Structural and biophysical studies of ICBP90, a potential target for anti-cancer drugs

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Inverted CCAAT box binding protein of 90 kDa (ICBP90) is a human protein involved in cancer [1]. It was named from its ability to bind one of the five inverted CCAAT box in the topoisomerase II α promoter. In normal cells, expression of the protein is cell cycle- controlled, whereas it is constantly expressed in cancer cells.

Bio-informatic analyses indicate the occurrence of several functional domains: an ubiquitin like domain, a PHD (Plant HomoDomain), a SRA (Set and Ring Associated) domain and a C-terminal RING finger. The function of most of these domains is unknown, except for the RING finger, which has an ubiquitin ligase E3 activity [2].

According to cell biology experiments on ICBP90 and its potential orthologue in mouse, NP95, the central SRA domain is essential for the function of the protein in transcription regulation and in cell cycle control [3, 4, 5]. Taken together, these reports suggest that ICBP90 may be involved in chromatin remodeling and may represent an interesting target for anti-cancer drugs.

We recently solved the X-ray structure of the SRA domain of ICBP90 by the multi-wavelength anomalous diffraction method using the anomalous property of the selenium (unpublished). Our structure is the first structure of a SRA domain and shows that this domain adopts a new fold. In house biophysical investigations, in line with the X-ray structure, suggest that 30 residues should adopt, in the solution state, a conformation different to the one observed in the crystal structure. This flexibility likely impacts the binding of macromolecular partners.

SAXS was the method of choice to investigate the flexibility of these residues. Several batches of protein, purified and stored in different buffers conditions were analysed.

CRYSOL was used to evaluate the fit between the experimental scattering data and those calculated from the atomic coordinates of different models in which the 30 residues adopt different conformations. In all conditions that we tested, it was apparent that the compact X-ray structure is not representative of the solution state. The conformation observed in the crystal for these residues is likely induced by crystal packing. The evidences for flexibility of these 30 residues, which can now be assigned as part of an important linker region, also allow to draw structure-function relationships that are consistent with our biochemical investigations.
References


