Cell Cycle and DNA Damage Repair

Adapted from Edition 3 of the Tocris Cancer Product Guide
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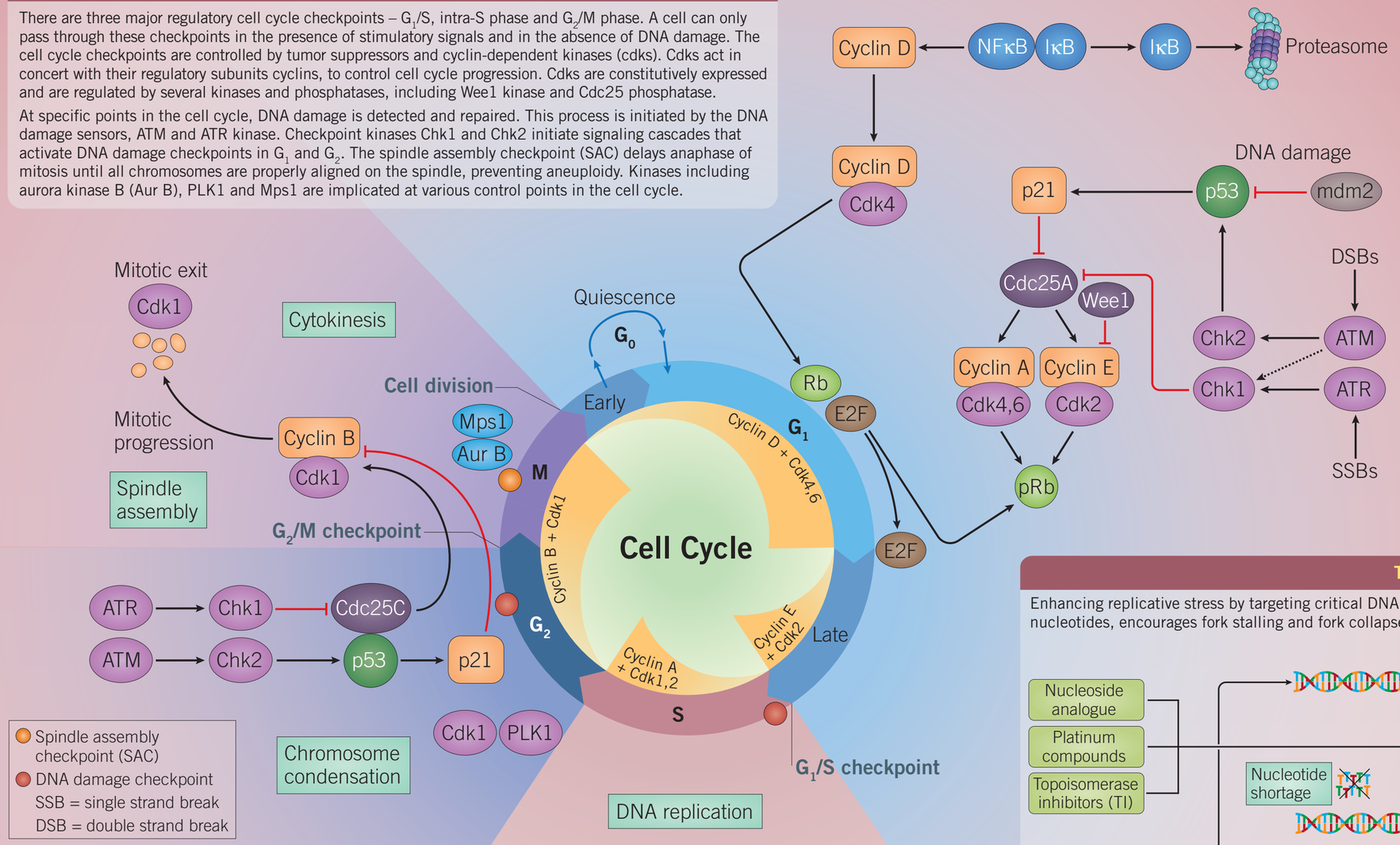
In normal cells, each stage of the cell cycle is tightly regulated. In cancer cells, many genes and proteins that influence the progression of the cell cycle are mutated or overexpressed – they become oncogenes. The proteins/molecules involved in the regulation of the cell cycle, in particular DNA replication and DNA damage are important cancer therapeutic targets.

Cell Cycle Progression and DNA Repair

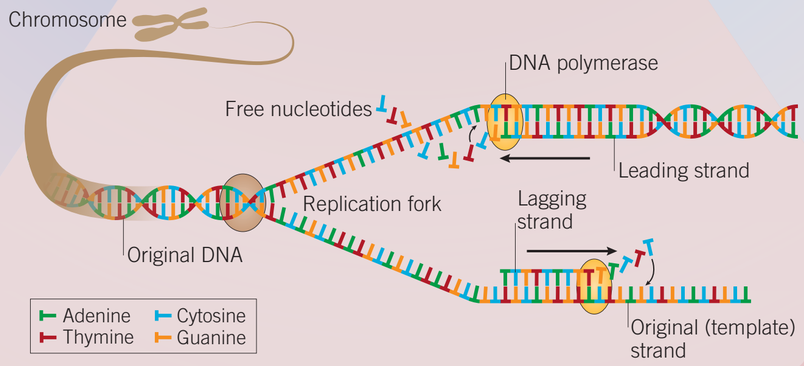
There are three major regulatory cell cycle checkpoints – G_1/S, intra-S phase and G_2/M phase. A cell can only pass through these checkpoints in the presence of stimulatory signals and in the absence of DNA damage. The cell cycle checkpoints are controlled by tumor suppressors and cyclin-dependent kinases (cdks). Cdks act in concert with their regulatory subunits cyclins, to control cell cycle progression. Cdks 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 G_1 and G_2. 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. Helicase enzymes 'unwind' the DNA double helix, and telomerases reduce the resulting torsional strain, the single stands 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 doubled stranded DNA.



Products available from Tocris

ATM & ATR Kinase	AZ 20, CGK 733, KU 55933, KU 60019, Mirin
Aurora Kinases	Hesperadin, TC-A 2317, VX 680, ZM 447439
Calpains	Acetyl-Calpastatin (184-210) (human), Calpeptin, E 64, MDL 28170, MG 101, MG 132, PD 150606
Casein Kinase 1	D 4476, (*R*)-DRF053, LH 846, PF 4800567, PF 670462
Casein Kinase 2	TBB, TBCA, TMCB, TTP 22
Cdc25 Phosphatase	NSC 663284, NSC 95397
Cell Cycle Inhibitors	CFM 4, 10058-F4, Methotrexate, Narciclasine
Checkpoint Kinases	AZD 7762, CCT 241533, NSC 109555, PD 407824, PF 477736, SB 218078, TCS 2312
Cyclin-dependent Kinase	Kenpaullone, PD 0332991, Purvalanol A, Purvalanol B, Ro 3306, Senexin A
DNA-dependent Protein Kinase	Compound 401, DMNB, NU 7026, NU 7441
DNA, RNA and Protein Synthesis	4E1RCat, L189, Mithramycin A, NSC 617145, T2AA
Hsp70	VER 155008
Hsp90	17-AAG
IRE1	APY 29
Kinesin	BRD 9876, Dimethylenastron, K 858, Monastrol, SB 743921, *S*-Trityl-L-cysteine
Microtubules	Docetaxel, Dolastatin 10, Flutax 1, Taxol, Vinblastine, Vincristine
Monopolar Spindle 1 Kinase	AZ 3146, Mps BAY 2a, Mps1-IN-1, TC Mps1 12
p53	NSC 319726, Nutlin-3, PRIMA-1MET, RETRA, RITA
Pim Kinase	PIM-1 Inhibitor 2, R8-T198wt, TCS PIM-1 1, TCS PIM-1 4a
Polo-like Kinase	Cyclapolin 9, GW 843682X, SBE 13, TAK 960, TC-S 7005
Poly (ADP-ribose) Polymerase	JW 55, NU 1025, PJ 34, XAV 939
Telomerase	BIBR 1532, Costunolide, 5-TAMRA SE, TMPyP4 tosylate

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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.