QnAs with Jens Nielsen

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When a cell replicates, genetic material must be duplicated, new proteins synthesized, and replication machinery built, all of which are critical processes that require delivery of sufficient building blocks and energy. In his Inaugural Article (1), Jens Nielsen, elected to the National Academy of Sciences in 2019, uses a quantitative "multiomics" approach in yeast to understand how metabolism is coordinated with the cell cycle. Analyzing the transcriptome, proteome, and metabolome of actively growing yeast, *Saccharomyces cerevisiae*, Nielsen, currently the CEO of BioInnovation Institute in Copenhagen, Denmark, has found that biosynthetic building blocks are synthesized on demand during the cell cycle.

Jens Nielsen. Image courtesy of Jens Nielsen.

PNAS: Much of your recent work as a biochemical engineer has harnessed yeast as tiny factories for everything from alternative fuels to high-level production of fatty acids. What is it about yeast that makes it such a good organism for industrial uses?

Nielsen: We were interested to see if we could begin to produce jet fuel and also fuels for heavy trucks (2). They are hydrocarbons that need to have the right properties; they shouldn't freeze up at very low temperatures.

We were quite successful in making yeast to produce the fatty acids (3, 4). But it turned out that converting the fatty acids into the hydrocarbons was more complicated to express in yeast. We pivoted. Many of the fatty acids have different applications, outside the fuel space. The first focus was on fuels, but it ended up generating a platform technology of producing fatty acids that vary in chain length, using yeast (5).

Yeast is good as a cell factory as it is quite robust. It can tolerate relatively low pH, it is very ethanol-tolerant, and it is stress-tolerant, also toward salts, for example. These properties make it well suited for large-scale production in fermentation tanks.

It has the benefit also that it is a very widely used model organism, so we have an extensive knowledge on that organism. And I would say this is also kind of why I was intrigued, because we can actually combine, when we study yeast, some basic biology studies and immediate potential applications for improving cell factories.

PNAS: Your Inaugural Article (1) looks, in a detailed manner, at some of yeast's basic biology. What types of analyses are included in your multiomic analysis?

Nielsen: We have done quite a lot over the years on transcription profiling (6). We have, in recent years, started to look much more at proteomics, and there has been very good advancement in terms of quantitative proteomics. When we have the two, both the messenger and the protein level, we can begin to see, "are they correlating?" We could then also begin to see how the proteins or the enzymes are linked to function by measuring a lot of small molecules; this is the metabolome.

And so this is where we begin to see multiomics analysis. We measure the transcripts, the proteins, and the metabolites. In this particular study (1), we were interested to see how all these processes are coordinated during the cell cycle, which is of course, a strong, evolved process that needs to be coordinated in so many aspects. We monitor how these changes are reflected in the transcript, in the proteins, and in the metabolites.

Experimentally, it had to be extremely well planned, but as soon as the experiment was set up, it could be done within a day. For analysis, we sent the samples out to other [laboratories] for the proteomics or the sequencing and for the metabolome analysis. When we got the data back, that's when the really big job

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started. Most of the work really has been analysis of the data, and that's what many people sometimes tend to underestimate.

PNAS: What can looking at the metabolism of yeast and cell cycle preparation and coordination tell us about other organisms?

Nielsen: There's a very large fraction of the yeast proteins that have homologs in human cells. This is, of course, why yeast is such an excellent model organism. I sometimes say that a human cell is a yeast cell, but with many more things added on.

In this case here, the cell cycle has been studied extensively over years, so we did not find anything you could say that would be translated into a new drug target. But our question was also a little bit more fundamental. We were curious to see if metabolism was actually coordinated with the cell cycle, because nobody had been looking into that before. When the cell starts to replicate DNA and duplicate the chromosomes, that's a key decision point. Then they have to synthesize more proteins because the cell now has to be bigger and eventually become two cells. When you need to synthesize more proteins, you need also to provide the amino acids for that. And that's only one phase of the cell cycle.

We believe now that the overall regulation of the cell cycle puts a request on metabolism, and metabolism then delivers energy and material for the growing cell.

PNAS: You have long toggled between industry and academia and have founded several companies. What is your role at the BioInnovation Institute?

Nielsen: Our key objective is to take science from academia to spin out companies that can then bring products to the market. Translation of top-level science to be of use for society in terms of new products or services is something that is close to my heart: That academic science actually makes a difference. When I entered science and pursued an academic career, I discovered that academia was a fantastic platform, of course, to actually work much broader than [on] just one particular type of problem or certain business segments. I take my experience from working with industry and research in general to hire a team that can help other academics to actually go through that process.

1 K. Campbell *et al.*, Building blocks are synthesized on demand during the yeast cell cycle. *Proc. Natl. Acad. Sci. U.S.A.* 10.1073/pnas.1919535117 (2020).

2 Y. J. Zhou *et al.*, Production of fatty acid-derived oleochemicals and biofuels by synthetic yeast cell factories. *Nat. Commun.* **7**, 11709 (2016).

3 Y. Zhou *et al.*, Harnessing yeast peroxisomes for biosynthesis of fatty-acid-derived biofuels and chemicals with relieved side-pathway competition. *J. Am. Chem. Soc.* **138**, 15368–15377 (2016).

4 T. Yu *et al.*, Reprogramming yeast metabolism from alcoholic fermentation to lipogenesis. *Cell* **174**, 1549–1558.e14 (2018).

5 Z. Zhu *et al.*, Expanding the product portfolio of fungal type I fatty acid synthases. *Nat. Chem. Biol.* **13**, 360–362 (2017).

6 P.-J. Lahtvee *et al.*, Absolute quantification of protein and mRNA abundances demonstrate variability in gene-specific translation efficiency in yeast. *Cell Syst.* **4**, 495–504.e5 (2017).