Neurodegeneration

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Paraoxonases and Neurodegeneration

Paraoxonases (PONs) are enzymes involved in lipid peroxidation and the detoxification of organophosphate pesticides and chemical nerve-gas agents. There are three PON enzymes (PON1 found attached to HDL in circulation, PON3 in the liver and PON2 found ubiquitously in several tissues). The genes for PONs lie in tandem on chromosome 7. Common genetic variants (polymorphisms) in PONs are established risk factors in a variety of vascular disorders including coronary artery disease and carotid artery stenosis. Recently three studies implicate PONs in neurodegeneration.[1-3]

Erlich et al[1] tested genetic association of PON cluster genes with Alzheimer disease (AD) in Caucasian and African American family-based cohorts. A PON1 promoter polymorphism, -161[C/T] was strongly associated with AD in both cohorts. Saeed et al[2] investigated the genetic association of PON cluster polymorphisms with sporadic ALS (SALS) in a large family-based and case-control Caucasian cohort. They found significant evidence of association in their family-based cohort.[2] Slowik et al[3] investigated 3 variants in two PON genes (PON1 and PON2) and found a 3-fold higher risk of SALS in a moderate sized Polish case-control cohort. There is a 2-fold increased risk of ALS in Gulf War veterans, where nerve gas agents and organophosphates were used.[2] Taken together these studies are compatible with the hypothesis that environmental toxicity in a susceptible host may precipitate neurodegeneration.

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2. Saeed M, Siddique N, Hung WY, Usacheva E, Liu E, Sufit RL, Heller SL, Haines JL, Pericak-Vance M, Siddique T. Paraoxonase cluster polymorphisms are associated with sporadic ALS. Neurology. 2006 [Epub ahead of print]
3. Slowik A, Tomik B, Wolkow PP, Partyka D, Turaj W, Malecki MT, Pera J, Dziedzic T, Szczudlik A, Figlewicz DA. Paraoxonase gene polymorphisms and sporadic ALS. Neurology. 2006 Jul 5; [Epub ahead of print]

Mechanism of ALS causation unravelled

Two teams of researchers at Northwestern University found a novel pathological mechanism of amyotrophic lateral sclerosis (ALS) which may eventually be applicable to neurodegeneration in general. The two teams show how and why the mutated superoxide dismutase (SOD1) protein, which causes a familial form of ALS, becomes vulnerable and prone to aggregation and also provide evidence linking disease onset with the formation of intermolecular aggregates. These findings were published in two related papers by the Proceedings of the National Academy of Sciences (PNAS).

ALS is a progressive paralytic disorder caused by degeneration of motor neurons in the brain and spinal cord. Professor Teepu Siddique at Northwestern mapped the first ALS gene (SOD1) to chromosome 21 in 1991. This was the first major advance in this relentless devastating disorder in 124-years since its discovery by Charcot. Subsequently, his team found that mutations in the SOD1 gene are responsible for 20 percent of familial ALS cases. Dr. Siddique and his colleagues also made the first ALS transgenic mouse models. A key question remained to be answered: How does the genetic mutation(s) alter SOD1 protein to make it toxic enough to kill motor neurons and cause neurodegeneration?

The presence of aggregated proteins is common to many neurodegenerative disorders, including ALS and Alzheimer's, Parkinson's and prion diseases, but the relevance of these aggregates to the diseases is not well understood. Dr. Siddique's team developed and analyzed various SOD1 transgenic mouse models and found, as they report in the first of the two PNAS papers, that aggregated and insoluble SOD1 is the pathogenic form that causes disease.[1] The aggregation takes place in mitochondria which become damaged leading to cell death.[1] Another interesting finding of this study was that 'normal' molecules of SOD1 are recruited in the presence of mutant SOD1 proteins to participate in the pathogenesis of ALS by forming intermolecular disulfide bonds. This phenomenon is similar to the recruitment noted in prion disorders[1] and provides insight into molecular mechanisms underlying neurodegeneration in general.

The normal form of SOD1 is a molecule composed of two identical parts, each with an amino acid chain, a copper ion, a zinc ion and an intramolecular disulfide bond that stabilizes the structure. The second paper[2] led by Thomas V. O'Halloran, Professor of chemistry at Northwestern in collaboration with Teepu Siddique, reported in the second PNAS paper, that increased oxidative stress leads to the mutant SOD1 protein forming incorrect disulfide bonds resulting in the formation of insoluble

aggregates. The SOD1 aggregates were specific to the spinal cord.[2]

Oxidation and protein aggregation have been suspected to play an important role in the pathogenesis of neurodegenerative disorders as well as in the normal aging process. However, the relationship between protein oxidation, protein aggregation and neurodegeneration remained unclear. The oxidative intermolecular disulfide cross-linking paradigm presented in these two papers provides direct links between these processes and neurodegeneration in SOD1-mediated ALS. This mechanism may play an important role not only in ALS but also in other neurodegenerative disorders.

1: Deng HX, Shi Y, Furukawa Y, Zhai H, Fu R, Liu E, Gorrie GH, Khan MS, Hung WY, Bigio EH, Lukas T, Dal Canto MC, O'Halloran TV, Siddique T. Conversion to the amyotrophic lateral sclerosis phenotype is associated with intermolecular linked insoluble aggregates of SOD1 in mitochondria. Proc Natl Acad Sci USA. 2006;103:7142-7.

2: Furukawa Y, Fu R, Deng HX, Siddique T, O'Halloran TV. Disulfide cross-linked protein represents a significant fraction of ALS-associated Cu, Zn-superoxide dismutase aggregates in spinal cords of model mice. Proc Natl Acad Sci USA. 2006;103:7148-53.

Frontotemporal dementia (FTD)

FTD is the second most common cause of dementia in people under the age of 65 years. It is characterized by abnormalities in personality, behavior and language with relative preservation of perception and memory and may also be associated with motor dysfunction including both motor neuron disease (MND) and parkinsonism. On histopathology there are tau positive neuronal inclusions (40%) and ubiquitin immunoreactive neuritis and neuronal cytoplasmic inclusions. A significant proportion of FTD cases demonstrate family history of the disease (35-50%). In 1998 mutations in the gene (on chromosome 17) encoding the microtubule-associated protein tau (MAPT) were shown to cause familial FTD with parkinsonism.[1] Recently two papers in Nature describe mutations in the gene progranulin also located on chromosome 17.[2,3] Progranulin is a multifunctional growth factor. Mutations which truncated the protein were found associated with FTD.[2,3] Although the exact function of progranulin is as yet unknown it appears to be important for neuronal survival and even partial loss of the protein leads to neurodegeneration.

Recently three groups also confirmed the existence of a new genetic locus for FTD associated with MND on chromosome 9q21.[4-6] The identification of the causative gene is still pending. These advances have defined FTD as a unique dementia distinct from Alzheimer's disease and have laid the foundation for further understanding of common mechanisms of neurodegeneration.

1. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 1998;393:702-5.

2. Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006; [Epub ahead of print]

3. Cruts M, Gijselinck I, van der Zee J, Engelborghs S, et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 2006; [Epub ahead of print]

4. Vance C, Al-Chalabi A, Ruddy D, et al. Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2-21.3. Brain 2006;129:868-76.

5. Morita M, Al-Chalabi A, Andersen PM, Hosler B, et al. A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia. Neurology 2006;66:839-44.

6. Jianhua Yan, Nailah Siddique, Susan Slifer et al. A Major Novel Locus for ALS/FTD on Chromosome 9p21 and its Pathological Correlates: S61.006 Neurology 2006; 67: 186.