Title

Therapeutic agent for Niemann-Pick disease type C

Background and Purpose of Research

Niemann-Pick disease type C (NPC) is characterized by accumulation of cholesterol in cells caused by cholesterol transport disorder in cells. Treated NPC patients currently receive miglustat which yields extension of survival period of patients, but which provides no further therapeutic effect. It is also known that administration of cyclodextrin to NPC disease cellular model reduces accumulation of cholesterol. However, whilst cholesterol is removed by cyclodextrin, there is no act by cyclodextrin on alleviation of cholesterol transport disorder, therefore cyclodextrin will not lead to drastic treatment of NPC. Inasmuch as NPC is an intractable disease, and when contracted by infants, produces motor functional disorder and neurological disorder, and can cause death at their ages of around 10, there is urgent need for a novel drastic therapy. The purpose of this research is to remedy cholesterol transport disorder and provide a novel therapeutic agent, thus conducive to drastic therapy, for NPC.

Summary of Research Results

For NPC disease cellular model, researchers used NPC1 gene deficient cell (CHO-NPC) derived from Chinese hamster ovary (CHO) cells. Researchers demonstrated the effect of ceramide 1-phosphate (C1P) inhibitor on the accumulation of cholesterol in NPC disease cellular model. Based on that, researchers strive to develop a novel therapeutic agent for NPC, the action mechanism of which consists of remedy of cholesterol transport disorder by suppression of ceramide kinase.

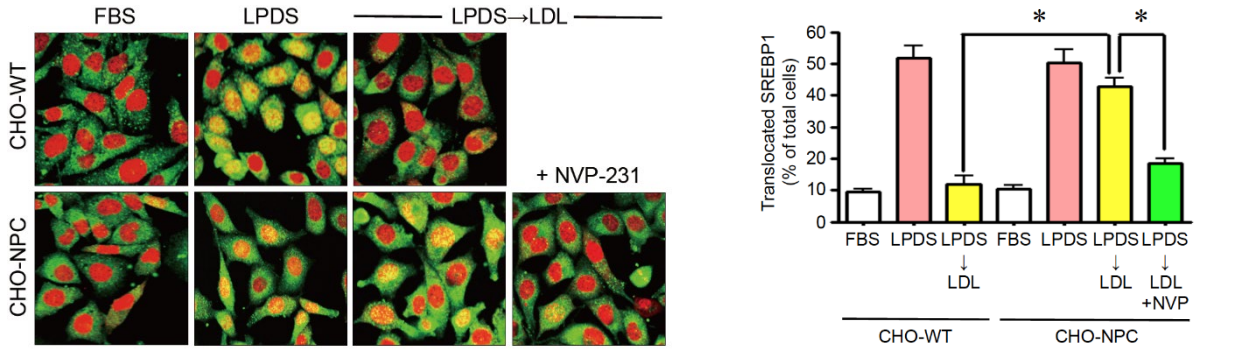

Figure 1: Applying a cell culture medium containing LPDS (lipoprotein-deficient serum) in culturing wild-type cell and NPC disease cell, there ensue depletion of cholesterol in the endoplasmic reticulum, and transition of SREBP1(lipid synthesis transcription factor) into nucleus of the cell (nucleus is colored yellow). Consequence of imposition thereonto of LDL (low-density lipoprotein) in the case of wild-type cell is such that SREBP1 disappear from nucleus (nucleus is colored red) because there occur cholesterol transport to the endoplasmic reticulum, whereas consequence in the case of NPC disease cell is such that disappear of SREBP1 is limited and restricted because cholesterol stays in the late endosome. This limitation and restriction is resolved by administration of ceramide kinase inhibitor (NVP-231) which

suppresses production of C1P. The implication is that suppression of ceramide kinase provides remedy to cholesterol transport disorder in NPC disease cell.

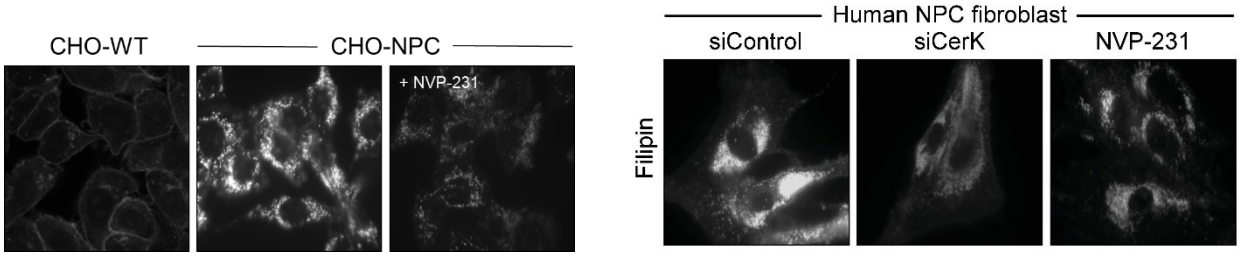

Figure 2: CHO-NPC indicates accumulation of cholesterol. However, administration of ceramide kinase inhibitor (NVP-231) thereon has the effect of reducing the accumulation of cholesterol. Additionally, whereas administration of control siRNA (siControl) on patient's skin fibroblasts indicates accumulation of cholesterol, administration of ceramide kinase selective siRNA (siCerK) or administration of NVP-231 on the same fibroblasts indicates reduction of accumulation of cholesterol.

Advantages

Capable of remedying cholesterol transport disorder and providing a novel, conducive to drastic treatment, for NPC, in contrast to existing technology which lacks such capability.

Applications

Therapy of NPC.

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