Séminaire

CONFÉRENCIER INVITÉ

Vendredi 24 Mars 2017 à 11h

Salle des séminaires

Institut de biologie structurale - 71 avenue des Martyrs CS 10090 38044 Grenoble Cedex 9 - T.+33 (0)4 57 42 85 00

www.ibs.fr

par **Elsa Garcin**

University of Maryland, Baltimore, USA

Department of Chemistry and Biochemistry

From housekeeping to moonlighting: structure and dynamics of a non-canonical RNA binding protein

The glycolytic enzyme, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), possesses a vast array of non-glycolytic functions, including regulation of protein expression via RNA binding. Despite the lack of a canonical RNA-binding motif, GAPDH binds to numerous adenine-uridine rich elements (AREs) from various mRNA 3'-untranslated regions *in vitro* and *in vivo*. How GAPDH binds to these AREs is still unknown.

We discovered that GAPDH binds, *in vitro*, with high affinity to the core ARE from tumor necrosis factor-α (TNF-α) mRNA via a two-step binding mechanism. We investigated the effect of a dimer-interface mutation on GAPDH oligomerization and RNA binding by fluorescence anisotropy, crystallography, small-angle x-ray scattering, nano-electrospray ionization native mass spectrometry, and hydrogen-deuterium exchange mass spectrometry. We showed that the mutation promotes short-range and long-range dynamic changes in regions located at the dimer and tetramer interface and in the NAD+ binding site, suggesting that these regions are crucial for RNA binding. We have recently obtained hydrogen-deuterium exchange mass spectrometry data on the GAPDH-RNA complex, providing the first "image" of the AU-rich TNF-α RNA binding site in GAPDH. We are currently investigating the effects of post-translational modifications on GAPDH binding to RNA.

TNF-α is a cytokine regulating inflammation and immune system development. Defects in TNF-α production and signaling underlie a number of autoimmune associated diseases. Results from these studies will be crucial for the design of small molecules that can modulate the GAPDH-RNA interaction to target TNF-α-associated inflammatory diseases.

Hôte : Thierry Vernet (IBS/Groupe Pneumocoque)