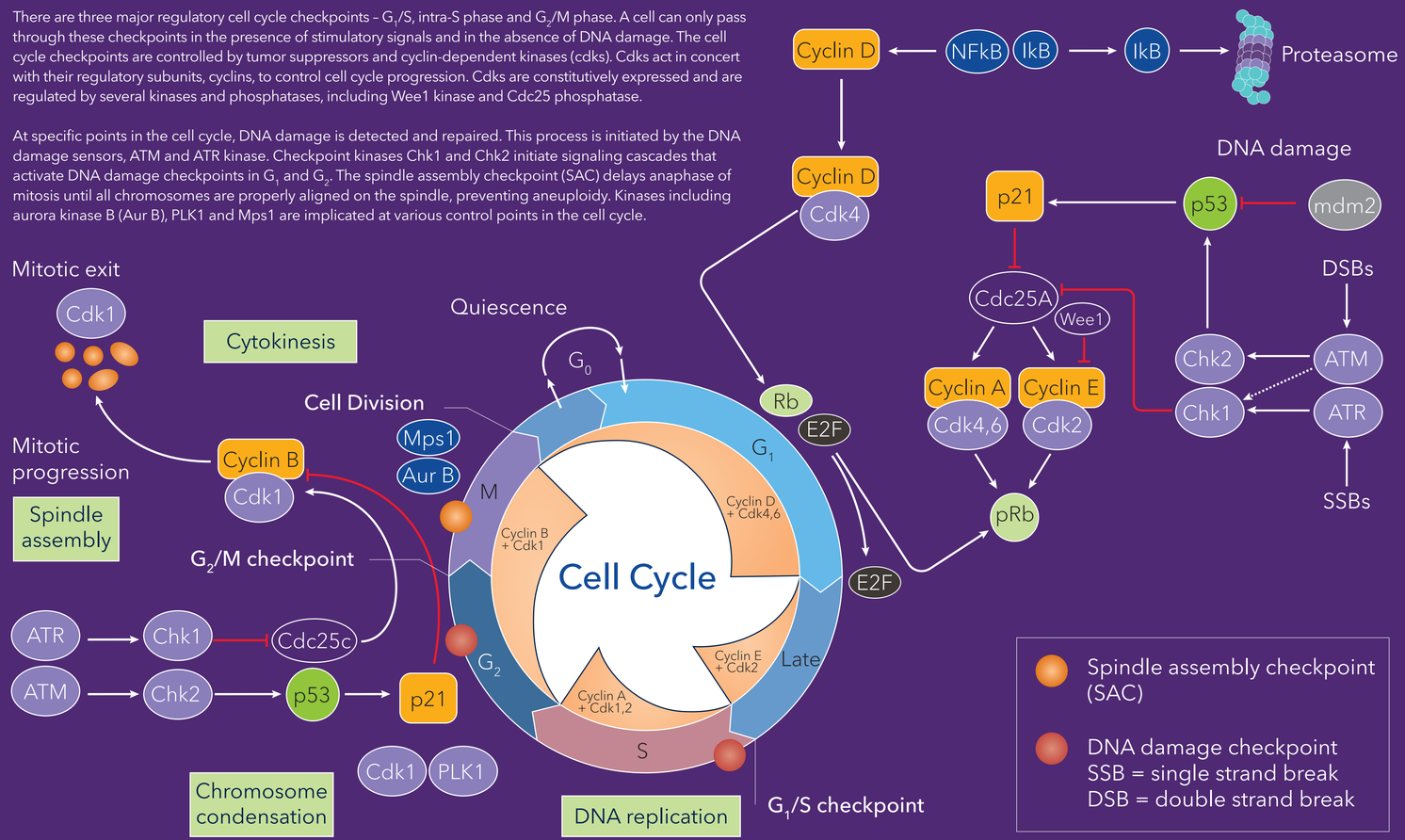
Cell Cycle and DNA Damage Repair

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.

Cell Cycle Progression and DNA Repair

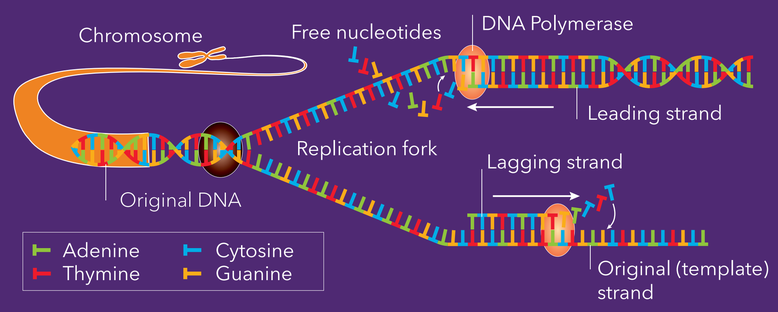
There are three major regulatory cell cycle checkpoints – G_1/S, intra-S phase and G_2/M phase. A cell can only pass through these checkpoints in the presence of stimulatory signals and in the absence of DNA damage. The cell cycle checkpoints are controlled by tumor suppressors and cyclin-dependent kinases (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.



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MG 132
PD 150606

Casein Kinase 1
D 4476
PF 4800567
PF 5006739
PF 670462

Casein Kinase 2
TBB
TBCA
TTP 22

Cdc25 Phosphatase
NSC 663284
NSC 95397

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Narciclasine
Pyridostatin

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LY 2603618
NSC 109555
PD 407824
PF 477736
SB 218078
TCS 2312

Cyclin-dependent Kinase
BSJ-03-123
BSJ-04-132
CDK8/19i
FMF-04-159-2
Kenpaullone
NVP 2
PD 0332991
Purvalanol A
Purvalanol B
Ro 3306
Senexin A
THAL SNS 032

DNA-dependent Protein Kinase
NU 7026
NU 7441

DNA, RNA and Protein Synthesis
L189
Mithramycin A
NSC 617145

Hsp70
VER 155008

Hsp90
17-AAG

IRE1
APY 29

Kinesin
Dimethylenastron
K 858
Monastrol
S-Trityl-L-cysteine

Microtubules
Docetaxel
Flutax 1
Taxol
Vinblastine
Vincristine

Monopolar Spindle 1 Kinase
AZ 3146

p53
Nutlin-3
PRIMA-1MET
RITA

Polo-like Kinase
GW 843682X
TC-S

Poly (ADP-ribose) Polymerase
Nicotinamide
PJ 34
WIKI 4
XAV 939

Telomerase
BRACO 19
BIBR 1532
RHPS 4
TMPyP4 tosylate

References

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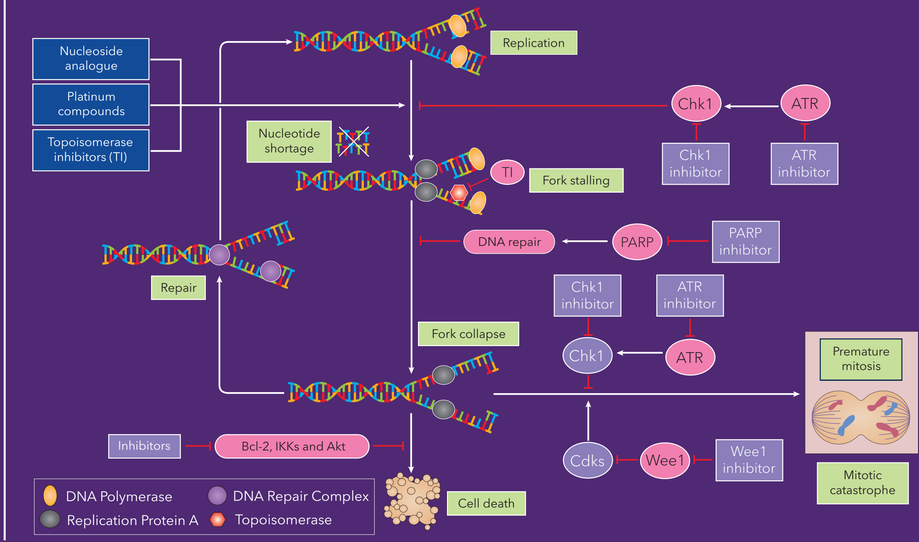
Targeting Cancer Cells

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.



NOTE: This poster conveys a general overview and should be considered neither comprehensive nor definitive. The details of this information are understood to be subject to interpretation.

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