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Cyclebase.org: version 2.0, an updated comprehensive, multi-species repository of cell cycle experiments and derived analysis results

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ABSTRACT

Cell division involves a complex series of events orchestrated by thousands of molecules. To study this process, researchers have employed mRNA expression profiling of synchronously growing cell cultures progressing through the cell cycle. These experiments, which have been carried out in several organisms, are not easy to access, combine and evaluate. Complicating factors include variation in interdivision time between experiments and differences in relative duration of each cell-cycle phase across organisms. To address these problems, we created Cyclebase, an online resource of cell-cycle-related experiments. This database provides an easy-to-use web interface that facilitates visualization and download of genome-wide cell-cycle data and analysis results. Data from different experiments are normalized to a common timescale and are complimented with key cell-cycle information and derived analysis results. In Cyclebase version 2.0, we have updated the entire database to reflect changes to genome annotations, included information on cyclin-dependent kinase (CDK) substrates, predicted degradation signals and loss-of-function phenotypes from genome-wide screens. The web interface has been improved and provides a single, gene-centric graph summarizing the available cell-cycle experiments. Finally, key information and links to orthologous and paralogous genes are now included to further facilitate comparison of cell-cycle regulation across species. Cyclebase version 2.0 is available at http://www.cyclebase.org.

INTRODUCTION

The process by which cells replicate and pass on their genetic information, termed the cell cycle, is fundamental to life and has been intensely studied in the biological sciences. The past decade has witnessed an explosion in data derived from cell-cycle specific and other high-throughput experiments. These data include mRNA expression profiling using microarrays (1–9), overexpression (10,11) and knock-down studies (12), prediction of degradation signals (13), and systematic determination of kinase substrates (14–16). Of particular interest are the mRNA profiling experiments, which are performed on samples aliquoted from synchronously growing cells progressing through the cell cycle. These studies provide a wealth of transcriptome data during the division process, which can be analyzed to deduce the subset of genes that are subjected to transcriptional regulation during the cell cycle. Gathering, comparing and analyzing such a vast amount of data require a significant effort.

In order to address the problems mentioned above, we developed Cyclebase (17), a web resource of cell-cycle microarray data sets and derived analysis results. The database was filled with over 20 time-series microarray experiments. In order to remove experimental condition differences and variation in the speed with which cells progress through the cell cycle, experimental data from each study were first normalized to a common time scale. Data from multiple studies were then plotted on a single chart for each gene. This intuitive visual representation, which depicts hundreds of experimental

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The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.

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measurments in a single image, allows researchers to
easily compare expression profiles across studies and
gage the reproducibility of the experimental data. Each
graph was supplemented by results from state-of-the-art
analyses, including measures for periodicity, magnitude of
regulation and the point in the division process when the
transcription level is highest.

The first version of Cyclebase made it possible to easily
assess transcriptional regulation of individual genes in
single organisms. However, within the cell-cycle community
there is a need for comparing both conservation of
transcriptional regulation across species as well as
assessing additional cell-cycle relevant information. To
address these needs, we have expanded the functionality
of Cyclebase, and further updated the database to account
for changes in genomic annotations.

CYCLEBASE VERSION 2.0

In order to provide easier access to more information
about each genes’ role in the cell cycle, we have performed
a major update of Cyclebase. The Gene Details page,
which is the centerpiece of the web site, contains many
of these updates (Figure 1). This section highlights the
major additions and changes to Cyclebase and describes
its core components.

Display of orthologous and paralogous genes

The recent findings that cell-cycle regulation is only rarely
conserved at the individual gene level, but appears to be
conserved at higher systemic levels (13), highlight the
importance of comparing transcriptional regulation
across species. To facilitate such comparisons, each gene
is now supplemented with a list of orthologous and
paralogous genes found in Cyclebase (Figure 1a4). These
assignments were taken from the eggNOG database (18).
The list contains analysis results, a link to display Reflect
information (19), and an icon that, when clicked on,
displays a graphic of all available normalized expression
profiles for the ortholog or paralog selected (see
Figure 1b). Multiple expression profiles can be opened
at the same time, further easing comparison between
homologous genes across organisms.

Addition of cell-cycle relevant data

Transcriptional regulation is one of the several regulatory
layers used to control the cell cycle. Easy access to addi-
tional data relevant to the division process helps to facil-
itate studies that focus on the interplay between different
regulatory mechanisms. Genes in Cyclebase version 2.0
now include a variety of other data related to the cell
cycle. We have included cell cycle relevant features
such as lists of CDK substrates (14–16), degradation
motifs (13) and phenotypic effects of knock-down (12)
and overexpression (10,11) experiments. These ‘gene
features’ are presented on the Gene Details page
(Figure 1a2).

Ability to search using BLAST

As with the original version of Cyclebase, the web-interface
still queries for genes by name, alias and description.
Users can continue to browse all the genes within
an organism, select example genes or enter complex
queries through the Advanced Search page. In addition,
Cyclebase version 2.0 introduces the ability to query for
genes using either amino acid or nucleotide sequence,
which can be useful when performing detailed searches,
e.g. searching for specific genomic sequences in the
human data derived from cDNA microarray experiments.
Users can either enter the primary sequence directly into
the search field or use the Advanced Search feature to
input a FASTA entry. Genes are queried with both
BLASTP and BLASTX, the results are combined and by
default are sorted by E-value.

Update to core Cyclebase components

In addition to the more visible updates, several aspects
in the underlying data structure have also changed. For
example, the original version of Cyclebase was organized
around microarray probesets rather than genes. Multiple
probesets often target the same gene and, unfortunately,
single probesets may target multiple genes (i.e. there is a
many-to-many relationship). Centering the new version
of Cyclebase around genes, the new interface is more intu-
itive and warns users when a many-to-many relationship
exists for the gene/probeset they are viewing. In another
major change to the backend database, we have updated
data sets to account for changes in genome
annotations, which provides up-to-date lists of periodi-
cally expressed genes.

Cyclebase continues to provide full documentation of
analysis methodology, frequently asked questions and
information on each individual experiment. In addition,
well-documented downloads are available for all analysis
results and, when permission from original authors has
been given, normalized expression data for each experi-
ment. All the documentation has been updated to
account for the changes introduced in Cyclebase
version 2.0 and all downloads have been updated with
more recent genome annotations.

PERSPECTIVES

With the new functional improvements and the updated
backend, Cyclebase is well positioned to store and present
other temporal cell-cycle-related data sets, e.g. protein
and phospho-protein expression profiles. Although only
sparsely available right now, experiments that generate
these types of data are expected to become more and
more common in the future. Such data will help
deconvolute the complexity of cell-cycle regulation,
allowing researchers to further understand how regulatory
mechanisms evolve, how differentiation and the cell cycle
are intimately linked and how errors in the process can
lead to complicated diseases such as cancer.
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