Chapter 11

CELL CYCLE COMPONENTS

11.1. CELL CYCLE

In continuously dividing cells, an individual cell passes through four phases, shown in Fig. 11.1. G1 is the resting phase. During S phase DNA synthesis occurs. The S phase is followed by G2 phase, which is again the resting phase after DNA synthesis. The three phases viz. G1, S and G2 constitute interphase, while the main mitosis takes place during M phase. The duration of different phases of cell cycle depends not only in different organisms but also varies in different tissues of same organism. The crucial features in cell cycle include the existence of two transition control points, at G2/M boundary and during G1 phase. The M phase is characterized by activation of a kinase, which is described by various names depending on the assay such as MPF or H1 kinase or by neutral name M phase kinase. The identification of multiple forms of protein kinases in cell cycle and cell cyclins in spermatogenesis indicates that mitotic and meiotic phases of spermatogenesis are regulated at multiple points and many fold more complicated than the cell cycle thought in yeast or Xenopus oocytes.

11.2. CELL CYCLE GENES IN YEAST

Earlier investigations on cell division conducted on budding yeast (Saccharomyces cerevisiae) and the fission yeast (Schizosaccharomyces pombe) were responsible for major breakthrough in the discovery of present day research in cell cycle. Budding yeast is an oval shaped cell that divides by forming a bud. The fission yeast is a rod shaped cell, which grows by elongation at its ends. Despite of differences in their shapes, they share a number of features, which are useful for genetic studies. A large number of mutants, which helped in the discovery of cell division cycle (cdc) were isolated. These mutants arrest the cell cycle at specific checkpoints. The products of mutant genes were analyzed and compared with the proteins isolated and studied through the biochemistry of the cell division. Cell cycle components controlling cell cycle are highly conserved from yeast to mammalian cells.

11.2.1. Cdc2, Cdc28 and Cdc13 Genes

The study on yeast mutants suggested that the Cdc2 gene in fission yeast and Cdc28 gene in budding yeast were responsible both for passage through start (i.e. transition from G1 to S phase), and for transition from G2 to M phase. Therefore, these two genes are considered to be equivalent to each other. The protein product of these genes and of their homologs in other organisms, named p34cdc2 (Mr 34kDa, p34cdc2), is found in all eukaryotic cells. Another
fission yeast gene Cdc13, which produces a cyclin or its homolog, is also required for the induction of mitosis. The products of Cdc2 and Cdc13 (p34cdc2 and cyclin) have been demonstrated to participate in cell division (Fig.11.2).

11.2.2. Cdc25 and Wee1 Genes

The coordinated activity of Cdc2 and Cdc13 is regulated by two additional genes: Cdc25 (stimulates entry into mitosis), and Wee1 (inhibits entry into mitosis), which act antagonistically to control and regulate the entry of cell into mitosis. Another gene nim1 exercises a negative control on Wee1. While nim1 and Wee1 produce kinases that cause phosphorylation, the Cdc25 produces a phosphatase, which causes dephosphorylation of phosphate group at a tyrosine residue of p34cdc2. Thus, these genes act through regulation of protein phosphorylation and dephosphorylation. An increase in the ratio of activities of two genes, namely that of Cdc25 to Wee 1, increases the cell size required for entry into mitosis, while a decrease in this ratio leads to a decrease in the critical cell size. The over-expression of Cdc25 in a mutant for Wee1, causes premature entry into mitosis resulting into lethality. Several nim mutants such as nim A (nim= never-in-mitosis; bim= blocked-in-mitosis) arrest cell cycle in G2 phase in Aspergillus. A Drosophila gene named string and and temperature sensitive nim T in Aspergillus are homologs of Cdc25 of fission yeast (Fig.11.2).

11.2.3. Cyclin and Other Genes in Budding Yeast

Two types of cyclins are mainly involved in mitotic cell division in budding yeast: G1 cyclins and M (mitotic) cyclins (called cyclin B). G1 cyclins play an essential role in start. Originally three cyclin genes (Cln1, Cln2, Cln3) were identified in budding yeast. The levels of cyclin 1 (CLN1) and CLN2 undergo periodic changes with the phase of cell cycle, peaking in late G1, whereas CLN3 is low throughout the cell cycle. In addition, two more genes SWI4 and SWI6 (and also Cdc 28) (SWI = for switching) are required for transcription of HO gene coding an endonuclease. The products of SWI4 and SWI6, required for transcription of Cln1 and Cln2 are components of a transcription factor (SBF) that binds the promoter element responsible for