Journal Club

THE DIFFERENT PHASES OF NUCLEAR ATP

Although most of the papers in the Journal Club series describe relatively old, classic studies that inaugurated a field of research, I choose to discuss a 2017 article that illuminated my understanding of an unexpected discovery in our lab. In 2016 we found that the accumulation of nucleus-synthesized ATP in cells is required for extensive chromatin remodelling in response to external signals. In the chosen paper, the group of Anthony Hyman (MPI, Dresden) describe their attempts to understand why the concentration of ATP in cells is in the millimolar range, although the enzymes that use ATP have affinities in the nanomolar or micromolar range.

Based on the amphipathic nature of the ATP molecule, Patel et al. considered the possibility that ATP could serve as a hydrotrope that helps to maintain in solution macromolecules that otherwise would aggregate. With a series of convincing experiments, they proved this concept in the test tube and in cells, and found that the function of ATP as a hydrotrope requires millimolar concentrations and is essential for cell homeostasis. Furthermore, failure of ATP function as a hydrotrope may explain the development of degenerative diseases and ageing.

> “the major fraction of ATP in the nucleus contributes to solubilizing chromatin and nuclear macromolecules”

This revolutionary view of a famous molecule, long considered a carrier of energy and a co-substrate for protein phosphorylation opens completely new avenues in the emerging research of biological phase transitions. We immediately realized that only a minor fraction of the ATP made in the nucleus serves as substrate for the ATPases of the chromatin-remodelling enzymes, while the major fraction of ATP in the nucleus contributes to solubilizing chromatin and nuclear macromolecules as a hydrotrope and as a chelator of free Mg^{2+} ions.

This insight has radically changed our approach to most of the biological processes we study, including DNA damage repair, development and cancer biology.

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ORIGINAL ARTICLE Patel, A. et al. ATP as a biological hydrotrope. *Science* **356**, 753–756 (2017)
FURTHER READING Wright, R. H. G. et al. ADP-ribose-derived nuclear ATP synthesis by NUDIX5 is required for chromatin remodeling. *Science* **352**, 1221–1225 (2016) | Wright, R. H. G. et al. ATP, Mg^{2+}, nuclear phase separation, and genome accessibility. *Trends Biochem. Sci.* https://doi.org/10.1016/j.tibs.2019.03.001 (2019)

CELL DEATH

Parkin and AMPK team up against necroptosis

Necroptosis is a pro-inflammatory mode of cell death that — when uncontrolled — can cause various pathologies, including inflammatory diseases, neurodegeneration and cancer. Necroptosis has been extensively studied, but how its execution is regulated remains elusive. Lee et al. now show that the ubiquitin ligase parkin — a key mediator of mitophagy — is induced in necroptotic conditions through the activity of AMP-activated protein kinase (AMPK) to restrain necroptosis and limit associated pathologies.

Studying physiological functions of parkin, the authors observed that at 10 months of age, *parkin* knockout mice developed inflammation that was associated with the activation of the necroptosis kinases RIPK1, RIPK3 and MLKL. Furthermore, parkin was found to bind and polyubiquitylate RIPK3 and to interfere with RIPK1–RIPK3 interaction, which is required for necroptosis execution.

Parkin activation during necroptosis was independent of mitophagy and its regulatory kinase PINK1. Instead, necroptosis induced AMPK, which phosphorylated parkin at Ser9 (in contrast to PINK1-mediated phosphorylation at Ser65). Interestingly, AMPK activation during necroptosis depended on the activity of necroptosis kinases, suggesting the existence of a feedback loop that controls necroptosis.

In addition to inflammation, *parkin* knockout mice were susceptible to intestinal tumorigenesis, which was curbed by RIPK3 inhibition. This indicated that the AMPK–parkin–RIPK3 axis suppresses

PLANT BIOLOGY

m^5C mRNAs on the move

Several types of RNA in plants are transported to different tissues via the phloem. Protein-encoding mRNAs are too large to diffuse through plasmodesmata, suggesting that specific motifs and/or endogenous factors support their mobility. For most plant mRNAs, these factors and motifs are unknown. Yang et al. now report that cytosine-5 methylation of mRNAs is required for their systemic transport in *Arabidopsis thaliana*.

The mobility of tRNAs has been previously associated with specific 5-methylcytosine (m^5C) modifications, so the authors went on to investigate whether m^5C has a role in the transport of mRNAs to distant tissues. By performing RNA immunoprecipitation against m^5C on mRNA isolated from seedlings and from rosette leaves of adult plants, the authors identified >500 distinct m^5C-containing mRNAs. When comparing these mRNAs against datasets of mobile and non-mobile transcripts, they found that almost two-thirds of the m^5C mRNAs were previously assigned as mobile, indicating that there is a relationship between m^5C and mRNA mobility.

The authors chose to study *TCTP1*, a transcript encoding an important growth regulator, known to be tissue-graft transmissible. They expressed full-length and deletions of *TCTP1* fused to *YFP* in wild-type plants, and grafted the shoots of these plants onto wild-type roots. Transcripts produced in wild-type shoots that lacked the 3′ and 5′ untranslated regions (UTRs) (which contain a ‘PTB motif’ previously proposed to trigger motility) were detected in the grafted roots, whereas a truncated transcript lacking a coding region predicted to contain m^5C was unable to move. Thus, cytosine methylation in the *TCTP1* mRNA coding region is required for mRNA mobility. Moreover, *YFP–TCTP1* and the endogenous *HSC70.1* transcript