On the trail of a biological puzzle: How does protein production scale in cells with more than two sets of chromosomes?

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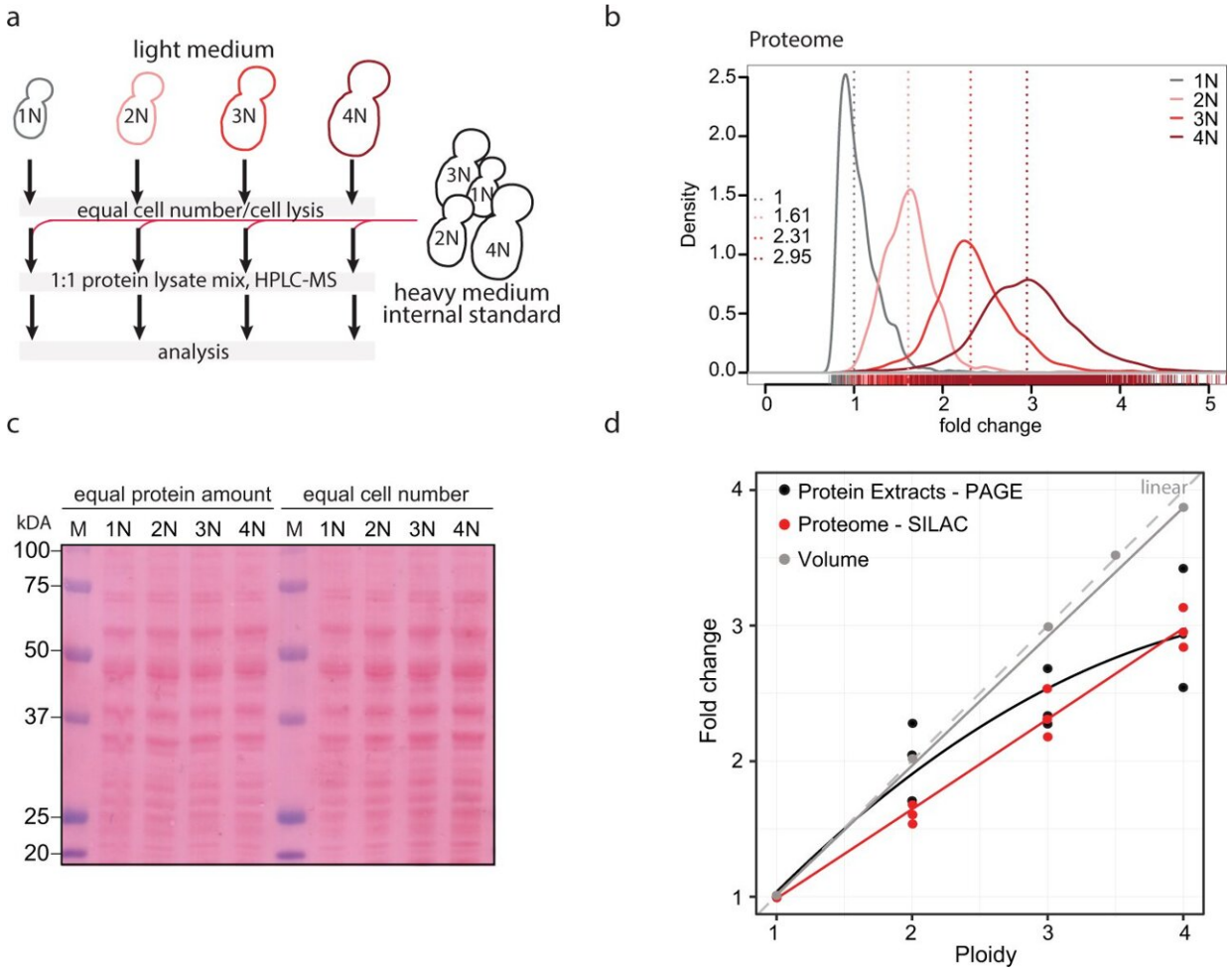

Proteome changes in response to increasing ploidy. a Schematic depiction of the strategy used for the proteome analysis. b Proteome scaling with increasing ploidy. 3109 protein groups were quantified in all ploidies. The values were

normalized to the internal standard, with haploids shifted to a median at 1. All other ploidies were then shifted by the same factor. c Representative Ponceau staining of the total protein amount in cell of different ploidy when equal protein amount was loaded (left) and when proteins isolated from equal cell numbers were loaded (right). d Quantification of the volume and protein content (three independent measurements) changes with increasing ploidy with best-fit trend lines. Theoretical linear scaling is depicted in gray dashed line. Source data are provided in Supplementary Table 1 and in a Source Data file. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-33904-7

Most cells of humans, animals, plants and fungi contain two sets of chromosomes with specific chromosome numbers—for example, in humans there are two sets of 23 chromosomes as carriers of genetic information. However, polyploid cells with more than two sets of chromosomes also frequently occur in nature. Polyploidy contributes to evolution, functional specialization or to the emergence of diseases.

A research team led by Professor Dr. Zuzana Storchova at the Technical University of Kaiserslautern (TUK) has investigated whether the protein content also increases linearly with the number of chromosome sets. The results of the study have been published in the journal *Nature Communications*.

With the number of chromosome sets, the cell volume also increases. Therefore, agriculture makes use of polyploidy as a strategy to obtain larger plants and thus larger fruits or yields. In addition, polyploidy plays an important role in the differentiation of multicellular organisms, where it occurs in a developmentally tightly controlled manner or in response to stress conditions in specialized organs and tissues. Polyploidy can also result from an error. Unscheduled polyploidy is common in tumorigenesis.

In an estimated 37% of all human cancers, whole genome duplication occurred during the course of the disease. "In general, polyploidy is considered a driving force in evolution and tumorigenesis. However, we do not know much about how cellular metabolism correlates with it," Storchova said, summarizing the initial situation.

To better understand the effects of polyploidy, the biologist and her team used baker's yeasts as a model organism, in which this condition is relatively stable. They focused on the proteome, i.e. the totality of proteins contained in a cell at a given time, which is important for the functioning of a cell. The blueprint for the proteins is provided by the genetic information localized on the chromosomes.

The researchers generated yeast strains that varied in the number of chromosome sets in the cells—from single to quadruple chromosome sets. Using liquid chromatography-tandem mass spectrometry, they quantified the composition of the proteome and compared the data from the different yeast strains. The crucial question was: do cells with fourfold chromosome sets also contain four times the amount of proteins?

"We found that number of chromosome sets and proteome do not scale linearly. The cells with quadruple chromosome sets contained only three times the amount of proteins," explained Galal Yahya, Ph.D., first author of the students and a former member of Storchova's research group. The coefficient (0.75) that actually relates the two is already known in biology and denotes the allometric scaling relationship between metabolic rate and body mass. It approximates the physical limits of life. For example, metabolic activity does not increase infinitely the larger the organism becomes, or does not scale linearly with the size of an organism.

"In the second step, we tried to understand how the cells with increased

number of chromosome sets regulate protein synthesis," says Yahya, who came to TUK with a Georg Forster Fellowship from the Alexander von Humboldt Foundation. "We ultimately observed that cytoplasmic translation and ribosome biogenesis were reduced with increasing ploidy. These processes play a crucial role in translating genetic information and assembling proteins from amino acids."

Responsible for the shutdown of protein biosynthesis is the so-called TOR kinase, which is found in all eukaryotic organisms and is considered a key metabolic regulator. It responds to environmental stresses, for example. "We found: The higher the ploidy, the less active the TOR kinase," Yahya explains. "The variation in activity also leads to a less stable state of polyploidy."

Finally, the research team investigated whether the observations made in yeast strains also apply to human cell lines. "We actually obtained comparable results. However, this study has not clarified comprehensively enough all the details. We see potential for further research here," Storchova concluded.

More information: G. Yahya et al, Sublinear scaling of the cellular proteome with ploidy, *Nature Communications* (2022). DOI: 10.1038/s41467-022-33904-7

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