[MS8-03] The Cop9 signalosome: Activity and regulation

A. Echalier, M. Birol, F. Hoh, Y. Yang, A. Padilla, C. Dumas

Centre de Biochimie Structurale. CNRS, INSERM, UM1, UM2. 29 rue de Navacelles. 34090 Montpellier cedex. France
E-mail: aude.echalier-glazer@cbs.cnrs.fr

The Cop9 (Constitutive photomorphogenesis 9) signalosome (CSN) is a large multiprotein complex that, through its role in the ubiquitin-proteasome pathway, is implicated in various cellular functions spanning from cell cycle to circadian rhythm and reaching the immunity of organisms. The interest on the CSN complex further lies on its potentially important link to various cancers. To date the CSN complex has mostly been studied for its implication in the regulation of the E3-cullin RING ubiquitin ligases (CRLs; [1]). The isopeptidase catalytic activity of the CSN is carried by the subunit 5, CSN5 (also known as Jab1). CSN5 is involved in the deneddylation of CRLs by performing the hydrolysis of the isopeptide bond between an ubiquitin-like molecule, Nedd8 (cullin-neural precursor cell expressed developmentally downregulated gene 8) and the CRL cullin scaffolding subunit [2].
CSN5 when incorporated within the CSN complex displays isopeptidase activity, however it is intrinsically inactive in a stand-alone form. In light of our work, the elucidation of the CSN5 crystal structure together with biochemical and *in silico* investigations contributed to understand the molecular regulation of CSN5 activity as well as to identify a potential molecular trigger that is involved in the transition of an inactive CSN5 to an active isopeptidase enzyme. A single point mutation located at a flexible region of the active site of CSN5, known as the Ins-1 segment, was used to obtain a restored biologically relevant deneddylase activity of CSN5 [3]. Further to that work we have characterised additional triggers, in particular in the contribution of other CSN subunits, that are of importance in the activation/ activity of CSN5. This work carried out using combination of X-ray crystallography, NMR, *in silico* simulations and functional assays substantially increased our knowledge of the regulation ofthe CSN deneddylase activity at the molecular level and is contributing to draw a clearer picture of the CSN molecular regulation.

[1] Kato JY & Yoneda-Kato N. (2009). Genes Cells. 14(11), 1209-1225.
[2] Enchev R.I. *et al.* (2012). Cell Rep. 2(3), 616-627.
[3] Echalier *et al.* (2013). PNAS. 110(4), 1273-1278.

Keywords: ubiquitin-proteasome pathway; conformational plasticity; multiprotein complex