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New approaches to Tay-Sachs disease therapy

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Abstract

Copyright © 2018 Solovyeva, Shaimardanova, Chulpanova, Kitaeva, Chakrabarti and Rizvanov. Tay-Sachs disease belongs to the group of autosomal-recessive lysosomal storage metabolic disorders. This disease is caused by β-hexosaminidase A (HexA) enzyme deficiency due to various mutations in α-subunit gene of this enzyme, resulting in GM2 ganglioside accumulation predominantly in lysosomes of nerve cells. Tay-Sachs disease is characterized by acute neurodegeneration preceded by activated microglia expansion, macrophage and astrocyte activation along with inflammatory mediator production. In most cases, the disease manifests itself during infancy, the “infantile form,” which characterizes the most severe disorders of the nervous system. The juvenile form, the symptoms of which appear in adolescence, and the most rare form with late onset of symptoms in adulthood are also described. The typical features of Tay-Sachs disease are muscle weakness, ataxia, speech, and mental disorders. Clinical symptom severity depends on residual HexA enzymatic activity associated with some mutations. Currently, Tay-Sachs disease treatment is based on symptom relief and, in case of the late-onset form, on the delay of progression. There are also clinical reports of substrate reduction therapy using miglustat and bone marrow or hematopoietic stem cell transplantation. At the development stage there are methods of Tay-Sachs disease gene therapy using adeno- or adeno-associated viruses as vectors for the delivery of cDNA encoding α and β HexA subunit genes. Effectiveness of this approach is evaluated in α or β HexA subunit defective model mice or Jacob sheep, in which Tay-Sachs disease arises spontaneously and is characterized by the same pathological features as in humans. This review discusses the possibilities of new therapeutic strategies in Tay-Sachs disease therapy aimed at preventing neurodegeneration and neuroinflammation.

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Keywords

Bone marrow transplantation, Gene therapy, GM2-gangliosidosis, Inflammation, Lysosomal storage diseases, Neurodegeneration, Tay-Sachs disease, B-hexosaminidase

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