1A deletion, although paternal inheritance of the deletion allows rescue of maternal inheritance of Gnas deficiency. In humans, there is again LOI (gain of silencing) and acquisition of DNA methylation, leading to PHP Ib when on the maternal chromosome, which should have higher expression. The human equivalent of paternal deficiency of XLαs[1] has yet to be described. There are rare human parallels to the mouse paternal and maternal uniparental disomy (UPD; MatDp(dist2) and PatDp(dist2) in Plagge *et al.*[2]). Maternal UPD 20 is associated with growth retardation[5] in several cases; a single report of mosaic paternal UPD 20 showed multiple birth defects, but the relevance of the UPD to the phenotype was not clear[6], and other cases would be instructive. Two individuals with constitutional deletions of chromosomes 20q were found to have Albright hereditary osteodystrophy; an individual with a paternal deletion had PPHP and an individual with a maternal deletion had PHP Ia[7].

The many uses of imprinting

Plagge *et al.*[2] conclude that their data provide "tangible molecular support for the parental conflict hypothesis of imprinting." In this hypothesis, genomic imprinting allows the paternal genome to promote growth of the fetus and the maternal genome to inhibit growth, with the interpretation that smaller offspring give advantage to the maternal genome and larger offspring give advantage to the paternal genome. There are many other hypotheses for the evolutionary advantages provided by genomic imprinting. We championed a 'rheostat' model based on the advantages of improved and reversible evolvability for certain genes associated with a continuous rather than discontinuous genotype-phenotype relationship[8]. This might be particularly true if fitness of the phenotypic spectrum varied with environmental conditions. In this context, increased heterogeneity among individuals for the abundance of such gene products might be advantageous, particularly in the context of advantages to the group. Genes with threshold effects, such as haploinsufficiency for transcription factors, often lead to deleterious malformation phenotypes, and increased heterogeneity among individuals for the abundance of such gene products would probably be deleterious, with no advantage for imprinting. The evolutionary selection for imprinted genes involves both genetic and epigenetic variation. In the conflict hypothesis, the genotype and epigenotype under selection relate to the individual parent and offspring, in contrast to the selection for the hypervariable population under the rheostat model. The conflict hypothesis and the rheostat hypothesis are not mutually exclusive. It is easy to imagine how the rheostat hypothesis might apply to a broad range of imprinted phenotypes, whereas the conflict hypothesis might be most relevant to imprinted control of growth. The data of Plagge *et al.*[2] might be equally interpreted to be compatible with a continuous genotype-phenotype relationship and for a rheostat model. In the case of Gnas, increased 'evolvability' of body size could be advantageous in itself, but it is also advantageous for the paternal genome to promote growth and the maternal genomes to promote the opposite.

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STARTing to recycle

Gavin Sherlock

A comprehensive microarray-based analysis of the cell cycle shows that periodic transcription of most genes is not conserved between *Schizosaccharomyces pombe* and *Saccharomyces cerevisiae*. A core group of ~40–80 genes have conserved patterns of transcription and may have key roles in cell cycle progression.

Proper regulation of the cell cycle is crucial to the growth and development of all organisms; understanding this regulation is central to the study of many diseases, most notably cancer. Since the discovery that *cdc2* mutants in *S. pombe* can be complemented by the orthologous gene *CDC28* from *S. cerevisiae*[1] and the gene *CDC2* from human[2], it has been known that essential components of the eukaryotic cell cycle machinery are conserved from yeast to humans. Numerous examples of orthologous cell cycle proteins in all eukaryotes have since been found (*e.g.*, the MCM proteins[3]). The genome-wide transcriptional program during the cell cycle has been investigated in a wide range of organisms, including budding yeast[4,5], bacteria[6], primary human fibroblasts[7,8], mouse fibroblasts[9] and HeLa cells[10,11]. But a comprehensive analysis of the level of conservation of periodic expression of genes involved in the cell cycle has been lacking. On page 809 of this issue, Gabriella Rustici and colleagues[12] present a comprehensive characterization of transcription during the *S. pombe* cell cycle and show, by comparison with *S. cerevisiae* data, that relatively few genes have conserved transcriptional regulation during the cell cycle (**Fig. 1**).

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Conserved expression

Rustici *et al.*[12] identified 407 periodically transcribed genes using eight time-course experiments and several different synchronization procedures. The 'phaseogram' in Figure 1 of their paper shows periodic expression, which is reproduced with similar kinetics and phases of peak transcription across all of their experiments. Of these 407 genes, 136 have 'high-amplitude' changes and cluster in four waves of expression. Among these 136 high-amplitude genes, 87 have clear orthologs in *S. cerevisiae* and about 40 of these are periodically expressed in both yeasts. In and of itself, 40 of these 87 genes being periodically expressed in both organisms is highly significant ($P = 4.3 \times 10^{-32}$), because choosing 87 *S. pombe* genes at

random from all *S. pombe* genes that have orthologs in *S. cerevisiae* would be expected to yield far fewer periodically expressed *S. cerevisiae* genes by chance. But the 136 high-amplitude genes in *S. pombe* is clearly a conservative set. Similarly, the 301 genes from *S. cerevisiae* used for this analysis was a conservative set, because it consisted of the intersection of genes defined to be periodically expressed by two previous studies[4,5]. In all likelihood, the number of periodically expressed genes in *S. cerevisiae* is more than double that. A less conservative analysis, using all the periodically identified genes in the papers by Rustici *et al.*[12] and Spellman *et al.*[4], identifies 81 orthologs that are periodically expressed in both organisms[12]. Thus, although the exact number of orthologous genes that are periodically expressed in both yeasts is ambiguous, two facts are abundantly clear. First, the number of orthologs periodically expressed in both organisms is significant, suggesting that it is a result of a selective pressure to maintain periodic expression in these genes. Furthermore, among those genes periodically expressed in both organisms, there are a significant number expressed at equivalent points in the cell cycle in each organism. Second, although the exact number of conserved periodically expressed genes may be debated, it is a minority of the periodically expressed genes that have conserved expression patterns, indicating that for many transcripts, there does not necessarily exist a strong pressure to be periodically transcribed through evolution. There are significant numbers of genes whose transcriptional patterns have been maintained through more than 1,000 million years. This result may not be surprising but will hopefully lay to rest those arguments that suggest that periodic cell cycle–dependent expression does not exist[13].

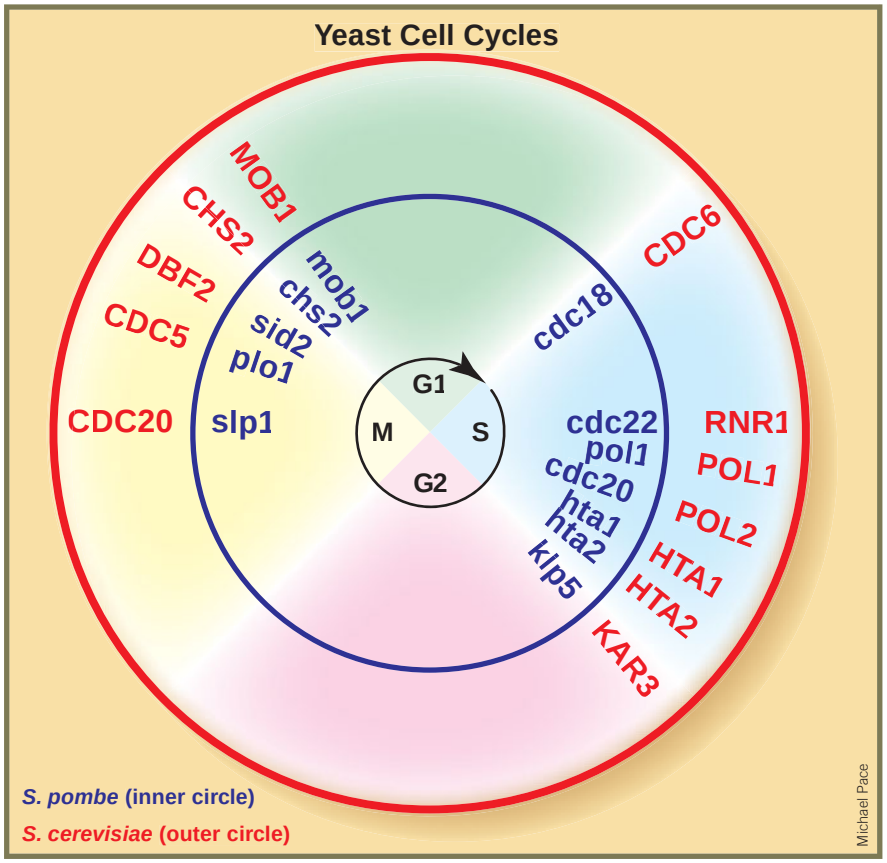

Figure 1 Generalized yeast cell cycle, showing a subset of orthologous proteins from *S. pombe* (inner circle, blue) and *S. cerevisiae* (outer circle, red) and when they are periodically transcribed in both organisms.

Cycle and recycle

A key question that remains unanswered is why different organisms have different sets of regulated transcripts, despite the fact that many more of the proteins that are involved in regulating and executing their cell cycles are common. For example, *S. cerevisiae* has periodic expression of all six genes encoding proteins of the MCM complex, whereas *S. pombe* regulates only one of them and humans regulate three of them. It has been argued that both parsimony and functional necessity are reasons to periodically transcribe genes required in the cell cycle, although there are examples where periodic transcription can be deregulated with little or no phenotypic effect. Currently, the data are still too limited to know whether many genes were periodically transcribed in a common ancestor, with selective loss of this control in different lineages, or whether mainly the core conserved genes were periodically transcribed in the common ancestor, with different lineages acquiring periodic transcription of other genes in response to different selective pressures. Some questions can be answered with the existing data, but additional comprehensive data sets will be required to understand fully the selective pressures and reasons for different organisms to periodically transcribe different sets of genes.

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