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Editorial Open Access

Can Proteins Use Electricity for Signaling One Another?

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Editorial

Base excision repair is of paramount importance in maintaining integrity of bacteria as well human genomes against chemical and oxidative damage. The enzymatic activity of the proteins involved in this process is well characterized. More obscure, though, is how DNA repair proteins effectively scan the genome in order to find these lesions. Scanning the genome by simply sliding through the double helix, or through random diffusion, takes up to 100 times longer than DNA repair proteins actually take to detect the lesions. For example, only 30 copies of DNA-repair protein MutY are usually found in an *E. coli* cell. If these 30 proteins slide through the 5 million base pairs of *E. coli* genome at 200 bps^{-1}, it would take more than 13 min to scan the genome entirely. This is not compatible to an organism that can replicate every 30 minutes. Similarly, transcriptional regulators are able to find its binding site much faster than the theoretical limit of diffusion within the cell. This faster-than-diffusion paradox was originally described for transcriptional repressors, but it could be applied to most, if not all target-specific DNA-binding proteins. Several mathematical models were created to explain this paradox, but still numbers do not seem to match up.

For more than 20 years, a group at the California Institute of Technology, led by Dr. Jacqueline K. Barton has accumulated compelling evidence for a provocative model that could elucidate this paradox. By conducting electricity, the DNA could act as a molecular wire, through which DNA-binding proteins far away from each other communicate by donating and receiving electrons. In fact, the notion that DNA is able to conduct electricity using the core π-stacked base pairs was introduced long time ago. And by the end of the 1990s, Barton and colleagues showed evidence of charge transport (CT) through up to 200 Å of the DNA π-stack. They postulated that DNA-binding proteins that contain a redox-active [4Fe-4S] cluster could use DNA CT to communicate to one another and cooperatively locate lesions in the DNA. Proteins in the $[4Fe\text{-}4S]^{2+}$ state are more likely not to be bound to DNA. Upon binding, the protein would transfer an electron to the DNA (going to a $[4Fe\text{-}4S]^{3+}$ state), increasing its affinity to DNA. In undamaged DNA, the electron would reduce the iron-sulfur cluster of a distant DNA-bound recipient protein, thus decreasing its affinity and releasing it from DNA. The existence of lesions or mismatches between donor and recipient proteins would interrupt DNA CT, making the recipient protein remain attached to DNA. Therefore, DNA damage would increase the concentration of repair proteins near a lesion, accelerating recognition and repair.

This sophisticate mechanism is yet not universally accepted, since all data were obtained by in vitro experiments or on modified organisms. However, if (or when) the definitive proof comes, it will have major impact on our understanding in a myriad of biological processes and implications to fields such as systems biology and synthetic biology.