Summary

Based on a bioinformatics study the protein MA4561 from the methanogenic archaeon *Methanosarcina acetivorans* was originally predicted to be a multidomain phytochrome-like photosensory kinase possibly binding open-chain tetrapyrroles. MA4561 contains a histidine kinase-like ATPase domain (H_ATPase) but seems to lack the H-box, containing the conserved histidine residue that functions as the phosphoacceptor during autophosphorylation. While it could be demonstrated that recombinantly produced and purified protein does not bind any known phytochrome chromophores, UV-vis spectroscopy revealed the presence of a heme tetrapyrrole cofactor. In contrast to many other known cytoplasmic heme-containing proteins, the heme was covalently attached via one vinyl side chain to cysteine 656 in the second GAF domain. This GAF domain by itself is sufficient for covalent attachment. Resonance Raman and magnetic circular dichroism data support a model of a six-coordinate heme species with additional features of a five-coordination structure. Initial mutational analyses of putative axial ligands to the heme revealed histidine residue 702 to be a very likely proximal heme ligand. Additional amino acid residues (Met_{645}, Tyr_{632}) are most likely also involved in ligating the heme directly or indirectly.

The heme cofactor is redox active and able to coordinate various ligands like imidazole, dimethyl sulfide and carbon monoxide depending on the redox state. Interestingly, the redox state of the heme cofactor has a substantial influence on autophosphorylation activity. While reduced protein does not autophosphorylate, oxidized protein gives a strong autophosphorylation signal, independent from bound external ligands. Two-dimensional thin layer chromatography data give rise to an atypical signal transduction scheme indicating the involvement of phosphotyrosine and phosphoserine residues.

Based on its genomic localization, MA4561 is most likely a sensor kinase of a two-component system affecting regulation of the Mts system, a set of three homologous corrinoid/methyltransferase fusion protein isoforms involved in methyl sulfide metabolism. Consistent with this prediction, an *M. acetivorans* mutant devoid of MA4561 constitutively synthesized MtsF. On the basis of these results a heme-based redox/dimethyl sulfide sensory function of MA4561 was postulated and it is proposed to designate it MsmS (methyl sulfide methyltransferase associated sensor).