研究報告書

Therapeutic Approaches For X-drenoleukodystrophy.

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X-Adrenoleukodystrophy (X-ALD) is an inherited metabolicdisorder of very-long-chain fatty acids (VLCFA) as a result of dysfunction of their activation to their CoA derivatives. The resulting pathognomonic accumulation of VLCFA subsequently leads to neuroinflammatory disease marked by induction of proinflammatory cytokines. We have previously reported that the inflammatory cytokines down regulate the peroxisomal VLCFA oxidation resulting in three times higher accumulation of VLCFA in the inflammatory region as compared to histological normal area of X-ALD brain. Studies from our laboratory have also shown that astrocytes , microglia and infiltrating cells express inducible Nitric Oxide Synthase (iNOS) in inflammatory area around the plaque in X-ALD brain leading to nitrosylation of cellular components. This observed excessive nitrosylation may be responsible for the loss of oligodendrocytes and loss of myelin in X-ALD.

X-ALD disease is caused by mutation or deletion of ALD-gene, a member of ABC cassette of transporters, that codes for a peroxisomal membrane protein. Studies from our laboratory have shown that the VLCFA acyl-CoA synthase is a membrane associated protein and is localized on the luminal surface of peroxisomes and that X-ALD cells have normal amounts of VLCFA acyl-CoA synthase protein. Although the precise function for ALD-gene product (ALDP) in the VLCFA activation and oxidation is not known so far, transfection of cDNA for ALDP or other peroxisomal membrane transporters(ALDRP, PMP-70 or PMRP-70) does corrects the metabolic defect in cultures skin fibroblasts from X-ALD patients.

Studies from our laboratory have shown that lovastatin has both anti-inflammatory properties as well as corrects the VLCFA defect in cultured skin fibroblasts of X-ALD patients. The treatment of cells with lovastatin increased peroxisomal oxidation and decreased the VLCFA levels. A combination of RT-PCR and immunoblot analysis of various peroxisomal proteins showed that increased expression of ALDRP by lovastatin treatment complimented the function of ALDP in the oxidation of VLCFA in peroxisomes in cultured skin fibroblasts. The lovastatin treatment of X-ALD patients also lowered the plasma level of VLCFA but to a lesser degree than fibroblasts. The basis for these differences is not known at present. We have also reported that lovastatin down regulates the induction of pro-inflammatory mediators in cultured astrocytes, microglia and macrophages and in CNS of animal model of experimental allergic encephalomyelitis, an animal model for Multiple Sclerosis. These observations indicate that a drug that corrects the metabolic defect as well as anti-inflammatory action may be of potential benefit to X-ALD patients.

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発表業績　：　著者氏名・発表論文名・学協会誌名・発表年・(西暦)・巻号(最初と最後の頁)

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