T16-070B

UBE3A PROMOTES FOAM CELL FORMATION AND COUNTERS REMYELINATION BY TARGETING ABCA1 FOR PROTEASOMAL DEGRADATION

M. Loix[1,2], S. Vanherle[1,2], L. Bolkaerts[1,2], F. Wouters[1,2], S. G. Verberk[1,2], B. Moonen[1,2], M. Punt[3,4], S. A. van Wouw[5], R. Verhagen[3,4], A. Jongejan[6], B. Distel[3,4], Y. Elgersma[3,4], M. Haidar[1,2], N. Zelcer[5], J. J. Hendriks[1,2], J. F. Bogie[1,2]

[1] Hasselt University, Biomedical Research Institute, Diepenbeek, Belgium; [2] Hasselt University, University MS Center, Pelt, Belgium; [3] Erasmus University Medical Center, Department of Clinical Genetics, Rotterdam, Netherlands; [4] Erasmus University Medical Center, ENCORE Expertise Center for Neurodevelopmental Disorders, Rotterdam, Netherlands; [5] University of Amsterdam, Department of Medical Biochemistry, Amsterdam Institutes of Cardiovascular Sciences and Gastroenterology Endocrinology and Metabolism, Amsterdam, Netherlands; [6] University of Amsterdam, Bioinformatics Laboratory, Amsterdam, Netherlands

Multiple sclerosis (MS) is a devastating neurological disease and one of the most prevalent autoimmune diseases in the Western world. Foamy macrophages loaded with myelin-derived lipids are a pathological hallmark of MS lesions. Emerging evidence indicates that perturbed metabolism and efflux of intracellular lipids underlies the development of a harmful foamy macrophage phenotype in these disorders. To date, the molecular mechanisms that underlie dysregulation of cellular lipid metabolism are not fully understood.

Here, we show that the ubiquitin-proteasome system controls turnover of the cholesterol efflux transporter ATP-binding cassette A1 (ABCA1) in lipid-loaded macrophages in the brain. We report that sustained intracellular accumulation of myelin-derived lipids promotes the abundance and activity of ubiquitin-protein E3 ligase A (UBE3A) in macrophages, which in turn stimulates ABCA1 ubiquitination and subsequent degradation. UBE3A-mediated ABCA1 degradation boosted cellular lipid accumulation, and induced the formation of an inflammatory macrophage phenotype that impaired remyelination. By using RNA sequencing analysis, we further established Tat-interacting protein 30 (TIP30), an inhibitor of importin β-mediated nuclear import, as an essential regulator of cytosolic UBE3A levels.

Collectively, our findings identify UBE3A as a driver of foam cell formation, and indicate that targeting UBE3A-mediated ABCA1 degradation is a promising strategy to mend faulty lipid metabolism in foamy macrophages and enhance central nervous system repair.