Cell Proliferation and Apoptosis (24 marks MCQ)

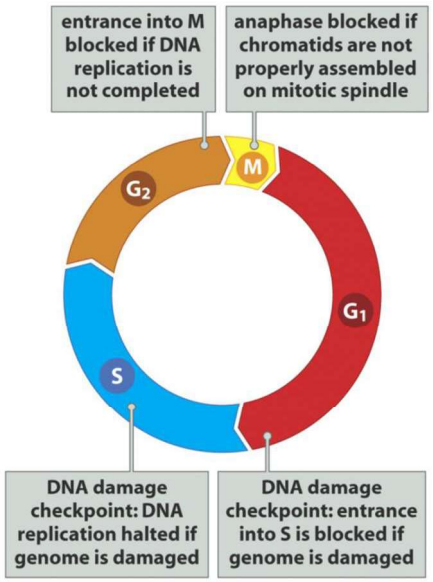
Molecular circuitry in the nucleus for cell cycle control

- Cells are stimulated to proliferate by mitogenic growth factors
- Transforming growth factor-β may halt growth (TGF-β)
- Differentiated cells do not proliferate
- Diversity of signals from multiple growth factors (>20) collectively result in binary decision grow/arrest, don't/do differentiate – 'Cell Cycle Clock' a network of interacting proteins
- Oncogenes and tumour suppressor genes disrupt the Cell Cycle Clock

The mammalian cell cycle, defects in DNA replication or chromosome segregation are disastrous.

- Growth factors (mitogenic/growth inhibitory) determine whether a newly formed cell divides again or enters the quiescent G0 phase (the resting phase)
- Cell's genome must be duplicated
- G1 phase the first gap phase of the cell cycle, decisions about growth/ quiescence/differentiation
- S phase is the synthetic phase (~6.4 X 109 base pairs per diploid genome)
- Transition from S phase to M phase is delayed by a second gap phase G2 where the cell prepares itself for mitosis

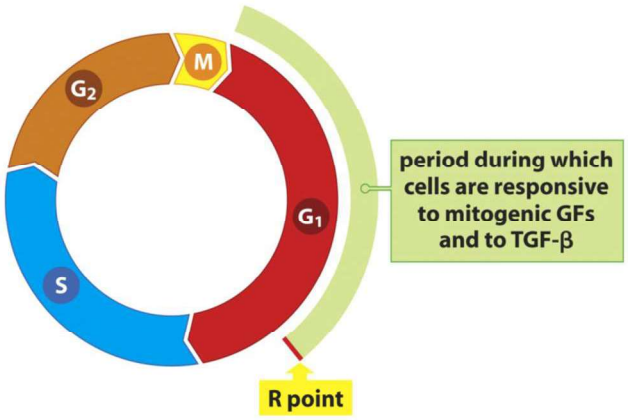
There are 4 checkpoints in the cell cycle, no entry into S or M phase if DNA damaged. S phase checkpoint slows/ stops DNA replication if there is damage. Block entering G2 until all DNA is replicated. Block at anaphase until all chromosomes are assembled on the spindle during metaphase. (If the cell's DNA cannot be repaired, the cell will start apoptosis)

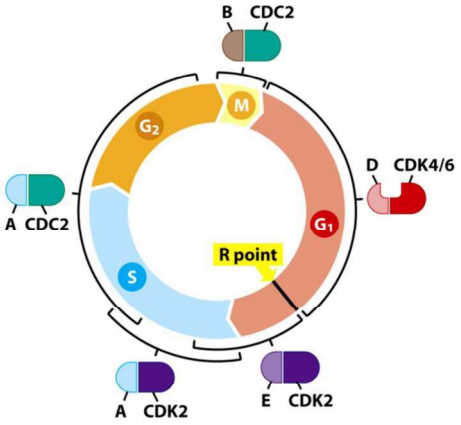


Many cancers have inactivated one of their checkpoint controls enabling accumulation of mutation.

Response to extracellular signals during the cell cycle

- Only embryonic cells can grow without stimulation from external growth factors
- pRb regulation is not present in embryonic cells
- embryonic stem cells are able to maintain growth in culture without external growth factors, can form benign tumours
- Cells consult growth-regulating signals during G1 phase
- TGF β can inhibit cell cycle progression only during a limited portion of G1 phase
- Cell decides whether to commit to cell cycle at restriction (R) point (the checkpoint at the end of G1 phase; not reversible)
- Once committed, the cycle continues even if growth factors are removed
- Metabolic genetic or physical disasters may still halt the cycle
- Deregulation of the R points is associated with most cancers





Cyclins and cyclin-dependent kinases

- During much of G1 phase, CDK4 and CDK6 associate with the related cyclins D1, D2 and D3
- After the R point in late G1, cyclins E1 and E2 associate with CDK2 to phosphorylate substrates for entry into S phase
- In S phase, cyclins A1 and A2 replace the E cyclins with CDK2 for S phase progression
- Later in S phase, CDK2 is replaced with CDC2 or CDK1
- Moving into G2, cyclins B1 and B2 replace cyclins A1 and A2 as partners for CDC2
- At the onset of M phase, the complexes of CDC2 with Cyclins B1 and B2 trigger events of prophase, metaphase, anaphase and telophase

Cyclins are ubiquitinylated are rapidly degraded.

Cyclin D1 is over-expressed in most breast cancers