論文の内容の要旨

論文題目：Intracellular dynamics of non-coding RNA in humans

（ヒトにおける非翻訳 RNA の細胞内動態）

氏名　　宮川　隆

The stress response, which can trigger various physiological phenomena, is important for living organisms. For instance, a number of stress-induced granules such as P-body and stress granule have been identified. These granules are formed in the cytoplasm under stress conditions and are associated with translational inhibition and mRNA decay. In the nucleus, there is a focus named nuclear stress body (nSB) that distinguishes these structures from cytoplasmic stress granules. Many splicing factors and long non-coding RNA species localize in nSBs as a result of stress.

tRNA is a primitive short non-coding RNA. Indeed, tRNAs respond to several kinds of stress such as heat, oxidation or starvation. Although nuclear accumulation of tRNAs occurs in starved *Saccharomyces cerevisiae*, this phenomenon is not found in mammalian cells. We observed that initiator $tRNA^{Met}$ (Meti) is actively translocated into the nucleus of human cells under heat stress. During this study, we identified unique granules of Meti that overlapped with

nSBs. Similarly, elongator $tRNA^{Met}$ was translocated into the nucleus and formed granules during heat stress. Formation of tRNA granules is closely related to the translocation ratio. Then, all tRNAs may form the specific granules.

Additionally, there are also several functional domains in unstressed nucleus. Nuclear speckles are a one of the domains. Long non-coding RNA MALAT-1 is localized to nuclear speckles despite its mRNA-like characteristics. Here we report the identification of several key factors that promote the localization of MALAT-1 to nuclear speckles and also provide evidence that MALAT-1 is involved in the regulation of gene expression. Heterokaryon assays revealed that MALAT-1 does not shuttle between the nucleus and cytoplasm. RNAi-mediated repression of the nuclear speckle proteins, RNPS1, SRm160 or IBP160, which are well-known mRNA processing factors, resulted in the diffusion of MALAT-1 to the nucleoplasm. We demonstrated that MALAT-1 contains two distinct elements directing transcripts to nuclear speckles, which were also capable of binding to RNPS1 *in vitro*. Depletion of MALAT-1 represses the expression of several genes. Taken together, our results suggest that RNPS1, SRm160, and IBP160 contribute to the localization of MALAT-1 to nuclear speckles. These results show that MALAT-1 could be involved in regulating gene expression.