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Probing single protein with electron spin resonance in combination with shallow nitrogen vacancy

Proteins are the main power of life with vast functions within living organisms, such as assembling the cell structure, catalyzing metabolic reactions, transcribing and replicating DNA, responding to stimuli, and transporting molecules from one location to another. The proteins' functions are closely related to their sequence, conformation and interaction network. For understanding the mechanism of protein function, it is essential to visualize the single protein at work, solve the three dimensional structure at atomic resolution, and address the partnership and dynamics of protein interaction. The analytical techniques or tools are fundamental for achieving such goals. In the past decades, tremendous efforts have been made in order to develop new methods with ultra sensitivity and resolution. Significant progresses have emerged continuously, such as super-resolved fluorescence microscopy, single electron spin magnetic resonance, Cryo-electron microscopy with direct detecting device, which are highly appreciated not only by chemists, but also by biologists. Among all those methods developed, electron spin resonance (ESR) and nuclear magnetic resonance (NMR) based approaches attract more attentions as they can provide both structural and dynamic information of proteins at atomic resolution. In 2004, Rugar *et al.* detected a single electron spin by magnetic resonance force microscopy at cryogenic (mK) temperature [1].

Recently, Prof. Jiangfeng Du's group at University of Science and Technology of China, and his collaborators reported an important breakthrough toward single protein detection [2]. They successfully detected the ESR signal from a single protein with paramagnetic spin labeling under ambient conditions. They created isolated shallow nitrogen vacancy (NV) centers in bulk diamond about 5 nm below the surface. The target protein, located on the diamond surface, was labeled with nitroxide bearing an unpaired electron, which serves as both electron spin label and nuclear spin label (^{14}N). By utilizing double resonance of labeled electron spin and the NV spin to generate the polarization via magnetic dipole interaction, three ESR signals, resulting from the coupling of the electron spin and the nuclear spin, were detected under ambient conditions. As the interaction is extremely short in distance, the observed signals are purely from a single protein. In addition, the dipole coupling constant and relaxation time were measured. This implies that the protein conformational and dynamic information could be derived by the new methods.

Du's work opens up a new possibility to study biomacromolecular structure, interaction and dynamics at single molecule level by means of combination of NV sensor in bulk diamond, paramagnetic label and ESR. A lot of further works and efforts are certainly needed to make the method become routinely used for solving biological relevant problem.

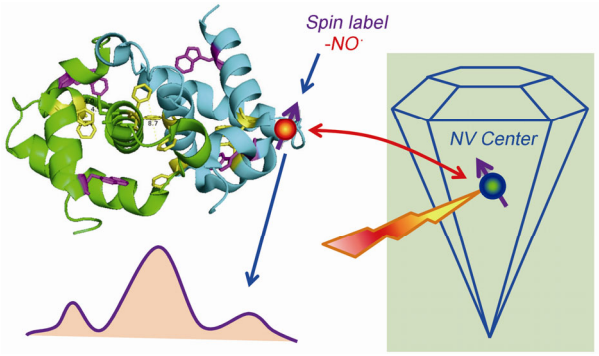

Figure 1 Schematic illustration of a single protein detection by utilizing magnetic dipole interaction between a single nitrogen vacancy (NV) spin in diamond and an electron spin of the paramagnetic labeled protein.

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1 Rugar D, Budakian R, Mamin HJ, Chui BW. *Nature*, 2004, 430: 329–332
2 Shi FZ, Zhang Q, Wang PF, Sun HB, Wang JR, Rong X, Chen M, Ju CY, Reinhard F, Chen HW, Wrachtrup J, Wang JF, Du JF. *Science*, 2015, 347: 1135–1138