SESSION X

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Can enzyme replacement therapy revert iNKT cell dysfunction in acid sphingomyelinase deficiency patients?

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Acid sphingomyelinase deficiency (ASMD) is a lysosomal storage disease caused by deficient activity of the enzyme acid sphingomyelinase (ASM), resulting in an abnormal accumulation of sphingomyelin in lysosomes. The abnormal accumulation of sphingomyelin, a crucial cell membrane component, ultimately impairs pulmonary, hepatic, and sometimes neurological functions, with severe forms of the disease being fatal in the first years of life.
Invariant Natural Killer T (iNKT) cells are lipid-reactive T cells that play a central role in a wide range of immune responses including cancer, infection and inflammation. iNKT cells are restricted to CD1d, depending on the presentation of lipids by this molecule for their function. Sphingomyelin is a lipid with affinity for CD1d and its accumulation in ASMD influences the role of iNKT cells by impairing normal lipid antigen presentation to these cells (1). Interestingly, ASM-/- mice have reduced number of iNKT cells and impaired iNKT cell activity, in ASMD patients a reduced frequency of iNKT cells is also observed (1). Noteworthy, enzyme replacement therapy (ERT) with recombinant ASM can prevent iNKT cell deficiency in ASM-/- mice (1). In the current study we are investigating the effect of ERT on iNKT cells in ASMD adult patients.
So far, five ASMD patients were recruited, having three initiated ERT with Olipudase alpha. Patients iNKT cells were analyzed pre-therapy and every 3 months after ERT started. In addition, twenty-two healthy donors were analyzed as controls.
The basal characterization of ASMD patients, before ERT, confirms patients' lower iNKT cell frequency. In addition, patients iNKT cells have a more immature profile indicated by lower CD161 and higher CD4 expression and increased activation state accessed by ICOS expression than control subjects.
During the course of these study three patients treated with ERT were recruited. So far patients have been on therapy for 3, 9 and 20 months. The two patients treated longer show improvement in the disease biomarker lyso-sphingomyelin and clinical features. Despite these improvements no recovery in the percentage or phenotype of iNKT cells was observed so far. It will be important to recruit more and younger patients and continue patient follow-up for a longer duration.

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Reference:

[1] Melum, et al Blumberg (2019)Nature Immunology, doi:10.1038/s41590-019-0504-0.