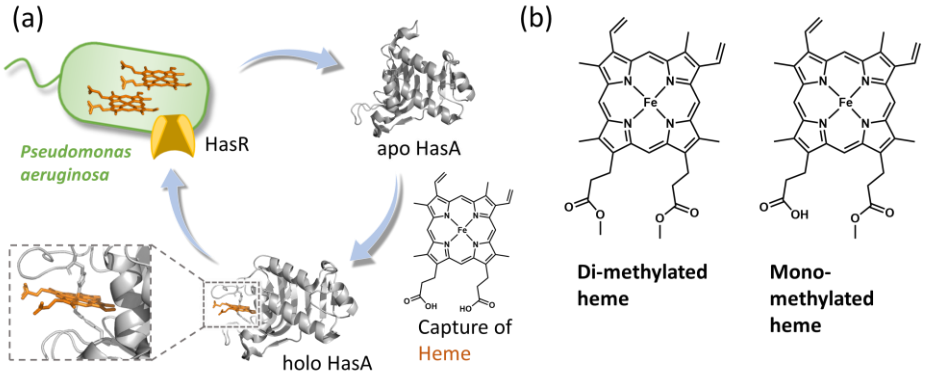
Effects of chemical modifications to heme on the heme acquisition of *Pseudomonas aeruginosa*

(*Graduate School of Science, Nagoya University*)
○Hiroki Matsui, Yuichiro Aiba, Shinya Ariyasu, Osami Shoji
Keywords: *Pseudomonas aeruginosa*; Peptide; Heme; Protein; Metal complex

Pseudomonas aeruginosa (*P. aeruginosa*) is a pathogen that causes opportunistic infections. The emergence of multidrug-resistant strains of *P. aeruginosa* has become a significant problem, and it is desirable to develop an antibiotic-free sterilization method. Our laboratory has been focusing on the heme acquisition system (Has) of *P. aeruginosa*. In an iron-deficient environment, *P. aeruginosa* secretes the heme acquisition protein called HasA. This HasA captures host heme and delivers it into the cell through the HasA-specific receptor HasR (Figure a).

Our previous work demonstrated that HasA can be reconstituted with artificial metal complexes, such as iron phthalocyanine, which are structurally distinct from natural heme.[1] Furthermore, these reconstituted HasA complexes exhibit growth inhibitory effect on *P. aeruginosa*, and the potency depends on the structure of the metal complex[2]. Although we have examined the growth inhibitory effects depending on the structures of metal complexes described above, the studies on modifying heme, a natural target of HasA, have been limited.

In this study, we examined the effect of chemical modifications to the carboxyl groups of heme on its acquisition by *P. aeruginosa*. Our study revealed that *P. aeruginosa* cannot utilize heme in which both carboxyl groups are methyl-esterified as an iron source. In contrast, heme with only one methyl-esterified carboxyl group was successfully used by *P. aeruginosa* (Figure b). Moreover, even heme modified with a peptide on one carboxy group was found to be an effective iron source. The results suggest that intracellular delivery of peptides is possible through this mechanism, offering potential applications for delivering modified compounds into cells.



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2) H. Uehara *et al.*, *Angew. Chem. Int. Ed*., **2017**, *56*, 15279-15283