Text Boxes

Replication Origins

Replication origins are the places on DNA where copying starts. A pair of replication forks are initiated at each origin, with the two forks facing away from each other. The replication forks then proceed along the DNA, replicating each strand as it goes. In most circumstances, replication forks only terminate (disassemble) when they encounter another fork heading in the opposite direction. For this process to result in the precise duplication of the genome, replication origins should never fire on DNA that has already been replicated in the current cell cycle; this limitation is enforced by the replication licensing system.

Eukaryotes use many replication origins to replicate their large chromosomes, origins typically being spaced 30 – 100 kb apart. Different replication origins fire (initiate a pair of forks) at different times during S phase, creating a 'replication timing programme' whereby different segments of chromosomal DNA are replicated at distinct times.

It is currently unclear precisely what determines where replication origins are located and when they fire. In budding yeast, replication origins contain conserved sequence elements which, at least in part, direct the recruitment of the Origin Recognition Complex (ORC). However, other factors must be involved, since not all sites possessing these sequences function as replication origins. In metazoans, no clearly conserved sequence elements have been identified at replication origins. The usage of replication origins can change during development and differentiation. Cells with shorter S phases, such as early embryonic cells, typically have more tightly spaced replication origins. These results suggest that factors other than DNA sequence, such as chromatin structure, play an important role in determining the position of replication origins.

Cyclin-dependent kinases

Cyclin-dependent kinases (CDKs) are the master drivers of cell cycle progression. They consist of a small protein kinase subunit that is inactive unless complexed with a larger cyclin partner. CDK activity is low or absent during most of G1, but is high through late G1, S phase, G2 and mitosis. Amongst the cell cycle transitions dependent on CDK activity are the transcriptional programme occurring in late G1 that commits cells to division, progression into and through S phase, and progression into and through mitosis. A number of cyclins and kinase subunits can drive these different transitions. In most cases, the abundance of the kinase subunit remains constant whilst the abundance of the cyclin partner varies throughout the cell cycle. An important component of this control is cell-cycle regulated degradation of cyclins, mediated by ubiquitin-dependent proteolysis. In metazoans, for example, A-type cyclins are degraded during metaphase whilst B-type cyclins are degraded during anaphase. CDK activity is also controlled in other ways. The kinase subunit is subject to both inhibitory and activating phosphorylation. A range of CDK inhibitors also play an important role in regulating CDK activity during the cell cycle. In understanding the regulation of DNA replication by CDKs, it should be noted that origin licensing typically occurs in G1 when CDK activity is low, whilst the initiation of replication forks is dependent on CDK activity.