How structural biologists understand the structure of protein in solution: the example of IscA

Proteins are macromolecules responsible for most of the biological activities required for life. Different proteins have different biological functions. Scientists have identified almost 8 million different proteins in 1,800 analyzed living species. Let's describe briefly proteins and see what makes them different from each other. Proteins are chains made of smaller units called amino acids which are linked to each other like beads in a necklace. Living organisms use 20 different of such beads to produce their own proteins. The length of a protein goes from ~50 up to several thousand amino acids. Two proteins of the same length can have completely different amino acid sequences. There is a limitless number of different bead sequences we can imagine from the same amino acid composition. Amino acids vary in base of their size, electrical charge and solubility. Once in the protein, they interact with each other allowing the protein chain to specifically fold into a three-dimensional structure. Different amino acid sequences usually lead to different structures thanks to the different properties of each bead such that some of them attract each other while other repulse.

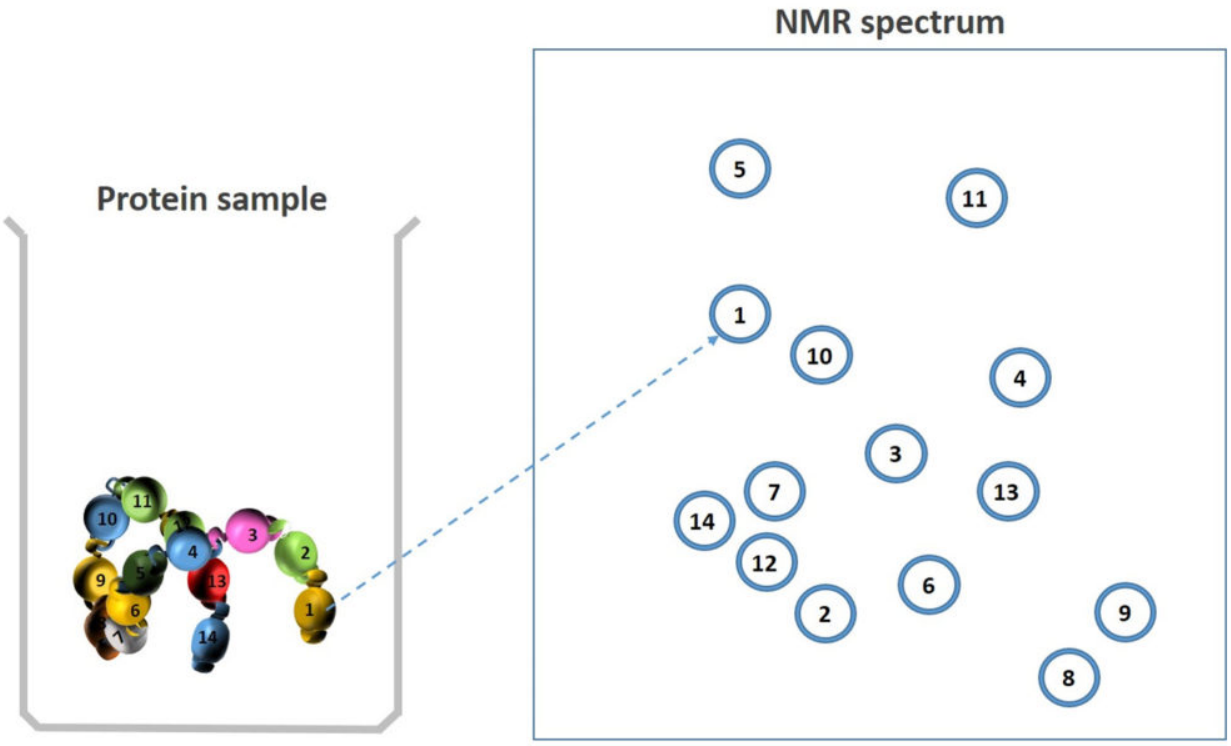

Fig. 1. Illustration of what an NMR looks like (right) and how each spot corresponds to an amino acid in a protein chain. Each amino acid is represented by a bead, like in a necklace.

The main goal of protein scientists is to determine the structure and functions of proteins. This is because knowing the structure makes it possible to predict protein function. It is thus in order to understand how different chemical and physical factors influence the protein overall structure and to know how a single amino acid residue behaves in different experimental conditions. A protein molecule is however too small to be visible by microscope and we need other tools, among which spectroscopic techniques, to observe proteins and their structure. Nuclear magnetic resonance (NMR) is a commonly used spectroscopic technique for these experiments.

Using just a few milligrams of a protein, dissolved in 1 ml of water solvent at controlled acidity (buffer), NMR can detect signals from the samples which can be translated into a two-dimensional graphic called spectrum which contains small spots each having its own XY-coordinate. Each spot corresponds to an amino acid of the protein and its position reflects somewhat the structure of the protein and is very sensitive to any change of the environment (Fig. 1). Changing experimental conditions (temperature, acidity or other environmental properties) the overall protein structure might change. This can be monitored by the shift of the spots in the spectrum. Likewise, addition of any chemical compound which binds to the protein, for example a drug or another protein, can lead to movement of the spots. However, given that the precise position of the spots depends on several aspects, ranging from the structure, the proximity of other amino acids and the solvent composition, assigning to which amino acid each spot corresponds to cannot easily predicted a priory and we need to go through a process which we call ‘spectrum assignment’. This process can some time very challenging.

In the article by Popovic et al., we used NMR experiments to analyze a bacterial protein, called IscA which plays an important role in the bacterial metabolism. IscA is supposed to be a transporter of a group of atoms which contain iron and sulfur (iron-sulfur clusters). These elements are essential for the cell because they can be converted into energy but, at the same time, are toxic if left to wonder around without control. This is why it is important understanding how iron-sulfur clusters form in the cell. We described the strategies by which the NMR spectrum of IscA was assigned and the information about IscA structure obtained. Our results are crucial for future studies of the interactions that IscA forms with other molecules.

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