Identification of novel clinical applications for acid sphingomyelinase inhibitors

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Abstract

Acid sphingomyelinase is a lysosomal enzyme that catalyzes the hydrolysis of sphingomyelin to ceramide. Acid sphingomyelinase/ceramide have been implicated in the pathogenesis of a number of different diseases. Pharmacological inhibitors of acid sphingomyelinase are already in clinical use and are well tolerated. Thus, this study aimed to expand the existing applications of known acid sphingomyelinase inhibitors to acid sphingomyelinase/ceramide-related diseases with a currently unmet clinical treatment need.

Farber disease is a rare lysosomal storage disorder caused by ceramide accumulation due to acid ceramidase deficiency. This study introduces a new mouse model to study FD that mirrors the human disease closely. Cross-breeding of these mice to acid sphingomyelinase-deficient mice reduced ceramide accumulation, improved disease manifestations and prolonged survival. Pharmacological inhibition of acid sphingomyelinase, however, failed due to unexpected, genotype-specific toxicity.

In rheumatoid arthritis, an autoimmune disorder affecting predominantly the joints, ceramide levels in the synovial fluid of patients have been reported to be elevated. Using a mouse model of inflammatory arthritis, this study analyzed the role of acid sphingomyelinase in joint inflammation and shows that both genetic ablation and pharmacological inhibition of acid sphingomyelinase ameliorates arthritis severity.