In normal cells, each stage of the cell cycle is tightly regulated. In cancer cells, many genes and proteins that influence the progression of the cell cycle are mutated or overexpressed – they become oncogenes. The proteins/molecules involved in the regulation of the cell cycle, in particular those with a role in DNA replication and DNA damage, are important cancer therapeutic targets.

CELL CYCLE AND DNA DAMAGE REPAIR

There are three major regulatory cell cycle checkpoints - G1/S, intra-S phase, and G2/M phase. A cell can only pass through these checkpoints in the presence of stimulatory signals and in the absence of DNA damage. The cell cycle checkpoints are controlled by tumor suppressors and cyclin-dependent kinases (cdks). Cdk’s act in concert with their regulatory subunits, cyclins, to control cell cycle progression. Cdk’s are constitutively expressed and are regulated by several kinases and phosphatases, including Wee1 kinase and Cdc25 phosphatase.

At specific points in the cell cycle, DNA damage is detected and repaired. This process is initiated by the DNA damage sensors, ATM and ATR kinase. Checkpoint kinases Chk1 and Chk2 initiate signaling cascades that activate DNA damage checkpoints in G1 and G2. The spindle assembly checkpoint (SAC) delays anaphase of mitosis until all chromosomes are properly aligned on the spindle, preventing aneuploidy. Kinases including aurora kinase B (Aur B), PLK1 and Mps1 are implicated at various control points in the cell cycle.

DNA REPLICATION
DNA replication occurs in five stages during S-phase; initiation, unwinding, primer synthesis, elongation and termination. Helicases enzymes “unwind” the DNA double helix, and telomerase reduce the resulting torsional strain, the single strands are now exposed and the replication fork is initiated. The leading strand of DNA is synthesized by Pol ε and the lagging strand is synthesized by Pol δ. PCNA is a cofactor for both DNA polymerase δ and ε, where it acts as a DNA clamp, which is important in both DNA synthesis and repair. At the end of the termination phase, DNA ligases form a phosphodiester bond, which joins the DNA strands together, forming new double stranded DNA.

REFERENCES


TARGETING CANCER CELLS
Enhancing replicative stress by targeting critical DNA replication checkpoints and replication machinery, as well as dewetting nucleotides, encourages fork stalling and fork collapse, which leads to mitotic catastrophe and death in cancer cells.