Contribution ID : **42** Type : **not specified**

Design of a miniaturized iron-sulfur protein

lunedì 28 febbraio 2022 18:05 (10)

Computational protein design has collected many successes in recent years,1,2 however de novo proteins with a tetrathiolate mononuclear metal site have never been characterized both in structure and function. In this case, the selection of the first and second sphere of the iron center able to purposely induce a chosen redox potential is still a difficult task3. Besides in repurposed natural scaffolds or in small cyclic peptide moieties4, de novo proteins featuring tetrathiolate metal clusters have never been structurally characterized before. We present, for the first time, the structural and functional features of a fully designed FeS4 protein and its cognate Zn adduct, namely METPsc. Inspired by natural rubredoxins, this miniaturized protein does not hold any sequence correlation to the known congeners, as assessed by BLASTP. Strikingly, METPsc 28-long sequence stores all the information required to fold around the metal in a tetrahedral geometry and to function as an electron-transfer protein, as confirmed by crystallography, UV-Vis and EPR spectroscopy, and cyclic voltammetry. Finally, we exploited its terminal electron acceptor properties in an artificial electron chain triggered by visible light. Its applicability in optoelectronics and light-harvesting biodevices is being explored.

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