Biochemical Analysis of Manganese Superoxide Dismutase Mutations

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Background

The mitochondria is the key organism responsible for cellular respiration and plays an influential role in the amount of superoxide radicals within the cell. Oxygen serves as the final electron acceptor during the production of ATP within the electron transport chain, but can also lead to oxidative stress within a cell or system [5]. Manganese Superoxide Dismutase, MnSOD, is a catalyst for antioxidant activity and provides a mechanism to convert highly active superoxide molecules radicals to a less toxic molecule in the form of hydrogen peroxide. This conversion allows initial protection from oxidative stress and the suppression of tumor forming activity [6].

Research has shown that the survival mechanisms of MnSOD are mediated by hydrogen peroxide generation. H_2O_2 accumulation is regulated by MnSOD by overwhelming the cell capacity, which increases cell survival and proliferative signaling [8].

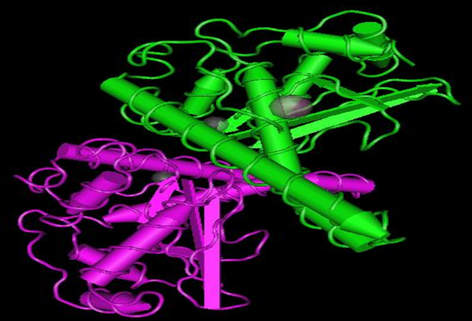

Figure 1: Crystal structure of nitrated human manganese superoxide dismutase. The green and purple coloring depicts the two subunits of the molecule. The round figures depict the manganese, the overall interaction is shown (Quint, 2006).

References

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Mechanism

MnSOD is found in all aerobic organisms and is highly populated in mitochondria of eukaryotic and bacterial cells, but is active in the cytoplasm of cells. The natural mechanism of MnSOD begins with an oxidative reaction in which a superoxide radical is oxidized to a dioxygen molecule. The next reaction is a reduction of the superoxide molecule to hydrogen peroxide [6].

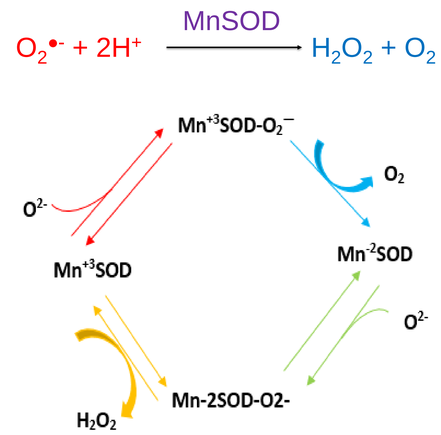

Figure 2: Continuous conversion of $O_2^{\bullet-}$ to H_2O_2 that is conducted by MnSOD is depicted above. Modified from (Luo, 2001).

Homology

MnSOD is highly conserved showing sequence homology among house mouse and zebra fish [11].

1: Human MnSOD sequence
2: House Mice MnSOD sequence
3: Zebra Fish MnSOD sequence

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1 MATKAVCVLKGDGPVQGIINFEQKESNGPVKVWGSIKGLTEGLHGFHVHEFGDNTAGCTSAGPHFNPLSRKHGGPKD
  EERHVGDLGNVTADKDGVADVSIEDSVISLSGDHCIIGRTLVVHEKADDLGKGGNEESTKTGNAGSRLACGVIGIAQ

2 MAMKAVCVLKGDGPVQGTIHFEQKASGEPVVLSGQITGLTEGQHGFHVHQYGDNTQGCTSAGPHFNPHSKKHGGPAD
  EERHVGDLGNVTAGKDGVANVSIEDRVISLSGEHSIIGRTMVVHEKQDDLGKGGNEESTKTGNAGSRLACGVIGIAQ

3 MVNKAVCVLKGIGPVTGTVYFNQEGEKKPVKVTGSITGLTPGKHGFHVHAFGDNTNGCISAGPHFNPHDKTHGGPTD
  SVRHVGDLGNVTADASGVAKIEIEDAMLTLSGQHSIIGRTMVIHEKEDDLGKGGNEESLKTGNAGGRLACGVIGIT
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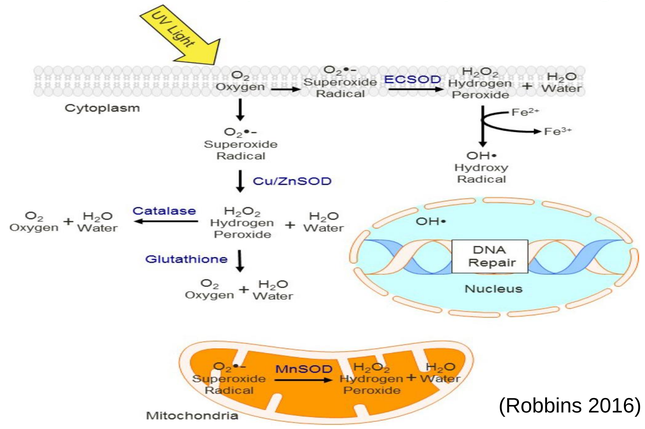
[11] NCBI - Cobalt

Mutation of MnSOD

Overexpression of MnSOD can lead to an accumulation of reactive oxygen species (ROS), which leads to oxidative stress and contributors to disease and tumor progression [8].

Discovered mutations:

- Substitution of valine to alanine in a single peptide at the -9 position. This may affect mitochondrial transport of MsSOD [9].
- Substitution of isoleucine to threonine at position 58. This decreases the thermal stability and enzymatic activity [3].
- Substitution of leucine to phenylalanine at position 60. This causes a decrease in the protein sensibility to redox regulation [4].

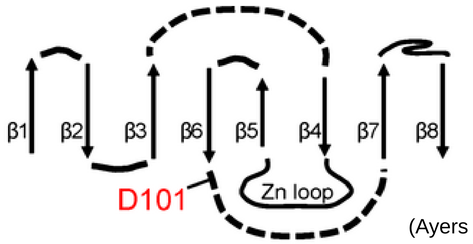


(Robbins 2016)

Figure 3: UV light causes free radicals and oxidative molecules to change the structure of multiple molecules and damage lipids, proteins, as well as nucleic acids. In order to remove the ROS's antioxidant enzymes such as MnSOD in the mitochondria are used. If not removed the ROS's can react and disrupt DNA and other signal proteins.

Discovered Disease:

- Familial amyotrophic lateral sclerosis is a progressive disease that effects nerve cells in the spinal cord and brain. Weakening and loss of muscle and a decreased control of movement results [2].



(Ayers 2013)

Figure 4: The overexpression mechanism of MnSOD during FALS. D101 is the mutation that causes a degradation of motor neurons.