T Y Chang et al., J Alzheimers Dis Parkinsonism 2018, Volume 8
DOI: 10.4172/2161-0460-C7-054

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Mobilizing cholesterol in the brain to treat Niemann-Pick type C disease and Alzheimer's disease

All cells require cholesterol and a portion of cellular cholesterol is stored as cholesterol esters; this process is catalyzed by the storage enzyme acyl-CoA:cholesterol acyltransferase 1 (ACAT1). Once formed, cholesterol esters cannot substitute the functions of cholesterol. In certain neurodegenerative dieases, needs for additional cholesterol in the brain arise. Inhibiting ACAT1 may benefit these diseases, by preventing cholesterol from being stored, thus providing the additional cholesterol that the diseased cells need. We tested this idea in two neurodegenerative dieases i.e., Niemann-Pick type C disease (NPCD) and Alzheimer's disease (AD). NPCD is a rare and genetic neurodegenerative disease. The NPCD patients almost invariably die before reaching teenage. In mutant NPC cells, malfunction in endosomal cholesterol egress occurs causing chronic functional cholesterol deficiency in the plasma membrane and golgi membrane. We show that ACAT1 KO or ACAT1 inhibitors provide more cholesterol to golgi membranes of mutant NPC1 cells. In vivo, ACAT1 KO increases the life span and improves several other distinguishing features of the mutant NPC1 mouse. We next show that in a mouse model for AD, inhibiting ACAT1 provides more cholesterol to cell membranes of neuronal cells and produces multiple benefits that includes reducing Abeta production, increasing oligomeric Abeta degradation and increasing unhyperphosphorylated mutant human tau degradation. ACAT1 blockage also ameliorates the cognitive deficits of the AD in mouse. In summary, we show that inhibiting ACAT1 mobilizes a specific cholesterol pool in the brain to benefit two different neurodegenerative diseases i.e., NPCD and AD.

Biography

TY Chang and Catherine Chang are a husband/wife team, and share the same laboratory, with TY as the PI and Cathy as the co-PI, at Geisel School of Medicine at Dartmouth. They have been working on cholesterol metabolism research for more than four decades. The Changs and their colleagues did ground breaking work by identifying the gene that encodes the cholesterol storage enzyme acyl-CoA:cholesterol acyltransferase 1 (ACAT1/SOAT1). Subsequently, they performed extensive functional analysis of the enzyme. More recently, they demonstrated ACAT1 as a potential target for treating several human diseases, including Alzheimer's disease and Niemann-Pick type C disease.

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