Review

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Coordinating genome expression with cell size

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Cell size is highly variable; cells from various tissues differ in volume over orders of magnitudes, from tiny lymphocytes to giant neurons, and cells of a given type change size during the cell cycle. Larger cells need to produce and maintain higher amounts of RNA and protein to sustain biomass and function, although the genome content often remains constant. Available data indicate that the transcriptional and translational outputs scale with cell size at a genome-wide level, but how such remarkably coordinated regulation is achieved remains largely mysterious. With global and systems-level approaches becoming more widespread and quantitative, it is worth revisiting this fascinating problem. Here, we outline current knowledge of the fundamental relations between genome regulation and cell size, and highlight the biological implications and potential mechanisms of the global tuning of gene expression to cellular volume.

RNA and protein content scale with cell size

Organisms vary in size over several orders of magnitude, from tiny bacteria to giant whales. The difference in size between large and small organisms is largely the result of differences in cell number. However, each organism comprises cells that can also vary greatly in size. Proliferating cells range approximately twofold in size as they grow during each cell cycle. Moreover, differentiated cells in tissues of multicellular organisms attain vastly different shapes and sizes to support their specific functions, which are then maintained over days, weeks, or even years. For example, cells in the human body range in size over nearly six orders of magnitude, from small lymphocytes approximately 7 μm in diameter to large liver cells (50–100 μm) and giant neurons that can stretch over 1 m to the tips of their axons. Current understanding of how cells coordinate their growth and division to acquire and maintain a defined cell size has been carefully reviewed elsewhere [1,2]. Here, we focus on the changes in gene expression that accommodate, or even drive, changes in cell size.

Large cells need to produce and maintain more cellular components than do small cells. As the half-lives of transcripts and proteins are limited, there is a constant need to replace these molecules, and the demand for such replacement scales with cell size. Moreover, protein concentrations within the cell are optimised for biochemical reactions [3]. Thus, as cells grow, they generally need to synthesise more proteins to maintain the appropriate concentrations of these molecules. Furthermore, the protein content in large cells must adapt to the increased burden of architectural and functional demands, although special organelles, such as large vacuoles, help to fill space in some cells. Accordingly, the cellular numbers of rRNAs, mRNAs, and ribosomes scale with cell size [4]. Note that we use cell size loosely here for cell volume or dry mass; although dry mass is likely to correspond best with protein content, most experiments rely on simpler measures for cell size, such as cell length or diameter.

The question of how large cells generate more RNA and protein than small cells attracted much attention from the 1960s to mid-1980s, when *in vivo* labelling techniques enabled the measurement of RNA and protein synthesis in growing cell cultures, [5]; however, such techniques then became unfashionable with the rise of molecular biology and reductionist approaches. Thus, it is still not understood how gene expression is adjusted at a global level to match cell size. Here, we review the current knowledge and implications of cell size-dependent gene regulation and propose possible mechanisms for coordinating genome expression with cell size, which we suggest will be a rich seam of research in the coming years.

Genome content and cell size

One way by which larger cells could sustain their larger biomass is by simply having more gene copies that can accordingly produce more RNAs and proteins. Indeed, most cells contain multiple copies of rRNA genes to satisfy the high demand for rRNA transcripts [6]. Intriguingly, genome size scales linearly with cell size across different organisms over almost a million-fold range [2,7]. However, as most parts of complex genomes are noncoding, the protein-coding capacity is not proportional to cell size [7], and cells with identical genome content can vary greatly in size within the same organism. Therefore, an increase in cell size is not always accompanied by an increase in genome content.

However, in special situations, the genome content is increased in selected cells. In myocytes (muscle cells) for instance, cell fusion leads to huge cells containing multiple genomes in several distinct nuclei. In other cases, cells increase genomic copies in single nuclei without cell fusion. This phenomenon is called 'polyploidy' and results from additional rounds of DNA replication without intervening nuclear divisions (endoreplication, endoreduplication, or polytenisation). In extreme cases, endoreplication can lead

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to cells containing hundreds of completely or partially replicated genomes [8,9]. Polyploidy is often associated with specific physiological requirements, such as in salivary gland cells of fruit flies (*Drosophila*) or in mammalian megakaryocytes (bone marrow cells) and trophoblasts (specialized placenta cells) [9]. In addition, a transient response to unusually high demands on biosynthesis can lead to polyploidy, as exemplified by the growing plant hypocotyl (stem of germinating seedling) or during tissue regeneration in the liver [9]. Some organisms, most notably plants, seem to have harnessed polyploidy during evolution to increase cell size and, as a consequence, the size of the entire organism [10,11]. For example, many important crop plants are polyploid, including potato, coffee, and wheat, and contain multiple identical or related genomes; the increased genome content may render these plants larger than their wild relatives and so helps to increase crop yield.

Thus, increased cell size can be associated with increased genome content in some cases, which provides one way to meet the physiological requirements of large cells or of cells with unusually high demands on biosynthesis. However, the cause–effect relation between cell ploidy and cell size is far from clear: does a large cell promote increased genome content, or does increased genome content allow a cell to grow larger? In any case, the observations outlined above raise the possibility that genes sometimes become limiting for protein production, and DNA amplification is a way around this limitation. Other cases in which genes becoming limiting are described below.

Although polyploidy is a well-known phenomenon, its quantitative impacts on global gene expression and cell mass production are poorly understood. Unicellular organisms, such as yeasts, provide valuable model systems to study this question. As expected, diploid cells of yeast are larger than haploid cells, and tetraploid cells are larger than diploid cells [12–15]. Genome-wide analyses in budding yeast (*Saccharomyces cerevisiae*) uncovered only a small number of mRNAs that are differentially regulated in cells of different ploidy [12,13]. Many of these genes encode cell surface proteins, probably reflecting an adjustment to the lower cell surface:volume ratio in large cells. Two mitogen-activated protein kinase (MAPK) pathways were shown to regulate these genes in response to cell size but not to ploidy, thus invoking a size-sensing mechanism that alters the transcription of selected genes [13].

Polyploid yeast cells probably contain more mRNA overall [16]. Notably, microarray results show only a few differentially regulated genes in cells of different ploidy [12,13]. Because microarray normalisation removes global changes in gene expression, there is probably a coordinated increase in the abundance of most mRNAs in polyploid cells (Figure 1, right). Below, we provide further evidence for such global gene expression and focus our discussion on genome-wide regulation associated with cell size.

Transcriptional output in cells of different size

The relation between post-mitotic, differentiated cells of varying size and their molecular contents has been explored for over 50 years [17]. It is known that the wet-tissue:DNA mass ratios of different organs in rats vary by a factor of over 20-fold, and the corresponding RNA:DNA ratios vary up to 16-fold [18]. These observations show that the total RNA amount produced by a given genome can differ greatly in cells of different size and physiology. Notably, the differences in RNA:DNA ratios for a few genes analysed in the rat are caused by differences in mRNA synthesis (transcriptional efficiency) rather than by differences in mRNA turnover [18]. Increased transcription was also observed in larger frog motor neurons, which vary in cell size but not in genome content [19].

These findings indicate that cells of a given type can boost their RNA and protein production together with cell size while maintaining constant genome content (Figure 1, left). Accordingly, the RNA:DNA and the protein:DNA ratios differ as a function of cell size, revealing cellular tuning of gene expression at a global scale. Some insights into this process are provided by studies with fission yeast (*Schizosaccharomyces pombe*). In 1979, using cell cycle

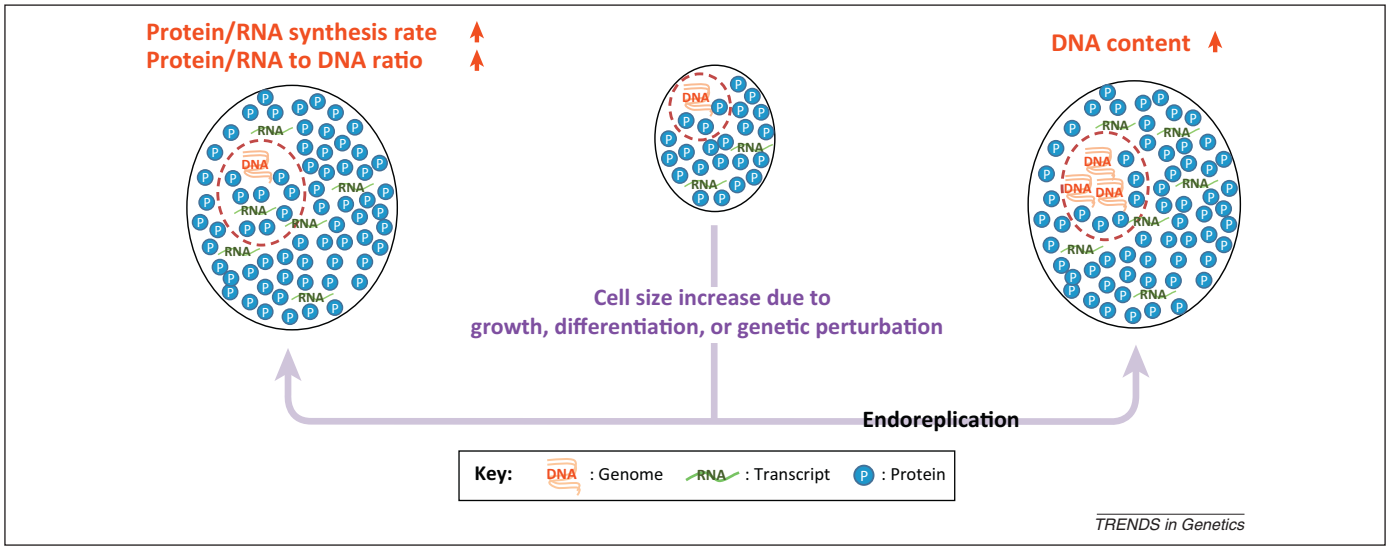

Figure 1. Global RNA and protein abundance as a function of size. Cell size can vary depending on internal or external factors, such as growth stage, differentiation, or mutations. Larger cells contain more RNA and proteins, larger nuclei and, in the case of polyploidy, more DNA (lower right).

mutants that uncouple cell growth from division resulting in altered cell size, Fraser and Nurse [20] showed that small cells produce less RNA than do large cells. This finding indicates that cell size is correlated with the transcription rate and that genome expression can be regulated to genetically triggered changes in cell size.

Although this work was illuminating, it did not answer the question as to whether these differences in RNA and protein content reflect the regulation of a few selected genes or more global gene expression changes. To address this issue, genome-wide approaches that analysed gene expression and transcriptional efficiency were recently used in *S. pombe* cell cycle mutants that show altered cell size due to uncoupled cell growth and division [21]. This study revealed global, coordinated transcriptional regulation of most mRNAs as a function of cell size (Figure 2a), as is the case for budding yeast cells with increased ploidy [12,13]. Notably, compared with wild-type cells of normal size, global mRNA expression not only increased in larger cells, but also decreased in smaller cells, suggesting that the transcriptional output of wild-type cells is precisely tuned and is not set at either a maximal or minimal default rate [21]. Interestingly, other studies showed that such global gene expression changes are accompanied by changes in nuclear size [14,15].

Fission yeast also provided insight into the question of whether gene copy numbers can become limiting for protein production. Another early yeast experiment [22] used cell cycle mutants that can grow without division to show that the maximal mRNA output per genome is indeed limited. A more recent study [21] showed that the transcriptional output of cell cycle mutants exceeding a certain size reaches a plateau and can only increase again after triggering a new round of DNA replication. These experiments reveal that DNA can be a limiting factor in cells that grow to an unusually large size. However, in most circumstances, the global transcriptional output can be tuned to differences in cell size without the need for increasing genome content.

Dynamic tuning of global gene expression in growing cells

Cells undergo a growth period in the cell-division cycle during which cellular size doubles. Clearly, cell growth and division increase the demand on protein synthesis and add another dimension to the coordination of genome regulation with cell size. Synthesis rate-based models for cell size propose that protein expression allows the cells to sense their size and coordinate growth with division: certain 'sizer' proteins, whose abundance would reflect the overall protein synthesis rate, could act as dose-dependent activators of cell cycle progression [2].

Experiments performed in yeast cells synchronised during the cell cycle suggest that growth rates as well as transcriptional and translational outputs are not constant but increase with increasing cell size. In budding yeast, RNA and protein synthesis increase exponentially during the cell cycle, indicating an increase in gene expression as cells grow; moreover, analysis of 111 different proteins revealed an exponential increase in their individual translation rates [23]. In fission yeast, the transcription rate shows a 'step increase' during cell growth, that is, an abrupt acceleration in mRNA synthesis occurs after DNA replication [20,24,25]. This step increase points to a possible link between genome copy number and the rate of transcription. However, the increase occurs some time after the completion of DNA replication, suggesting the presence of a regulatory mechanism that can adjust the transcriptional output to correct for the doubling in gene number. Such a regulatory mechanism could also adjust the rates of transcription for genes that are replicated early or late during S phase. Protein synthesis rates are also adjusted during cell growth in fission yeast, with a sharp increase late during the cell cycle [26]. Together, these data

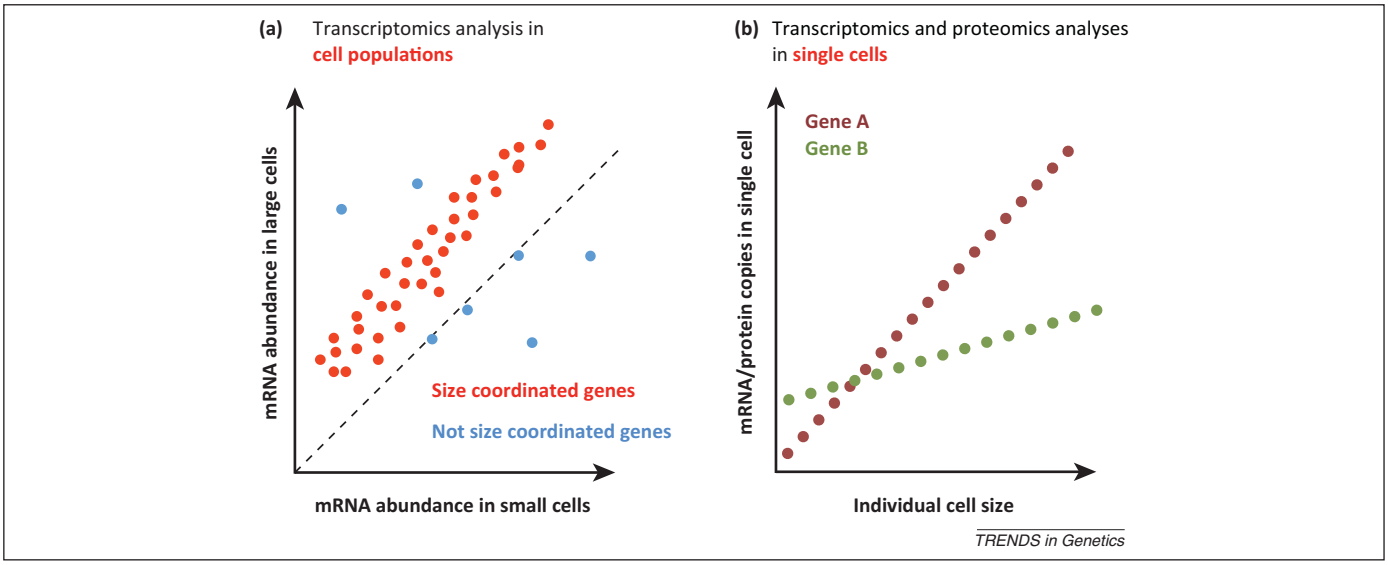

Figure 2. Coordinated increase in mRNA copy numbers in large cells of fission yeast. **(a)** Most *Schizosaccharomyces pombe* genes show transcriptional outputs that scale with cell size (based on [21]). Red dots: mRNAs whose copy numbers show coordinated changes in proportion to cell size, the main focus of this review. Blue dots: mRNAs whose copy numbers deviate from the coordinated changes to cell size, which have been focussed on elsewhere [12,13]. **(b)** Comparison of mRNA or protein numbers in single cells as a function of cell size. Two hypothetical genes with different size-coordinated expression patterns are shown, with each dot representing a single cell.

indicate that growing cells can boost the global synthesis of RNAs and proteins, independently of genome content. Therefore, gene expression can be tuned not only to increase cell size during growth, but also to compensate for increased genome content. Notably, the patterns of RNA and protein synthesis seem to mirror the growth kinetics of yeasts, which are thought to be exponential in budding yeast and bi-linear in fission yeast [4,27].

Data from mammalian cell lines, where cell growth is subject to regulation by growth factors rather than nutrients, are somewhat more complex. Synchronised HeLa cells and mouse fibroblasts show increasing rates of transcription during interphase, although this increase seems to result mainly from a sharp step increase at the time of DNA replication [28–30], similar to the step increase in fission yeast. However, in a mouse cell line, the rates of transcription increase in several steps during G1 phase, before the onset of DNA replication [31]. Thus, gene expression is generally tuned to cell size increases during growth with no universal relation to DNA replication. This regulation seems to be exponential in some cell types and more step-wise and linear in others. These differences in genome regulation could reflect differences in growth kinetics between different cell types.

Cell growth can be modulated by environmental signals, such as growth factors and nutrient availability. For example, yeast cells grow to a larger size under rich nutrient conditions than under poor nutrient conditions, which is mediated by a poorly understood adaptation of the growth control programme [2,32]. Nutrient-sensing signalling pathways, such as target of rapamycin (TOR), protein kinase A (PKA), and MAPK are involved in both cellular growth and size control in response to environmental signals [2,32,33]. These signalling pathways are also known to regulate gene expression at multiple levels, providing a potential means to coordinate cell growth, cell size, and genome regulation appropriately in changing environments.

Transcription factors and the tuning of genome regulation to cell size

The evidence discussed so far suggests that cells increase their global transcriptional outputs with increasing size. What are the implications for the cell if we assume that this upregulation affects the abundance of all or most proteins? Large cells obviously have an increased requirement for cellular components, such as microtubules or ribosomes. By contrast, if the genome content remains the same, there may not be an increased requirement for proteins that function in the context of the genome, such as transcription factors (TFs) or chromatin components, as the number of sites upon which these proteins act would remain constant. Changes in regulator:DNA ratios could indeed provide a possible mechanism that enables the cell to measure its size [2]. Moreover, this situation could also be used to upregulate the transcriptional output, because increased expression of TFs usually results in increased expression of their target genes. Thus, global tuning of gene expression to cell size could affect TF function if the TF itself is rate-limiting for transcription (but not if other factors, such as the general transcription machinery, are rate-limiting), and changes in TF abundance could themselves be a driving force for global gene regulation. In addition, one would predict that TF abundance could alter gene expression by affecting transcriptional noise [34]. An analysis of the expression levels of a few ubiquitous TFs in cells of different size and with different RNA:DNA ratios found that TF abundance can be independent of cell size due to transcriptional or post-transcriptional mechanisms buffering their expression against size regulation [18]. Consistent with this principle, a few mRNAs in yeast do not scale in abundance with cell size, including several TFs, although these are the exception rather than the rule [13,21]. By contrast, the expression of a TF that functions in the liver does scale with cell size, showing higher mRNA and protein expression in large liver cells, raising the possibility that size-dependent expression of some TFs supports tissue-specific regulation of transcription [18].

The local concentration of some TFs, rather than their protein:DNA ratio, could also determine their activity. In this case, a larger nucleus in a larger cell could compensate for increased protein numbers by buffering local protein concentrations. Indeed, the nucleus grows as the cell grows, albeit not to the same extent [14,15]. The cytoplasmic volume determines the nuclear size, and the rate of nuclear import is increased in large cells [15]. Therefore, it is possible that increased protein numbers in the cytoplasm, together with size-dependent rates of nuclear protein import [15,35], could also provide a way for the cell to modulate nuclear concentrations of TFs and other regulatory proteins. In conclusion, the global tuning of gene expression to cell size can differentially affect the functions of some proteins, such as TFs, and cells seem to adopt various strategies to buffer or exploit such effects.

How is genome regulation tuned to cell size?

Considering the complexity of gene regulation, it is both remarkable and surprising that the cell manages to change the expression of most genes in a highly coordinated manner. How can transcription rates increase at equal rates as a function of cell size, given the multitude of specific TFs and promoters, chromatin environments, and other differences among genes? The regulatory mechanism(s) by which cells tune genome regulation to cell size are not known, but below we highlight some published results that might bear on this issue and that inspired us to speculate about possible processes.

The phenomenon of a coordinated global tuning of gene expression to cell size hints at the existence of one or more limiting factors whose concentrations vary with cell size and that impact gene expression quantitatively. The available data suggest that size-dependent control occurs at the level of transcription rather than mRNA turnover [18,21], although both processes are now thought to be intimately coordinated [36]. A plausible hypothesis would be a system controlling the global transcriptional output via RNA polymerases, general TFs, and/or chromatin structure. Although mutants in RNA polymerase II (Pol II) complex subunits do not seem to have a strong effect on cell size [37,38], several Pol II subunits are haplo-insufficient for growth in yeast [39,40], that is, diploid cells need both

copies of a Pol II subunit gene to function properly. The latter findings suggest that the expression level of Pol II can become limiting. Consistent with this view, tuning the expression level of Pol II components or of general TFs (including components of the mediator complex) leads to global changes in the levels of most mRNAs [41,42]. Therefore, one could imagine that increased abundance of Pol II in large cells supports higher transcription rates in a positive feedback loop. Moreover, the nuclear import of Pol II is regulated by a specific protein, Iwr1, which raises the possibility of another mechanism by which nuclear Pol II concentration is regulated [43,44]. A system in which the levels of Pol II expression or nuclear import could be manipulated would allow the hypothesis that the cell size is adjusted to the overall transcriptional activity to be tested.

Alternatively or in addition, increased transcription could also result from increased Pol II processivity: one study [45] analysed the average rates of transcription in single metazoan cells and found that global rates of RNA synthesis vary substantially between cells owing to variation in Pol II elongation rates. These rate differences are correlated with cellular ATP levels and mitochondrial mass, highlighting a link between energy metabolism and transcription rates [45]. This observation could be relevant for size-dependent control of transcription rates as energy metabolism is likely to vary with size. ATP could affect Pol II processivity either directly or by affecting the function of other factors, such as chromatin remodelling enzymes. Experiments by the same group using artificial chromatin decondensation suggest that transcription rates also depend on changes in chromatin structure that are responsive to changes in intracellular ATP levels [45]. Regulation of chromatin structure via global, untargeted histone tail acetylation also affects gene expression in several systems [46]. Acetyl co-enzyme A (CoA) synthetases are key enzymes for glucose metabolism, but they also control the pool of acetyl-CoA used by histone acetyltransferases and, therefore, can modulate the global acetylation status of chromatin and thereby affect transcription [47]. Indeed, acetyl-CoA drives the transcriptional growth programme in budding yeast [48]. Histone acetylation also participates in the chromosome-wide modulation of gene expression during dosage compensation of the X chromosomes of male flies [49]. These examples point to possible mechanisms by which global transcription could be linked to cellular metabolism and histone acetylation, which could accordingly be modulated as a function of cell size and growth.

Changes in nuclear size and architecture could also impact global gene expression, and nuclear envelope components, such as lamins, are linked to gene regulation [7,10,50]. Moreover, yeast haplo-insufficient genes are enriched for functions involved in translation, raising the possibility that similar mechanisms involving rate-limiting factors also apply to the control of translation rates as a function of size. Translation rates and ribosome biogenesis are known to be controlled globally in response to growth conditions via the TOR pathway [33], providing a potential system for the cell to adjust global protein synthesis and cell size.

Concluding remarks

Clearly, researchers are far from a satisfying understanding of how cells globally tune gene expression with cell size, and how they manage the remarkable feat of coordinating the regulation of all or most genes. It is also not known to what extent gene expression is adjusted to cell size at regulatory levels other than transcription, such as translation or protein turnover. Moreover, the cause–effect relations between cell size and gene regulation are not clear. Is gene expression regulated by cell size or vice versa? What aspect of cell size is most relevant for gene expression, length, volume or mass, and how does the cell 'know' its size? How do changes in cell growth and division affect the coordination between genome regulation and cell size? Are gene expression and cell size mutually dependent on each other and, if yes, how? Experiments that could uncouple cell size from global gene expression would provide insight into regulatory dependencies; for example, approaches to change transiently the size of cells (e.g., by osmosis) would enable studies of the effects on gene expression; likewise, genetic manipulation of global gene expression would enable studies of the effects on cell size. Emerging quantitative transcriptomics and proteomics approaches now provide fresh opportunities to address the fundamental question of how cells globally coordinate gene expression with cell size, and how environmental conditions, such as nutrients, affect this coordination. Comparing large proliferating cells with small quiescent cells of fission yeast, the total number of proteins scaled largely with cell volume, whereas the concentration of mRNAs was much lower in the quiescent cells, suggesting more complex relations that also depend on the regulation of cell growth and division [51]. Ultimately, transcriptomics and proteomics approaches applied to single cells, in combination with high-throughput phenotyping, will enable the mapping of global gene expression to individual cellular features, such as size, without the loss of information characteristic of population average measurements (Figure 2b). Such future approaches should provide unique insight into this fascinating, but surprisingly little explored biological process that ultimately will require understanding at a systems level.

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References

1 Jorgensen, P. and Tyers, M. (2004) How cells coordinate growth and division. *Curr. Biol.* 14, R1014–R1027
2 Turner, J.J. *et al.* (2012) Cell size control in yeast. *Curr. Biol.* 22, R350–R359
3 Dill, K.A. *et al.* (2011) Physical limits of cells and proteomes. *Proc. Natl. Acad. Sci. U.S.A.* 108, 17876–17882
4 Mitchison, J.M. (2003) Growth during the cell cycle. *Int. Rev. Cytol.* 226, 165–258
5 Dungrawala, H. *et al.* (2010) Gene regulation: global transcription rates scale with size. *Curr. Biol.* 20, R979–R981
6 Kobayashi, T. (2011) Regulation of ribosomal RNA gene copy number and its role in modulating genome integrity and evolutionary adaptability in yeast. *Cell. Mol. Life Sci.* 68, 1395–1403
7 Cavalier-Smith, T. (2005) Economy, speed and size matter: evolutionary forces driving nuclear genome miniaturization and expansion. *Ann. Bot.* 95, 147–175

8 Edgar, B.A. and Orr-Weaver, T.L. (2001) Endoreplication cell cycles: more for less. *Cell* 105, 297–306
9 Lee, H.O. *et al.* (2009) Endoreplication: polyploidy with purpose. *Genes Dev.* 23, 2461–2477
10 Comai, L. (2005) The advantages and disadvantages of being polyploid. *Nat. Rev. Genet.* 6, 836–846
11 Yu, Z. *et al.* (2009) A large number of tetraploid *Arabidopsis thaliana* lines, generated by a rapid strategy, reveal high stability of neo-tetraploids during consecutive generations. *Theor. Appl. Genet.* 118, 1107–1119
12 Galitski, T. *et al.* (1999) Ploidy regulation of gene expression. *Science* 285, 251–254
13 Wu, C-Y. *et al.* (2010) Control of transcription by cell size. *PLoS Biol.* 8, e1000523
14 Jorgensen, P. *et al.* (2007) The size of the nucleus increases as yeast cells grow. *Mol. Biol. Cell* 18, 3523–3532
15 Neumann, F.R. and Nurse, P. (2007) Nuclear size control in fission yeast. *J. Cell Biol.* 179, 593–600
16 Weiss, R.L. *et al.* (1975) The relationship between enzyme activity, cell geometry, and fitness in *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci. U.S.A.* 72, 794–798
17 Altman, P.L. and Katz, D.D., eds (1976) *Cell Biology*, FASEB, Bethesda, MD
18 Schmidt, E.E. and Schibler, U. (1995) Cell size regulation, a mechanism that controls cellular RNA accumulation: consequences on regulation of the ubiquitous transcription factors Oct1 and NF-Y and the liver-enriched transcription factor DBP. *J. Cell Biol.* 128, 467–483
19 Sato, S. *et al.* (1994) Transcription and motoneuron size. *J. Neurochem.* 63, 1609–1615
20 Fraser, R.S. and Nurse, P. (1979) Altered patterns of ribonucleic acid synthesis during the cell cycle: a mechanism compensating for variation in gene concentration. *J. Cell Sci.* 35, 25–40
21 Zhurinsky, J. *et al.* (2010) A coordinated global control over cellular transcription. *Curr. Biol.* 20, 2010–2015
22 Elliott, S.G. (1983) Regulation of the maximal rate of RNA synthesis in the fission yeast *Schizosaccharomyces pombe*. *Mol. Gen. Genet.* 192, 212–217
23 Elliott, S.G. and McLaughlin, C.S. (1978) Rate of macromolecular synthesis through the cell cycle of the yeast *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci. U.S.A.* 75, 4384–4388
24 Elliott, S.G. (1983) Coordination of growth with cell division: regulation of synthesis of RNA during the cell cycle of the fission yeast *Schizosaccharomyces pombe*. *Mol. Gen. Genet.* 192, 204–211
25 Fraser, R.S. and Nurse, P. (1978) Novel cell cycle control of RNA synthesis in yeast. *Nature* 271, 726–730
26 Creanor, J. and Mitchison, J.M. (1982) Patterns of protein synthesis during the cell cycle of the fission yeast *Schizosaccharomyces pombe*. *J. Cell Sci.* 58, 263–285
27 Baumgärtner, S. and Tolić-Nørrelykke, I.M. (2009) Growth pattern of single fission yeast cells is bilinear and depends on temperature and DNA synthesis. *Biophys. J.* 96, 4336–4347
28 Killander, D. and Zetterberg, A. (1965) Quantitative cytochemical studies on interphase growth. I. Determination of DNA, RNA and mass content of age determined mouse fibroblasts in vitro and of intercellular variation in generation time. *Exp. Cell Res.* 38, 272–284
29 Zetterberg, A. and Killander, D. (1965) Quantitative cytochemical studies on interphase growth. II. Derivation of synthesis curves from the distribution of DNA, RNA and mass values of individual mouse fibroblasts in vitro. *Exp. Cell Res.* 39, 22–32
30 Pfeiffer, S.E. (1968) RNA synthesis in synchronously growing populations of HeLa S3 cells. II. Rate of synthesis of individual RNA fractions. *J. Cell. Physiol.* 71, 95–104
31 Skog, S. and Tribukait, B. (1985) Discontinuous RNA and protein synthesis and accumulation during cell cycle of Ehrlich ascites tumour cells. *Exp. Cell Res.* 159, 510–518
32 Yanagida, M. *et al.* (2011) Nutrient limitations alter cell division control and chromosome segregation through growth-related kinases and phosphatases. *Philos. Trans. R. Soc. B.* 366, 3508–3520
33 Wullschleger, S. *et al.* (2006) TOR signaling in growth and metabolism. *Cell* 124, 471–484
34 Segal, E. and Widom, J. (2009) From DNA sequence to transcriptional behaviour: a quantitative approach. *Nat. Rev. Genet.* 10, 443–456
35 Levy, D.L. and Heald, R. (2010) Nuclear size is regulated by importin α and Ntf2 in *Xenopus*. *Cell* 143, 288–298
36 Sun, M. *et al.* (2012) Comparative dynamic transcriptome analysis (cDTA) reveals mutual feedback between mRNA synthesis and degradation. *Genome Res.* 22, 1350–1359
37 Jorgensen, P. *et al.* (2002) Systematic identification of pathways that couple cell growth and division in yeast. *Science* 297, 395–400
38 Zhang, J. *et al.* (2002) Genomic scale mutant hunt identifies cell size homeostasis genes in S. *cerevisiae*. *Curr. Biol.* 12, 1992–2001
39 Kim, D-U. *et al.* (2010) Analysis of a genome-wide set of gene deletions in the fission yeast *Schizosaccharomyces pombe*. *Nat. Biotechnol.* 28, 617–623
40 Pir, P. *et al.* (2012) The genetic control of growth rate: a systems biology study in yeast. *BMC Syst. Biol.* 6, 4
41 Sharma, N. *et al.* (2006) The fission yeast Rpb4 subunit of RNA polymerase II plays a specialized role in cell separation. *Mol. Genet. Genomics* 276, 545–554
42 Lee, K.M. *et al.* (2005) Impairment of the TFIIH-associated CDK-activating kinase selectively affects cell cycle-regulated gene expression in fission yeast. *Mol. Biol. Cell* 16, 2734–2745
43 Czeko, E. *et al.* (2011) Iwr1 directs RNA polymerase II nuclear import. *Mol. Cell* 42, 261–266
44 Wild, T. and Cramer, P. (2012) Biogenesis of multisubunit RNA polymerases. *Trends Biochem. Sci.* 37, 99–105
45 das Neves, R.P. *et al.* (2010) Connecting variability in global transcription rate to mitochondrial variability. *PLoS Biol.* 8, e1000560
46 Friis, R.M.N. and Schultz, M.C. (2009) Untargeted tail acetylation of histones in chromatin: lessons from yeast. *Biochem. Cell Biol.* 87, 107–116
47 Takahashi, H. *et al.* (2006) Nucleocytosolic acetyl-coenzyme a synthetase is required for histone acetylation and global transcription. *Mol. Cell* 23, 207–217
48 Cai, L. *et al.* (2011) Acetyl-CoA induces cell growth and proliferation by promoting the acetylation of histones at growth genes. *Mol. Cell* 42, 426–437
49 Straub, T. and Becker, P.B. (2011) Transcription modulation chromosome-wide: universal features and principles of dosage compensation in worms and flies. *Curr. Opin. Genet. Dev.* 21, 147–153
50 Dittmer, T.A. and Misteli, T. (2011) The lamin protein family. *Genome Biol.* 12, 222
51 Marguerat, S. *et al.* (in press) Quantitative analysis of fission yeast transcriptomes and proteomes in proliferating and quiescent cells. *Cell*