Alzheimer’s disease (ad) and oxidative stress relationship

Alzheimer’s disease (AD) is a neurodegenerative disease which causes a lethal twist in the structural integrity, and a roadblock in the function of brain, this eventually channel the situation to degeneration and shrinkage of brain, and override the control of brain over other parts of the body, and comes to the final closing remark of the disease- death. Studies done on the topic have corroborated that the disease is not reversible, and the only patch of hope is slowing down its progress. But as the disease advances through mid stage and evolves into severe AD, the condition of patient becomes pathetic and care giving becomes more painful. Studies have reported that notable symptoms of AD are seen only after 60 years of age, even though the disease has started before that. Initial symptoms are loss of short term memory- being forgetful about the recent events, and gradually over a period of time patient seems more absent –minded about the environment, things which are chemically etched in the long term memory begins to be erased, and the final stage starts pushing the patient into severe AD which is tremendously pathetic.

Studies have proved that loss of function of neurons is the cause of AD. A closer look into the aspect revealed a complex set of events that precede the neuronal degeneration- oxidative stress and imbalance in homeostasis, formation of roadblocks in communication, falling apart of integrity and death of neurons. This enabled to go beyond the findings of superficial studies done and hypothesis developed, and helped to delve much deeper into the inner workings and mechanism of the disease. Hypotheses developed to explain mechanism of AD are: amyloid cascade hypothesis, cholinergic hypothesis and tau hypothesis. Amyloid cascade hypothesis says,

APP- Amyloid Precursor Protein, a transmembrane protein involved in main roles of growth, survival and repair of nerve cells- is snipped at wrong places by an enzyme called secretase, leading to the formation of amyloid β peptides which accumulates to form plaques- amyloid plaques- and bind to synapses blocking the communication channel, eventually causes memory loss. According to cholinergic hypothesis, downward drift in the levels of acetylcholine in brain is the cause for Alzheimer’s disease. Loss of function of cholinergic neurons was found in Alzheimer’s disease patients. Shift in the level of acetylcholine happens due to the lack of two enzymes involved in synthesis and breaking down of acetylcholine. This will lead to loss of function of neurons; brain’s functionality falls apart, and eventually leads to symptoms of Alzheimer’s disease. Tau hypothesis approaches the problem in another perspective, tau protein- a protein associated with microtubules in nerve cells- gets hyperphosphorylated, this enables cross linking among tau protein units, and they back off from being attached to the microtubules. This causes loss of structural integrity of nerve cells, and they collapse and clump to form tangles- neurofibrillary tangles. Studies conducted focusing on the inner workings of these hypothesis have found that oxidative stress is the reason that enhances plaque and tangle formation, repair mechanisms in cells are unable to solve the situation as the oligomer formation and cross linking are predominantly made by non peptide bonds. In another study, amyloid β peptides have shown close relation with some causes of mad cow disease. Studies related to genetics of AD have found the link between APOE gene on chromosome 21 and the disease. APOE gene codes for apolipoprotein, and one among its functions is breaking down of APP. APOE has variants, APOEε4 is the one which codes for less active protein whose

capacity to break down APP is sluggish. People with this variant gene are more tend to develop AD in later stages of life, and any abnormality related to chromosome 21 also results in AD over a period of time.

To know more about the mechanism of disease and its attachment to oxidative stress, further studies have done from different angles, and all the studies have come to a common point, the findings from all the studies stitched together gave a complex and elaborate picture about the mechanism of the disease. Free radical damage leads to oxidation of products in cell. Oxidation leads to new end products of glycation, nitration, lipid peroxidation, and oxidation of nucleic acids. These new end products chemically modify other proteins and compartments inside the cell. Oxidized derivatives impede with the channel of trace elements, and imbalances their homeostasis, and enables proteins like tau to form non peptide cross linking. In response to changes cell up the levels of heme oxygenase-1 (HO-1)- an antioxidant enzyme to mitigate the bad effects from free radical damage- but rapid heaping up of neurotoxic substances goes beyond control leading to severe imbalances, blockage of communication channels, and eventually death of neuron. Since mitochondria is the main source of free radicals and oxidative precursors. Certain deletions in mtDNA resulted in change in normal levels and rates of metabolism and production of free radicals. Free radicals formed in mitochondria are short lived and they do not have the ability to cross membrane and reach cytoplasm to cause damage, this led studies in a new direction and found free radicals- OH^- from cytoplasm- can attack guanidine in RNAs in cytoplasm and this both can cross the membrane and reach into mitochondria, and cause imbalance and

production of more stable $H_2O_2^-$ radicals which can come to cytoplasm and react with the channel of trace elements, and starts the primary events for the major causes for AD to come into being. AD starts at neocortex area of brain, and as the neurons die and rupture, the neurotoxic substances- plaques, free radicals, tangles, etc. – pervade the nearby nerve cells, and the cycle goes on and gradually covers the brain and makes it slip out of its normal being.