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Bioengineering a Single-Protein Wire

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Biological Electron Transfer (ET) is the key step in many basic cellular processes such as respiration and photosynthesis [1]. Nature has developed highly specialized molecular building blocks capable of transporting charge with unprecedented efficiency, i.e. fast and at long distances [2]. Understanding the mechanisms behind biological ET is key to elucidate the changes in the charge transport regime caused by specific structural variations of the associated molecular machinery, which ultimately lead to, for instance, malfunctioning of the mitochondria. Fundamental knowledge gained from studying biological ET can also be exploited to design bioelectronic devices. Such studies would ultimately unveil what are the key parameters to be controlled in the transduction of electrical signals from active biomolecules, and direct us to the design of the next generation of highly specific optoelectronic sensors [3]. In order to comply with the downsizing demands of the microelectronics industry, the latest bioelectronic advances focus on bottom-up perspectives [3], aiming for maximum sensitivities, high signal-to-noise ratios and enhanced efficiency in order to reduce energy consumption.

Model redox proteins have been integrated in nano/micro-scale devices as the charge transport material. Cu-Azurin conductance signatures have been recently observed in microscale solid-state devices [4-6], which demonstrates their compatibility when hybridized to an electronic platform. Furthermore, Cu-Azurin and cytochrome b562 have also been extensively analysed at the single-protein level [7,8]. These pioneering studies established the sequential two-step ET tunneling mechanism for such systems26, and demonstrated the feasibility of such hybrid bio-interfaces to work as active components in nanoscale circuits.

Here [9] we present an example of bioengineering charge transport in a single-protein wire. The copper-binding protein Azurin has been exploited to compare charge transport of single-protein devices made of a wild-type (Wt) structure and a mutant (K41C), where, in the latter, the natural lysine (Lys) 41 residue has been replaced by a cysteine (Cys) (Fig. 1a). This single point mutation has a two-fold effect; first, the new solvent-exposed thiol (-SH) group will serve as a new chemical connection to one of the external device terminals, and second, the modification is in the secondary coordination sphere of the Cu centre, which is expected to influence the metal redox behavior [10,11] and, hence, the transport regime through the protein matrix. Individual proteins of both variants were trapped between two metal electrodes in a physiological environment using an Electrochemical Scanning Tunneling Microscope (EC-STM) configuration, and the charge transport characterized as a function of an applied electrochemical gate voltage and temperature [12,13]. All-atom molecular-dynamics (MD) simulations suggest that the electrode-protein-electrode junction occurs via two well-localized sites on the protein, i.e. the hydrophobic patch and the natural Cys residues. Despite comparable orientations of both Wt and K41C proteins bridges are expected, the results show acute differences in the charge transport mechanism of the single-protein wire between the Wt and the mutant variant, observing in the latter a complete shutdown of the two-step sequential tunneling character typically described in the Wt [26]. Ab initio calculations of the relevant ET pathway fragment including the modified residue 41 show the poor participation of the Cu centre in the transport-relevant molecular frontier orbital of the K41C mutant. These results fully account for the observed conduction changes within the framework of coherent tunneling mechanism for the single-protein wire of bioengineered proteins.

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