Cell Cycle and DNA Damage Repair

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.

**DNA Replication**

DNA replication occurs in five stages during S-phase; initiation, unwinding, primer synthesis, elongation and termination. Helicase enzymes "unwind" the DNA double helix, and telomeres (important in both DNA synthesis and repair) at the end of the termination phase.

**Cell Cycle Progression and DNA 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. Cdns are constitutively expressed and are regulated by various proteins and kinases, including Wee1 kinase and Cdk2 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 kinase Chk1 and Chk2 initiate signaling cascades that activate DNA damage-checkpoint kinases (cdks). The spindle assembly checkpoint (SAC) delays anaphase 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.

**Mitotic exit**

Quiescence

Cyclin D Cdk 4 /6

Cyclin A Cdk 2

Cyclin E Cdk 2

Cyclin B Cdk 1

Cell Cycle

G1/S checkpoint

DNS damage checkpoint

SSB = single strand break

DSB = double strand break

**Targeting Cancer Cells**

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

**DNA Repair**

DNA repair is a complex process that helps maintain genomic stability and repair damaged DNA. The primary types of DNA repair mechanisms include base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR), and non-homologous end joining (NHEJ). These processes are crucial for maintaining genome integrity and preventing the development of cancer.

**References**


**Tocris Products**

- Cell Cycle Products
- DNA Replication Components
- DNA Damage Repair Complexes