論 文 の 内 容 の 要 旨

論文題目　Characterization of influenza A virus protein PA-X
（A型インフルエンザウイルス蛋白質PA-Xの性状解析）

氏　　名　大石　康平

Influenza A virus, which is a negative-strand RNA virus of the *Orthomyxoviridae* family, inhibits host protein expression in infected cells. PA-X is expressed from the PA mRNA via a ribosomal frameshift and plays central roles in the shutoff activity of the virus through the cleavage of specific host mRNAs in cells. PA-X modulates virus pathogenicity in mice by inhibiting IFN-β production and antiviral antibody production. The shutoff activity of PA-X is dependent on its N-terminal endonuclease activity. Although PA shares the N-terminal endonuclease domain with PA-X, PA has lower shutoff activity than PA-X, suggesting that at least one other region of PA-X is important for the shutoff activity. Although functional analysis of PA-X had been performed, it was not known whether any host genes were involved in the shutoff activity. Therefore, the aim of my study was to identify amino acid residues and host genes that are required for the shutoff activity of PA-X.

I showed that the C-terminal PA-X-specific region, particularly the 6 basic amino acid residues, was important for the shutoff activity of PA-X. I attempted to identify host genes involved in the shutoff activity of PA-X by screening against a yeast knockout library, and revealed that the host NatB complex, which comprises NAA20 and NAA25, is required for the shutoff activity of PA-X. Members of the N-terminal acetyltransferase family, which includes NatB, catalyze the N-terminal acetylation of newly synthesized proteins. My studies showed that N-terminal acetylation by NatB is also required for the shutoff activity of PA-X. Furthermore, I obtained false-positive colonies harboring plasmids encoding unintentional mutations in PA-X during this screening. By analyzing these clones, I identified 22 amino acid residues in the N-terminal endonuclease region of PA-X that are important for its shutoff activity.

In conclusion, I identified amino acid residues and host genes that are required for the shutoff activity of PA-X. My findings will help clarify the shutoff mechanism of PA-X.