論　文　概　要 (Thesis Abstract)

論文題目　Elucidation of leukemia-associated nucleoporin fusion genes' effects on the nuclear pore complexes and nuclear-cytoplasmic transport (白血病で見られる Nup 融合タンパク質が核膜孔複合体と核－細胞質間物質輸送に与える影響の解明)

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目的：　This thesis aimed to elucidate the effects of *NUP214*- and *NUP98*-fusion genes on the nuclear pore complexes and nuclear-cytoplasmic transport.

対象と方法：　Immunofluorescence assay, western blot and immunoprecipitation assay, siRNA-mediated gene knockdown, and cycloheximide chase assay were used to examine the effect of Nup fusion genes in LOUCY and FKH1 leukemia cell lines as well as HeLa and HEK293T cells.

結　果：　Chapter 1: Nup62, Nup88, and Nup98 were mislocalized upon the expression of Nup214-fusion proteins. Nup62 was also mislocalized upon the expression of Nup98-fusion proteins. The mislocalizations were induced by Nup214 and Nup98 portions of Nup-fusion proteins. Fusion proteins interacted with endogenous Nups to tethered them to nuclear granular dots in the nucleoplasm. In addition, Nup98 was required for the stabilization of Nup214-fusion proteins. Moreover, *NUP98* knockdown caused a decreased expression of most Nups tested, whereas *NUP214* knockdown decreased Nup88, which is a component in the cytoplasmic

subcomplex. These results suggest an impairment in the integrity of NPCs upon the generation of *NUP* fusion genes.

Chapter 2: SET-Nup214 induces mislocalization of exportin 4, exportin 6, and exportin 7 while DEK-Nup214 and Nup98-fusion proteins did not affect other exportins, except for exportin 1.

考　察：

Chromosome translocations of the NUP98 and NUP214 genes lead to two outcomes. One involves the appearance of mutant proteins containing parts of Nup98 or Nup214; the other involves a reduction of wild-type Nup98 or Nup214 in cells.

In chapter 1, it can be speculated that the aberrant localization of some Nups induced by Nup98- or Nup214-fusion proteins affects the integrity of NPCs, which may compromise the nuclear-cytoplasmic transport system. Regarding the reduction of wild-type Nup214 and Nup98, the decreases of Nups upon *NUP214* or *NUP98* depletion suggest that when the amount of Nup98 or Nup214 is decreased to half by chromosome rearrangement, the expression levels of other Nups decrease, which also affects the nuclear-cytoplasmic transport system. Disturbance of nuclear-cytoplasmic transport is implicated in the development of cancer. Thus, the impairment of NPC formation may be related to oncogenesis. In addition, it has been reported that some Nups are engaged in transcription regulation, so tethering Nups to the nucleus may directly affect the transcription regulation.

In chapter 2, SET-Nup214 recruited exportins to its site in the nucleus, suggesting an impairment in nuclear export of oncogenic proteins that involve in leukemogenesis.

結　論：

Chapter 1: Chromosome translocations involving *NUP98* and *NUP214* impair the integrity of NPCs by inducing mislocalization and decreased expression of NPC components.

Chapter 2: SET-Nup214 interacts with and induces mislocalization of exportins