論文の内容の要旨

論文題目　Lipodystrophy and cold intolerance in mice lacking *Cnot3* in adipose tissue-specific manner
（脂肪組織特異的 *Cnot3* 欠損マウスに見られる脂肪異栄養症と寒冷不耐症）

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Adipose tissue has two essential biological roles in controlling energy balance and lipid homeostasis: first, it is the major storage site of excess energy in the form of triglycerides and, second, it is an important endocrine organ that synthesizes and secretes hormones and adipokines. Dysfunction of adipose tissue can result in not only obesity (an excess of adipose tissue) but also lipodystrophy (a deficiency of adipose tissue). Although these two conditions are opposite pathological states of adipose tissue mass, they are both accompanied by similar metabolic consequences, including dyslipidemia, hepatic steatosis, severe insulin resistance, and diabetes mellitus (Figure 1). Lipodystrophy can be caused by either genetic or acquired factors and can be classified as either generalized or partial, depending on the degree and locality of the fat. Currently, the most common form of lipodystrophy is induced by the protease inhibitors used to treat HIV-infected AIDS patients and affects up to 50% of the patients. Thus, elucidating the mechanisms that underlie lipodystrophy is extremely important for developing therapeutic strategies for not only lipodystrophy but also related metabolic complications.

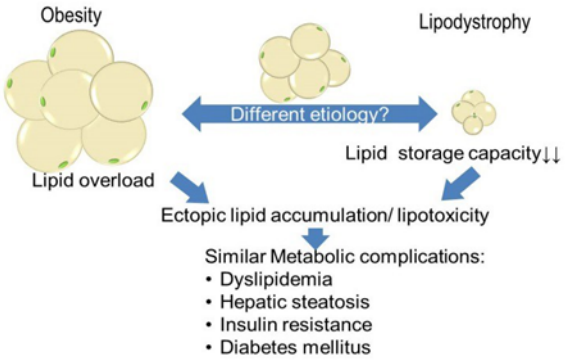

Figure 1. Schematic illustration of lipodystrophy

The CCR4-NOT complex is an evolutionarily conserved complex that has been implicated in the control of multiple steps of mRNA metabolism, including repression and activation of transcription, elongation of mRNA, and deadenylation and subsequent degradation of mRNA. Given these diverse activities, it is not surprising that this complex is relevant to a wide range of biological functions. The CCR4-NOT complex plays important roles in cell proliferation, apoptosis, oogenesis and embryogenesis,

spermatogenesis, heart function, bone formation and energy metabolism. Recent evidence shows that aberrant regulation of this complex causes metabolic abnormality, heart disease, and osteoporosis. Mice haplodeficient in *Cnot3* are lean because of poor fat accumulation. Liver size white and brown adipose tissues (WAT and BAT, respectively) are reduced in these mice, and adipocytes are smaller than those in wild-type mice. These data suggest that *Cnot3* has a specific function in liver and adipose tissues. Indeed, a reduction in CNOT3 levels affects the expression of mRNAs that encode proteins that are important for lipid metabolism, glucose metabolism, oxidative phosphorylation, and growth regulation in the liver. However, the mechanism by which *Cnot3* regulates the lipid metabolism in adipose tissue remains unknown.

In this study, to understand the role of *Cnot3* in adipose tissue, and particularly the relevance of CNOT3 in fat mass and energy metabolism, I specifically depleted *Cnot3* from mouse adipose tissue using the cre/loxP system. I show that mice with adipose tissue-specific depletion of *Cnot3* share many of the features reported in human patients with Congenital Generalized Lipodystrophy (CGL) and in other lipodystrophy mouse models, such as *aP2- nSrebp1c* mice (*Sr*), which express a truncated, constitutively active *Srebp-1c* transgene in adipocytes. These features include a marked reduction in the amount of white adipose tissue, hypertrophy of brown adipose tissue containing fat-laden cells resembling immature white adipocytes, and hyperinsulinemia and hyperglycemia that are associated with insulin resistance and glucose intolerance. Accordingly, plasma triglyceride levels are elevated, and lipid accumulates ectopically in the liver and other insulin sensitive organs.

I further provide evidence that CNOT3 depletion increased apoptosis in peripheral adipocytes and was associated with aberrant fat storage and lipid release, which could be a direct cause of the lipodystrophic phenotype of mice lacking *Cnot3* in a manner specific to adipose tissue. To examine the underlying mechanisms, I have compared the gene expression profiles of wild-type and mice that lack *Cnot3* in adipose tissue. The results show that pathways involved in apoptosis and inflammation were significantly up-regulated in mice in which *Cnot3* is depleted in adipose tissue. The microarray data also revealed that the expression of SREBP (SREBF) target genes was up-regulated in the adipose tissues of mice in which *Cnot3* is depleted. Taken together, these data suggest that *Cnot3* depletion in adipose tissue confers the lipodystrophic phenotype on mice through apoptosis induction and inflammation and that CNOT3-deficiency contributes to lipodystrophy by regulating a subset of mRNAs, including *Srebp1* mRNA (Figure 2). Thus, CCR4-NOT deadenylase may be a potential therapeutic target for lipodystrophy and the metabolic disorders in HIV-associated lipodystrophy patients.

In conclusion, this study described the lipotrophic phenotype caused by deletion of *Cnot3* specifically in adipose tissue. Microarray analysis revealed that a reduction in CNOT3 levels specifically in adipose tissue affects the expression of mRNAs that encode proteins important for lipid metabolism, inflammation, and apoptosis. Thus, the $Cnot3^{ad-/-}$ mice may be a new valuable animal model of partial lipodystrophy and insulin resistance in humans. Overall, for the first time, this study links CCR4-NOTcomplex function to lipodystrophy syndrome, our findings raise the intriguing possibility that

CNOT3 and CCR4-NOT deadenylase complex can serve as therapeutic targets to treat lipodystrophy and the metabolic disorders.

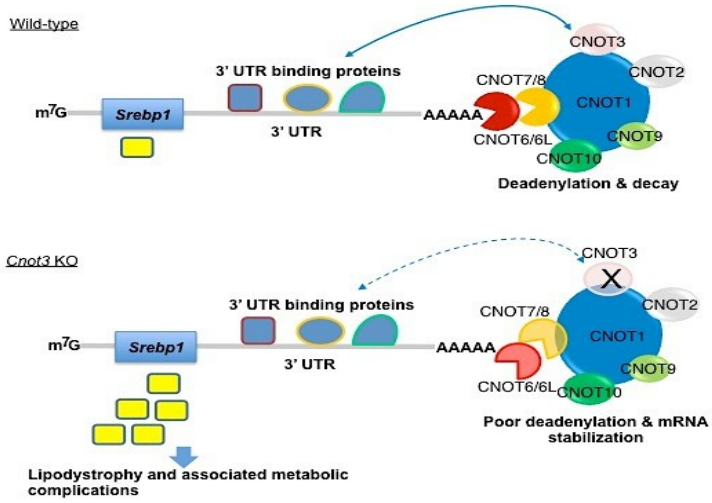

Figure 2. Model of possible involvement of CNOT3 in specific mRNA decay. In *Cnot3*-deficient adipose tissue, degradation of mRNA related to lipodystrophy such as *Srebp1* is not completely triggered, resulting in lipodystrophy and associated metabolic complications.