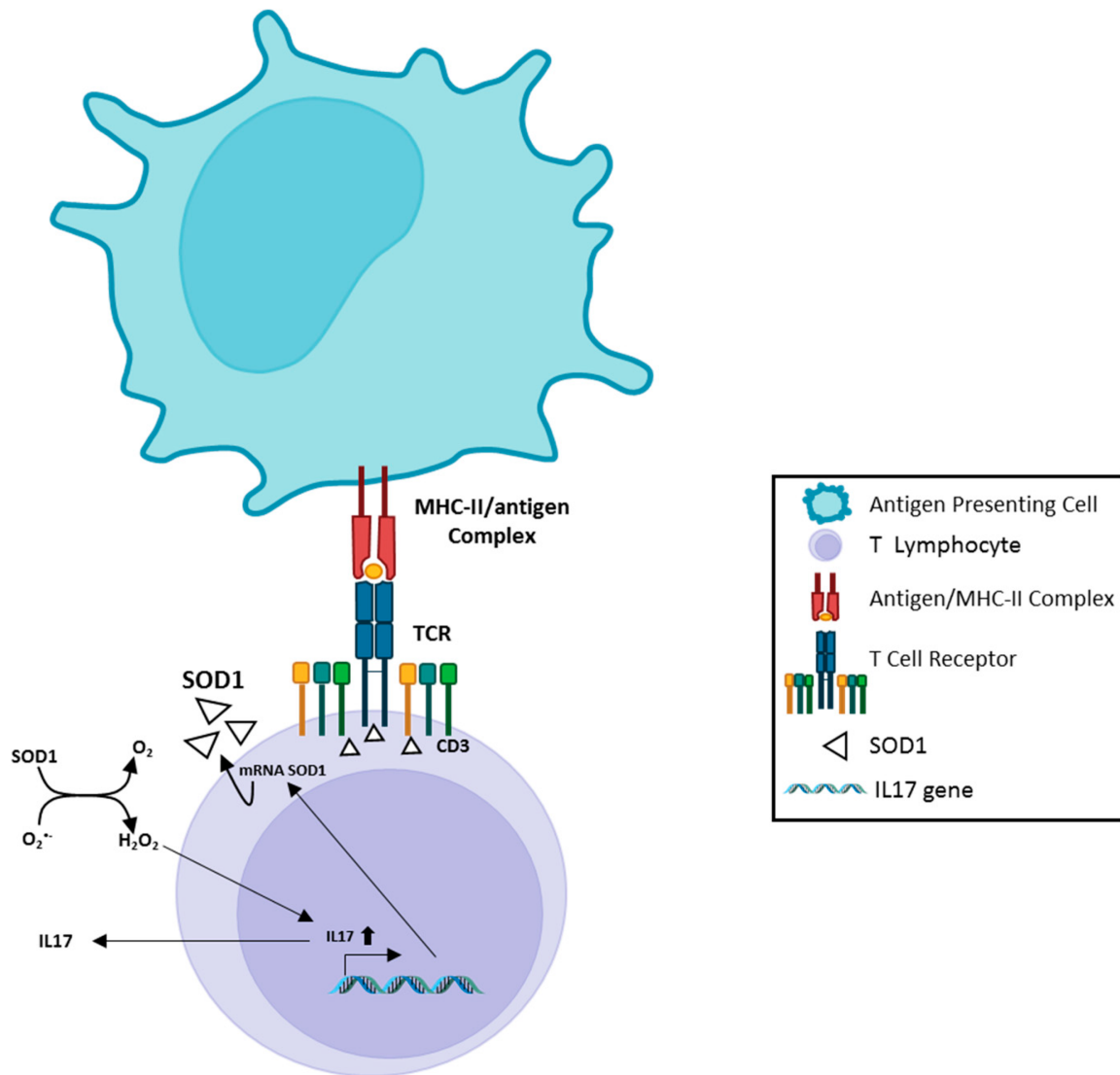


Figure 1. A scheme of SOD1 involvement in antigen-dependent T cell response. Recognition of antigen by TCR, inside MHC complex expressed on the surface of the Antigen Presenting Cell, induces rapid recruitment of SOD1 molecules near the TCR clusters; this phenomenon is accompanied by increased SOD1-mRNA, followed by SOD1 export by a microvesicle pathway. Extracellular SOD1 has been observed to mediate enhanced IL17 production by activated T lymphocytes. This effect depends on enzymatic activity of SOD1; the involvement of IL17 in induction/maintenance of chronic proinflammatory processes has been extensively studied by others. The image has been partially created by using BioRender.com.

Thus, a very complex scenario involving multiple molecular networks, including SOD1-dependent pathways, might be involved in the regulation of T cell activation and differentiation in the neuroinflammatory context.

4. SOD1, Muscarinic M1 receptor and Ca^{2+} level in neurons

Accumulation of Ca^{2+} in neurons, with consequent activation of Ca-dependent pathways, has been largely associated with cell death [59]. Intracellular Ca^{2+} increase might be mediated by different mechanisms, as

represented by several voltage-gate-dependent calcium channels (VGCCs), metabotropic (M1 muscarinic) receptors and ionotropic glutamate-dependent receptors (N-Methyl-D-aspartate (NMDA) and non-NMDA molecules). In addition, the intracellular Ca^{2+} increase can be mediated by the involvement of metabotropic glutamate receptors (GRM) [60].

SOD1 interaction with muscarinic M1 receptor, in human neuroblastoma SK-N-BE cells, can activate ERK1/2 and AKT kinases in a dose/time-dependent manner. This effect was strongly reduced by M1 receptor silencing, as well as by using the M1 antagonist pirenzepine. Moreover, the incubation of SK-N-BE and the neuroblastoma–spinal motoneuron fusion NSC-34 cell line with mutant SOD1^{G93A} significantly increased their intracellular Ca^{2+} concentration, as compared with wild-type SOD1 treatment [61].

Five muscarinic receptor subtypes (m1–m5) have been identified in T lymphocytes [62][63]; m1, m3 and m5 muscarinic receptor subtypes are coupled to Gq/11, which, upon stimulation, mediate activation of phospholipase C activity, resulting in increases in Ca^{2+} availability inside cells [64]. Moreover, acetylcholine is synthesized and released by T-lymphocytes, acting as an autocrine/paracrine factor, likely involved in immune function regulation [64].

These observations add further complexity to the biological scenario involved in the regulation of the neuroinflammatory context.

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