IN THE NEWS

Protein giants

This year's Nobel Prize for Chemistry went to three scientists who were instrumental in the development of two key analytical methods for studying biological macromolecules.

John B. Fenn and Koichi Tanaka shared one half of the Prize for their contributions to mass spectrometry (MS), and the other half was awarded to Kurt Wüthrich who made it possible to use NMR on proteins.

The Nobel Assembly awarded the Prize "…for the development of methods for identification and structure analyses of biological macromolecules." In addition, MS, by enabling the identification of the different proteins in a sample, and NMR, by determining the structure of these proteins in solution, have helped to lay the foundations for the field of proteomics.

Fenn and Tanaka developed two alternative principles — electrospray ionization and soft laser desorption, respectively — that made the use of macromolecules in MS possible by creating freely hovering proteins.

Fenn was lauded by one of his former Ph.D. students, Matthias Mann (Odense University, Denmark), who is one of the leaders in the proteomics field. "He developed the technique on a shoestring and many people at the time didn't believe he could do it.", said Mann (*Nature Science Update*, 7 October).

Kurt Wüthrich has been pushing the boundaries of protein- and nucleic-acid-structure determination by NMR for the past 35 years, and is still very much at the forefront of NMR. His most recent challenge has been to tackle large protein complexes that defy the 40–50-kDa size limit for structure determination by NMR.

Arianne Heinrichs

TRANSCRIPTION

Release and relocate

Post-translational attachment of the ubiquitin-like modifier SUMO-1 to proteins is thought to regulate their subcellular localization, stability and transcriptional activity. Sumoylated transcription factors p53 and c-Jun, for example, have been reported to have enhanced or repressed transcriptional activity, respectively. Leonard Zon and colleagues now describe in *Molecular Cell* evidence that supports a transcriptional function for SUMO-1 proteases — the enzymes that hydrolyse SUMO-1-conjugated proteins.

The authors isolated SUMO-1 protease-1 (SuPr-1) in a screen for positive regulators of c-Jun-dependent transcription, and showed that transciptional activation by SuPr-1 did not require c-Jun sumoylation or phosphorylation. So is SuPr-1 a functional SUMO-1 protease? To address this question, Zon and colleagues analysed potential SuPr-1 substrates — promyelocytic leukaemia (PML) protein and RanGAP1. SuPr-1 hydrolysed both sumoylated proteins *in vitro*, but with selectivity for PML over RanGAP1 *in vivo*, whereas a SuPr-1 mutant (C466S) was unable to hydrolyse either substrate.

Intriguingly, the C466S mutant bound SUMO-modified PML efficiently and was equally able to stimulate c-Jun-dependent transcription as wild-type SuPr-1. Addition of exogenous SUMO-1 partially inhibited the transcriptional activation by the C466S mutant but not the wild-type protein, implying that the binding of SuPr-1 to SUMO-1-modified protein might be enough to activate transcription by c-Jun.

Next, Zon and co-workers carried out cellular-localization studies using green fluorescent protein (GFP)-tagged SuPr-1 and found that SuPr-1 localizes to nuclear subdomains called nuclear PODs (PML oncogenic domains). This result might explain SuPr-1's preference for the PML substrate, which also localizes to nuclear PODs — RanGAP1 localizes to the nuclear rim instead. SuPr-1 and the C466S mutant were able to disrupt PML localization at nuclear PODs to a few larger aggregates that only partially colocalize with SuPr-1.

Sumoylated PML can modulate transcription by recruiting cofactors such as CREB-binding protein (CBP) to the nuclear PODs. When examining CBP's cellular localization in the presence of SuPr-1, Zon and colleagues found that both wild-type SuPr-1 and the C466S mutant caused a redistribution of CBP in a similar fashion to PML.

So how do the effects of SuPr-1 on PML localization and deconjugation of SUMO-1 affect c-Jun transcription? Zon and colleagues showed that PML activates c-Jun transcription, and that the presence of either PML or CBP enhances SuPr-1 activation of c-Jun transcription. By contrast, activation of transcription by SuPr-1 is inhibited in *PML*$^{-/-}$ cells or in the presence of a mutant PML that cannot be conjugated to SUMO-1. These results imply that SuPr-1 stimulation of c-Jun transcriptional activity is dependent on PML and the proper accumulation of proteins such as PML and CBP at the nuclear PODs.

Whereas SuPr-1 seems to stimulate c-Jun activity indirectly, by increasing the availability of transcriptional co-activators such as CBP, an alternative scenario for SuPr-1 action has been reported. Grace Gill and colleagues showed in the same issue of *Molecular Cell*, that SuPr-1 catalyses the removal of SUMO-1 from transcription factor Sp3 and stimulates its transcriptional activity, thereby reversing the repressing effect of SUMO-1 modification. So, in this case, SUMO-1 acts catalytically as a regulatory switch that controls whether or not Sp3 functions as an activator.

In conclusion, SuPr-1 might have several mechanisms by which it regulates transcription, and it will be interesting to see whether different SUMO-1 proteases have specialized functions.

Arianne Heinrichs

References and links

ORIGINAL RESEARCH PAPERS Ross, S. *et al.* SUMO-1 modification represses Sp3 transcriptional activation and modulates its subnuclear localization. *Mol. Cell* **10**, 831–842 (2002) | Best, J. L. *et al.* SUMO-1 protease-1 regulates gene transcription through PML. *Mol. Cell* **10**, 843–855 (2002)

© 2002 Nature Publishing Group