Effect of glucosylceramide accumulation on the neuronal homeostasis: a new neuronal in vitro model of Gaucher disease

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E.V. Carsana[I], M. Samarani[I], E. Frattini[I], A. Di Fonzo[I], N. Loberto[I], R. Bassi[I], G. Lunghi[I], M. Aureli[I]

[I]L.I.T.A, Segrate, Italy

Gaucher disease (GD) is a lysosomal storage disorder due to an impairment of the lysosomal β-glucocerebrosidase (GCase) activity with consequent accumulation of glucosylceramide (GlcCer). Nowadays it is clear that a common feature of all the different phenotypes of GD is the onset of neuronal degeneration; nevertheless, the molecular mechanism underlying the relation between GBA mutations and the onset of neuronal damage in GD remains unclear so far.

To figure out which is the possible molecular mechanism linking GCase loss of function with the onset of neuronal damage, we developed an in vitro model of the neuronal form of GD represented by iPSCs-derived dopaminergic neurons, obtained from healthy subjects' fibroblasts and treated for 7, 13 and 29 days with conduritol B epoxide (CBE), a specific inhibitor of GCase.

In CBE-treated neurons we found a progressive and time-dependent accumulation of GlcCer. Upon reaching a threshold of GlcCer accumulation, CBE-treated neurons showed: i) a significant neuronal damage as demonstrated by the reduction of the main neuronal markers such as Tau, Synapsin, MAP2 beta3-tubulin, and PSD95, ii) increased volume of intracellular acidic organelles and augmented lysosomal biogenesis, iii) impairment of the lysosomal sphingolipid catabolism, iv) block of the autophagic flow in term of augmented LC3IIB and p62, and v) as occurs in several other lysosomal storage disorders, the secondary accumulation of not catabolized glycosphingolipids. In addition, we found that the accumulated GlcCer is not just confined to the lysosome but affects also the plasma membrane.

In conclusion, this in vitro model helps to investigate the onset of cell damage induced by GlcCer accumulation and lysosomal dysfunction. The obtained results let to speculate on the existence of a mechanism involving the plasma membrane in the onset of neuronal degeneration occurring in the brain pathology of GD .