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## Future challenges in rare diseases: Transcranial magnetic stimulation a new therapeutic strategy for Huntington's disease

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Rare disease are a group of degenerative processes with genetic basis that can affect different organs, systems and structures of the human body, altering the normal development of the patient's life and limiting their quality of life and in many cases shortened significantly their hope life. Four guide axes should be to enhance and intensify the study of etiology and pathophysiology for understanding of the mechanisms involved and to design specific therapeutic strategies improving the quality of life and life expectancy of these patients. These movements would be to establish networks and synergies that allow interaction between groups working in these diseases; to design frameworks specific funding for rare diseases by public administration; to design strategies that encourage the direct or indirect involvement of the pharmaceutical industry; and to involve patients and families' societies or foundations. In this line, a new strategy for treatment of rare diseases and specifically Huntington's disease could be repetitive transcranial magnetic stimulation (rTMS). In recent decades data indicate the possibility use of rTMS on Huntington's disease. This tool show beneficial effects on Choreiform disorder. On the other hand, experimental studies from our group have found that TMS produces protective effects on behavior, oxidative and cell damage and neurogenesis in a 3-nitropropionic acid-induced Huntington's disease-like model. In brief, rTMS is an important therapeutical strategy for Huntington's disease and others rare degenerative diseases such as amyotrophic lateral sclerosis (ALS) and Duchenne muscular dystrophy, as well as for neurodegenerative disease as Parkinson's disease, Alzheimer's disease or multiple sclerosis.

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## Impairment of regulated exocytosis in rare human diseases with immunodeficiency: Lessons learned from Chediak-Higashi syndrome

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Several rare human diseases, including familial hemophagocytic lymphohistiocytosis, Hermansky-Pudlak syndrome, Griscelli syndrome or Chediak-Higashi syndrome (CHS), display similarities in terms of their clinical manifestations and immunologic mechanisms, for example the presence of hemophagocytosis and decreased or absent cytotoxic activity of Natural Killer (NK) cells. NK cells, a subset of lymphocytes involved in protection against tumors and microbial pathogens are best known for their ability to mediate cytotoxic elimination of abnormal cells. The killing of target cells is a complex process, culminating in the localized delivery of lysosome-related lytic granules to the cell-cell contact site (immunological synapse), where the granules navigate through the cortical actin meshwork before fusing with the plasma membrane and releasing their content. It has been proposed that defects in exocytosis of lytic granules, resulting in decreased cytolytic function of NK cells could be primarily responsible for the lack of elimination of over-activated cells and thus contribute to the persistent inflammation and uncontrolled cell proliferation observed in lymphohistiocytic syndromes. CHS is characterized by immunodeficiency and formation of giant lysosomes or lysosome-related organelles in several cell types. The treatment of CHS has been limited by the insufficient knowledge about the cellular mechanisms involved in disease development and progression. Using NK cells isolated from CHS patients and a newly generated human cellular model of CHS, we have gained new insights into the disease pathology, regulation of exocytosis and mechanisms underlying faulty granule secretion in CHS. We discovered that the large granules are functional but actin remodeling at the immunological synapse is a major factor limiting their release from CHS NK cells. Those data suggests that the faulty exocytosis in CHS is of a physical nature rather than a functional defect. Indeed, manipulation of cortical actin density or granule size allows restoring CHS NK cell function and offers new therapeutic strategy for CHS patients.

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