"Good relatives: How a redundant gene could save X-linked adrenoleukodystrophy patients"

X-linked adrenoleukodystrophy (X-ALD) is a rare, inherited disorder with a broad clinical variability. Whereas essentially all male X-ALD patients develop a slowly progressive dying-back axonopathy affecting both ascending and descending spinal cord tracts in young adults, in about 60%, a devastating, rapidly progressive form of cerebral inflammatory demyelination occur either in childhood or adulthood. Only if the cerebral inflammation is diagnosed and treated at an early stage, the exchange of the immune cells by hematopoietic stem cell transplantation can stop the inflammation and rescue the patients. We could demonstrate that, among the different immune cell types, predominantly the macrophages are metabolically affected in X-ALD. Moreover, we demonstrated, both in vitro and in vivo, that the intrinsic defect of X-ALD macrophages impairs their ability to convert from a pro-inflammatory to an anti-inflammatory status. A direct comparison between pro-inflammatory lesions of post-mortem brain tissue from patients with multiple sclerosis or cerebral X-ALD clearly demonstrated a lack of anti-inflammatory macrophages in X-ALD. This inability to establish an anti-inflammatory milieu would explain why spreading of the inflammatory, demyelinating lesion in X-ALD cannot halt spontaneously and why it is refractory to anti-inflammatory treatments. Moreover, this might also explain the success of hematopoietic stem cell transplantation in X-ALD, in which – among other cell types – also the patient's macrophages are exchanged by those derived from the donor stem cells. However, often the inflammatory demyelination in X-ALD patients is diagnosed at an advanced stage, too late for hematopoietic stem cell transplantation to be beneficial, leaving many patients without any curative treatment. Our research results identified macrophages as a main therapeutic target for stopping the devastating inflammatory demyelination in X-ALD. Moreover, we identified compounds that are able to induce a homologous gene, which is intact in X-ALD, to an extent that may be sufficient for rescue of the inherited defect in X-ALD macrophages. The application of such compounds to cerebral X-ALD patients potentially represent a novel therapeutic pharmacological approach to halt the inflammation in X-ALD.
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Johannes Berger graduated from University of Vienna for biology/genetics in 1989. He performed his PhD at the Sandoz Research Institute (now Novartis), Department of Antiretroviral Therapy or training in molecular biology and biochemistry. He then joined the Institute of Neurology, University of Vienna. He improved his technical skills at the Kennedy Krieger Institute in Baltimore, received his habilitation for Molecular Biology in 1999 from the Medical University of Vienna and in 2003 for Biochemistry from the University of Vienna.

Since 2006 he is coordinator of the PhD program neuroscience at the Medical University Vienna. He is currently Professor for Pathobiology of the Nervous System at the Center for Brain Research, Medical University of Vienna. His current research activities concentrate on the role of peroxisomes in the nervous system for health and disease. A main focus concerns the molecular mechanisms underlying X-linked Adrenoleukodystrophy and the development of novel therapeutic strategies to compensate peroxisomal dysfunction in the nervous system.