Irina Ionescu

Inducing the early-onset, inflammatory phenotype of demyelinating cerebral childhood adrenoleukodystrophy (CCALD) in the Abcd1null-mouse model of X-ALD

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder caused by mutations affecting the adrenoleukodystrophy protein (ALDP), also termed ABCD1, a peroxisomal membrane protein belonging to the ABC (ATP-binding cassette)-transporter superfamily. ALDP has been suggested to play a role in the peroxisomal β-oxidation of very long-chain fatty acids (VLCFA), since the biochemical hallmark of the disease are increased VLCFA-levels. The two most common phenotypes of the disease are the inflammatory cerebral childhood demyelinating form of ALD (CCALD), characterized by an early onset and a rapid progression, as well as by demyelinating lesions and inflammation in the brain; and adrenomyeloneuropathy (AMN), a milder phenotype restricted to the degeneration of axons in the spinal cord and peripheral nerves. It has hitherto remained unknown which factors determine the disease course; however, variable expression of modifier genes as well as environmental factors have been suggested to play a role. The Abcd1null mice are a genetically exact model of the disease. They do not develop the CCALD-like phenotype, instead showing a late-onset, AMN-like disease course. The purpose of this work was to examine whether the CCALD-like phenotype could be induced in the Abcd1null mouse with the aid of a cryolesion applied at an early age to the developing cortex as a model of neurotrauma. In order to evaluate motor and cognitive functions, the Abcd1null mice with cold lesion were subjected to a battery of behavioural tests including rotarod, grid-running, open-field, hole-boards and a fear conditioning/extinction paradigm. The results showed no significant differences between Abcd1null mice with cold lesion and the control groups as far as motor functions, coordination skills and exploratory behaviour are concerned. However, extinction to a conditioned auditory stimulus was reduced as compared to wild-type mice with cold lesion, suggesting impaired function of the ventromedial prefrontal cortex. Histological analysis of the brain focusing on the genu of the corpus callosum, the anterior commissure and the spinal cord revealed no significant differences between groups regarding the degree of myelination, the number of APP-positive axonal swellings and the extent of astrocyte reactivity. There was no inflammation present in Abcd1null mice with cold lesion, as shown by investigation of the presence of reactive microglia and lymphocyte infiltration. Taken together, these results indicate that a cold lesion may not be sufficient to induce the inflammatory phenotype of CCALD in mice lacking ALDP.