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140 YEARS SINCE THE IDENTIFICATION OF GAUCHER DISEASE: WHAT IS THERE LEFT TO LEARN?

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Gaucher disease (GD) is an autosomal recessive genetic disease caused by mutations in the *GBA1* gene, which encodes for the lysosomal hydrolase, glucocerebrosidase (GCase). GD is normally divided into three phenotypes. Type 1 GD, the most frequent form of the disease, is considered to have no obvious neuronopathic features, and the classical hallmark of the disease is glucosylceramide-laden alternatively-activated macrophages, known as 'Gaucher cells'. Type 2 and type 3 GD are neuronopathic forms (collectively referred to as neuronopathic GD (nGD)). Glucosylceramide (GlcCer) and glucosylsphingosine accumulation in the brain leads to neuronal loss in nGD patients and in nGD mouse models. However, the mode of neuronal death is not known. We recently demonstrated elevation of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β) and tumor necrosis factor-α (TNF α in a mouse model of Gaucher disease. Our data suggested that neuroinflammation induces cytotoxic effects in nGD. Inflammation is usually associated with necrotic rather than apoptotic cell death; cell death via necrosis leads to microglial activation and pro-inflammatory signaling cascades. I will now discuss our recent data that shows that modulating the receptor-interacting protein kinase 3 (Ripk3) pathway markedly improves neurological and visceral disease in a mouse model of Gaucher disease. Importantly, Ripk3 deficiency dramatically improved the clinical course of Gaucher disease mice with increased survival, motor coordination and salutary effects on cerebral as well as hepatic injury. I will also discuss additional data demonstrating the involvement of a number of other pathways in Gaucher disease pathology and suggest that these too might act as therapeutic targets.

Selected recent references:

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