Coordination of the cell cycle with carbohydrate metabolism

In *S. cerevisiae*, cell division rate and flux distribution across metabolic pathways is highly sensitive to the nutrient content of the growth medium (Gelade et al. 2003). The carbon source affects the rate of increase in cellular mass, as well as the rate of progression through the cell cycle (Newcomb et al. 2002; Sillje et al. 1997). Size- and nutrient-dependent modulation of the cell cycle occurs primarily at the G1/S transition, when information about numerous internal and external factors determines whether the cell passes START (thus initiating a new cell division cycle), enters a differentiation pathway (mating or sporulation), or enters a quiescent state. Because *S. cerevisiae* grows preferentially on glucose, it has evolved numerous signaling pathways that sense glucose and reprogram cellular metabolism accordingly (Gelade et al. 2003; Newcomb et al. 2003). That the cell cycle is partially regulated by glucose supply implies that these pathways must also regulate the cell cycle machinery. Recent work has deciphered many details of glucose signaling and cell cycle regulation (selected details summarized in Fig. 6 (Costanzo et al. 2003; Doolin et al. 2001; Frenz et al. 2001; Furuchi et al. 2001; Gelade et al. 2003; Hartwell et al. 1999; Hedges et al. 1995; Ho et al. 1999; Honigberg and Purnapatre 2003; Horak et al. 2002; Hubbard et al. 1994; Koranda et al. 2000; Lesage et al. 1994; Loy et al. 1999; Mead et al. 2002; Muller et al. 2003; Newcomb et al. 2003; Newcomb et al. 2002; Sillje et al. 1997; Williams et al. 2002; Willis et al. 2003; Young et al. 2003; Zhou and Winston 2001)), but the molecular mechanisms underlying their coordination are not completely understood (Gelade et al. 2003; Newcomb et al. 2003). We therefore chose to further analyze the interaction between these categories, as well as interactions between *Cell cycle* and each of *Reserves* and *Glycolysis*.

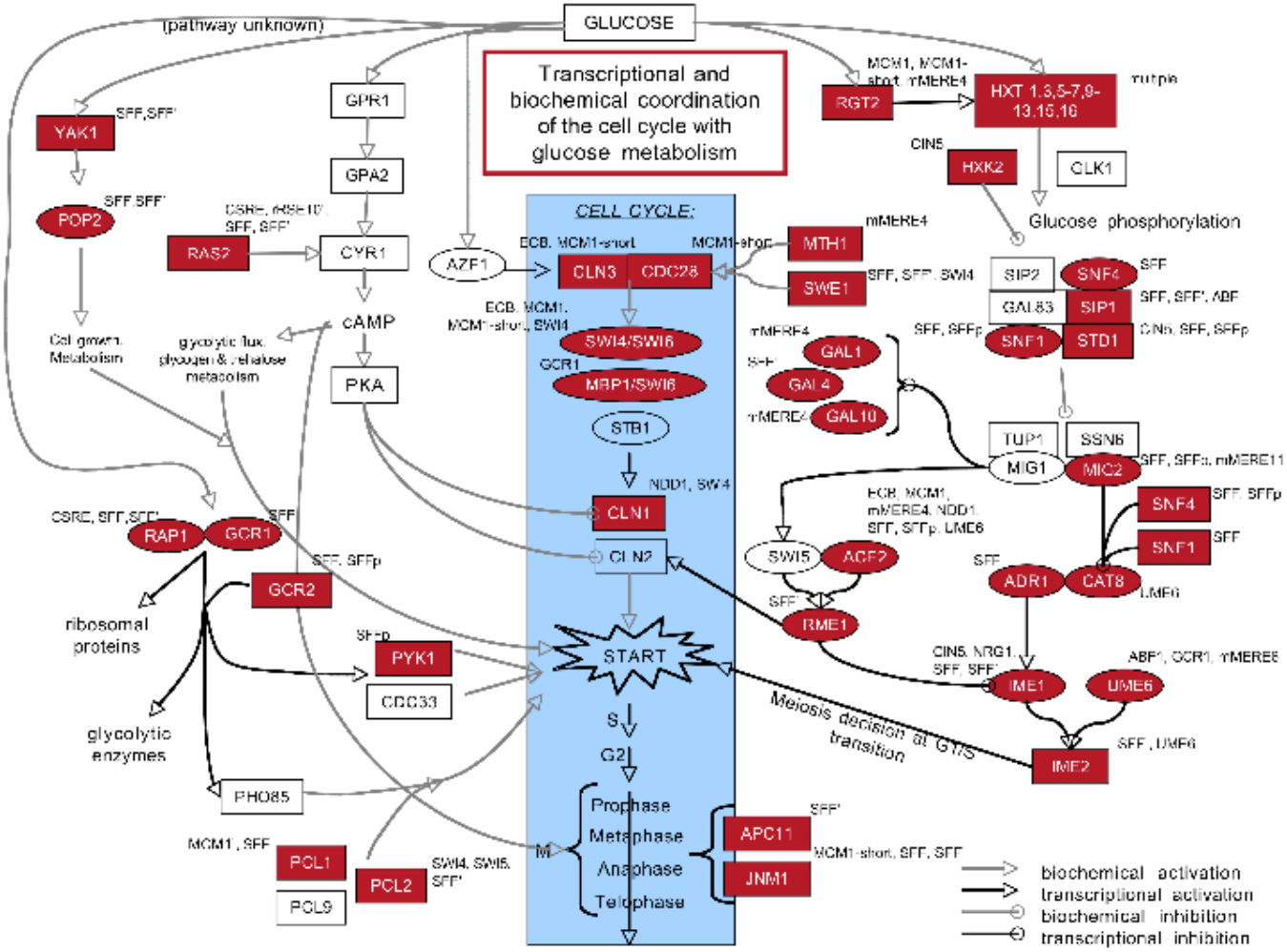
Using stringent and lenient criteria, SPIN found 15 TFs that coordinate the cell cycle with carbohydrate metabolism. To put these results in context with previously known information, some targets of these TFs that lie at the interface of the processes are highlighted in Fig. S9A. Consistent with current knowledge about nutrient-dependent regulation of the cell cycle, all of these target genes are involved in transcriptional or biochemical regulatory cascades that ultimately influence the timing of the G1/S transition.

Likewise, all of the TFs have documented roles in the cell cycle or in carbon compound metabolism, except for CIN5 and rRSE10. Furthermore, TFs that are known to cooperatively regulate the cell cycle, such as SFF/MCM1, NDD1/MCM1, were found to mediate some of the same interactions. The framework provided in Fig. S9A also helped us identify transcriptional cascades (in which a TF regulates genes that encode other TFs among those examined) within these processes. For example, SFF was found to regulate the *GCR1* gene, and GCR1 was found to regulate expression of the genes encoding UME6 and MBP1.

This analysis exemplifies the efficiency with which SPIN corroborates and synthesizes information from diverse studies. In addition, the algorithm generates hypotheses about regulatory mechanisms that effect this synthesis at the transcriptional level.

Figure S9A (following page). Coordination of Cell Cycle with carbohydrate metabolism (including Carbon compound and carbohydrate metabolism and Glycolysis and gluconeogenesis, and Metabolism of energy reserves)

The diagram summarizes selected knowledge about the relationship between carbohydrate metabolism and cell cycle regulation, and puts some of our results in the context of this knowledge. For clarity, genes that are traditionally associated primarily to the cell cycle are highlighted in the central blue rectangle. Ovals represent TF-encoding genes, and rectangles represent other genes. Filled ovals and rectangles signify that the corresponding gene is a target of at least one of the TFs we found to coordinate the processes. Black and gray edges reflect transcriptional and biochemical regulatory relationships, respectively, between the gene products; arrows and filled circles indicate activation and repression, respectively.


Transcriptional and biochemical coordination of the cell cycle with glucose metabolism
GLUCOSE
(pathway unknown)
YAK1
SFF,SFF'
POP2
SFF,SFF'
GPR1
GPA2
RAS2
CYR1
cAMP
PKA
Cell growth, Metabolism
glycolytic flux, glycogen & cellulose metabolism
AZF1
CELL CYCLE:
ECB, MCM1-short
CLN3
CDC28
MCM1-short
MTH1
mMERE4
SWE1
SFF, SFF', SWI4
ECB, MCM1, MCM1-short, SWI4
SWI4/SWI6
GCR1
MBP1/SWI6
STB1
NDD1, SWI4
CLN1
CLN2
START
S
G2
M
Prophase
Metaphase
Anaphase
Telophase
APC11
JNM1
MCM1-short, SFF, SFF'
RGT2
MCM1, MCM1-short, yMERE4
HXT 1,3,5-7,9-13,15,16
purple
CIN5
HXK2
CLK1
Glucose phosphorylation
SIP2
SNF4
SFF
GAL83
SIP1
SFF, SFF', ABF
SNF1
STD1
CIN5, SFF, SFFp
SFF, SFFp
yMERE4
GAL1
S+F
GAL4
yMERE4
GAL10
TUP1
SSN6
MIG1
MIG2
SFF, SFFp, mMERE11
SNF4
SFF, SFFp
SNF1
SFF
ECB, MCM1, mMERE4, NDD1, SFF, SFFp, UME6
SWI5
ACE2
SFF
ADR1
CAT8
UME6
SFF
RME1
CIN5, NRG1, SFF, SFF'
IME1
UME6
ABF1, GCR1, yMERE6
IME2
SFF, UME6
Meiosis decision at G1/S transition
CSRE, SFF,SFF'
RAP1
GCR1
SFF
GCR2
SFF, SFFp
ribosomal proteins
glycolytic enzymes
SFFp
PYK1
CDC33
PHO85
MCM1, SFF
PCL1
PCL9
PCL2
SWI4, SWI5, SFF'
biochemical activation
transcriptional activation
biochemical inhibition
transcriptional inhibition

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