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CANCER

The DNA damage response in tumorigenesis and cancer treatment

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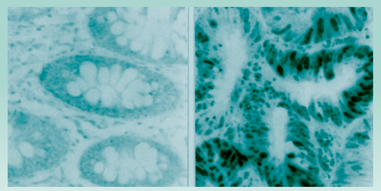
The cellular DNA damage response (DDR) machinery is intimately linked with cancer as damage to DNA causes cancer. The DDR provides an intrinsic biological barrier against the development of cancer, and tumours develop when maintenance of genome integrity fails. Germline and somatic defects in the hierarchical DDR network — from sensors of diverse types of DNA lesions, damage signalling and mechanisms of checkpoint activation, to multiple DNA repair pathways — can predispose to cancer and fuel tumour progression, respectively. Recently, promising anticancer agents have emerged that target components of DNA damage signalling, the checkpoint machinery and DNA repair. Several are in preclinical development or clinical trials, either as monotherapy or to be combined with standard-of-care genotoxic therapies, to selectively target tumour cells. These developments move further towards the exciting promise of personalized therapy.

The DDR as a barrier to tumorigenesis

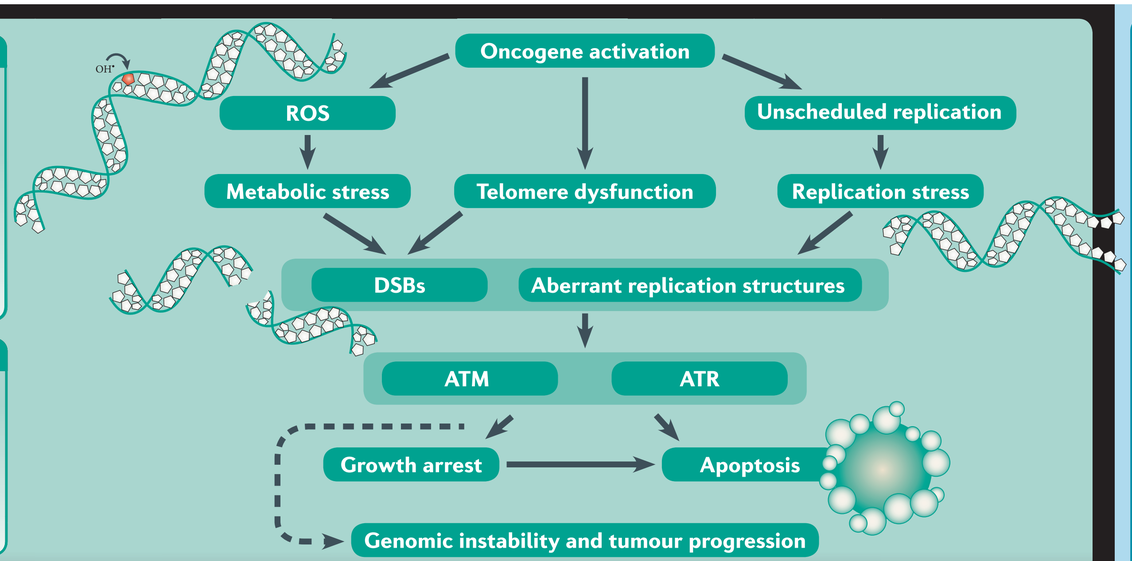


Immunohistochemistry image of phosphorylated histone H2AX, which indicates DDR activation, in human colorectal adenoma (right; a premaligant lesion) but not in normal colon (left).

Constitutive activation of the DDR commonly occurs in premalignant and early cancerous lesions, but not in corresponding normal tissues. Among the sources of such DNA damage in nascent tumour cells is oncogene-induced DNA replication stress, telomere attrition and possibly increased levels of ROS. The resulting aberrant replication structures and DSBs activate the ATR and/or ATM-orchestrated DDR network, which provides an inducible barrier that constrains tumour progression at the early stages by inducing senescence or cell death. This causes a 'Darwinian struggle' that may eventually select for genetic or epigenetic aberrations of activated DDR pathways, such as the ATM–CHK2–p53 cascade. Such a breach of this barrier would rescue the emerging malignant clones from senescence or cell death at the expense of genomic stability.

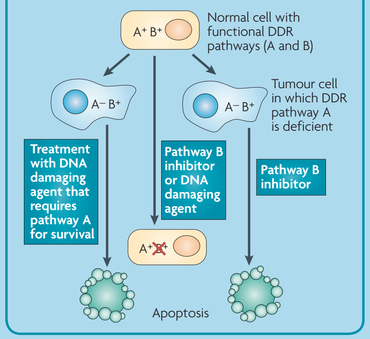
Inherited defects in the DDR

Germline mutations in DDR genes predispose to familial cancer (such as *BRCA1*- or *BRCA2*-associated breast and ovarian tumours) and cause a range of cancer-prone genetic instability syndromes. Such mutations affect DNA damage sensors (NBS1: Nijmegen breakage syndrome), signalling kinases (ATM: ataxia-telangiectasia), effectors (p53: Li–Fraumeni syndrome) or repair (MMR: hereditary non-polyposis colorectal cancer; NER: xeroderma pigmentosum; interstrand crosslink repair: Fanconi anaemia). The impaired ability to maintain genetic stability can foster tumorigenesis, including subsequent somatically acquired genetic and epigenetic alterations in the DDR machinery that promote tumour survival and disease progression. However, such DDR defects also represent weaknesses of cancer cells that provide opportunities for cancer-selective therapeutic intervention.

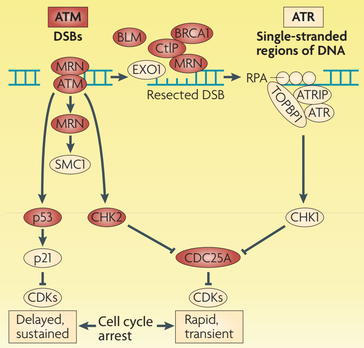


Targeting the DDR

The impairment of the DDR machinery in tumours and the dependency of cancer cells on stress survival pathways (including ongoing repair of endogenous DNA damage) provides the rationale for targeting the DDR. The approach selectively targets tumour cells while sparing normal cells, which improves efficacy and reduces toxicity. The major strategy to achieve such selective tumour cell killing has been the principle of synthetic lethality: defects in either of two genes or proteins have no effect on survival but combining the two defects results in cell death (see the figure). The best example of this strategy is the PARP inhibitors, which selectively kill hereditary breast and ovarian cancers that rely on PARP for DNA break repair owing to loss-of-function mutations in BRCA1 or BRCA2. Another example is sensitization of partially checkpoint-defective cancers to radiotherapy or chemotherapy by inhibiting ATM or CHK1. DDR inhibitors show promise for treatment of diverse tumour types, both familial and sporadic, either as monotherapy or in combination to improve the efficacy of genotoxic radiotherapy and chemotherapy. Identification and validation of predictive biomarkers to select patients who would benefit most from these treatments and understanding the basis of potential resistance to such treatments are among the key goals in this rapidly evolving area of translational cancer research.



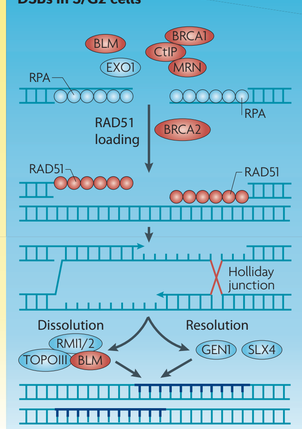
Checkpoint activation



In addition to checkpoint activation, ATM and ATR modify hundreds of substrates in DNA repair and other pathways.

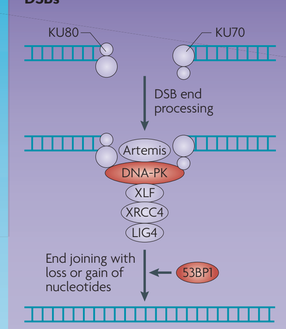
HR

DSBs in S/G2 cells



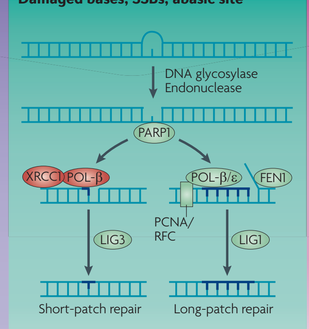
NHEJ

DSBs



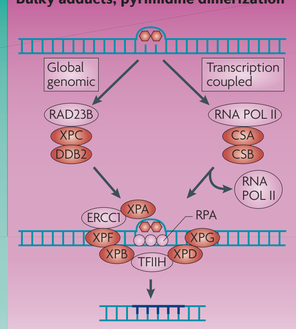
BER

Damaged bases, SSBs, abasic site



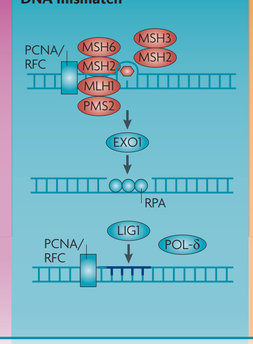
NER

Bulky adducts, pyrimidine dimerization



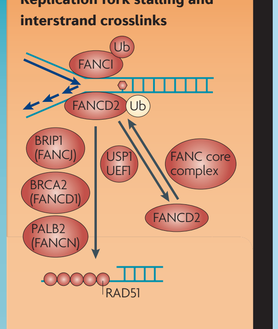
MMR

DNA mismatch



FA pathway

Replication fork stalling and interstrand crosslinks



The DDR network is extensive and only the major DNA repair pathways are shown; some pathways such as translesion synthesis are not shown although they can affect tumour development. The DDR pathways shown here are simplified representations to show the major components of these pathways. The proteins shown in red are those that are most commonly deficient in human cancer and thereby associated with tumorigenesis.

Examples of DDR inhibitors

Inhibitor	Target	Stage in clinical development
KU-55933	ATM	Preclinical
KU-60019	ATM	Preclinical
XL844	CHK1 and CHK2	Preclinical
AZD7762	CHK1 and CHK2	Phase I
PF-477736	CHK1	Phase I
NU 7441 (KU-57788)	DNA-PK	Preclinical
TRC102	Binds covalently to apurinic/ apyrimidinic sites and prevents BER	Phase I
AZD2281	PARP1	Phase II
AG014699	PARP1	Phase II
ABT-888	PARP1 and PARP2	Phase II
BSI-201	PARP1	Phase III
INO-1001	PARP1	Preclinical
O6-BG	MGMT	Phase II
Several	p53 (such as inhibitors of MDM2 and 're-activators' of mutant p53)	Phase I, preclinical

About KuDOS

KuDOS Pharmaceuticals holds a leading position in the identification and development of drugs that target the DNA damage response (DDR) processes in cells. The company was founded by Professor Steve Jackson, Cambridge University and the Cancer Research Campaign (now Cancer Research UK) in 1997 and in that time has identified potent inhibitors of a number of DDR targets including PARP, ATM and DNA-PK. The company was acquired in 2006 by AstraZeneca.

Inhibitors of DDR pathways offer exciting new prospects for identifying targeted cancer therapies. In addition to the potential to enhance the effectiveness of DNA damaging chemotherapies and ionizing radiation treatment, DDR inhibitors also have the possibility for single agent activity in specific tumour genetic backgrounds. This is exemplified by inhibitors of the DDR protein PARP, which are now in Phase II clinical trials and which have been shown to induce tumour-specific cell death (synthetic lethality) in cancers deficient in homologous recombination repair, including those deficient in BRCA1 and BRCA2.

Abbreviations

53BP1, p53 binding protein 1; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3 related; ATRIP, ATR-interacting protein; BER, base excision repair; BLM, Bloom syndrome, RecQ helicase-like; BRIP1, BRCA1-interacting protein C-terminal helicase 1 (also known as BACH1); CDC25A, cell division cycle 25A; CDK, cyclin-dependent kinase; CSA/B, Cockayne syndrome A/B; CtIP, CTBP-interacting protein (also known as RBBP8); DDB2, damage-specific DNA binding protein 2; DDR, DNA damage response; DNA-PK, DNA-dependent protein kinase; DSB, double-strand break; ERCC1, excision repair cross-complementing rodent repair deficiency, complementation group 1; EXO1, exonuclease 1; FA, Fanconi anaemia; FANC, Fanconi anaemia, complementation group; FEN1, flap structure-specific endonuclease 1; HR, homologous recombination; LIG, ligase; MGMT, O-6-methylguanine-DNA methyltransferase; MLH1, mutL homologue 1; MMR, mismatch repair; MRE11, meiotic recombination 11; MRN, MRE11-RAD50-NBS1 complex; MSH, mutS homologue; NBS1, nibrin (also known as NBN); NER, nucleotide excision repair; NHEJ, non-homologous end joining; PALB2, partner and localizer of BRCA2; PARP1, poly(ADP-ribose) polymerase 1; PCNA, proliferating cell nuclear antigen; PMS2, postmeiotic segregation increased 2; POL, polymerase; RFC, replication factor C; RMI1/2, RecQ mediated genome instability 1/2; ROS, reactive oxygen species; RPA, replication protein A; SLX4, structure-specific endonuclease subunit SLX4; SMC1, structural maintenance of chromosomes 1; SSB, single-strand break; TFIIH, transcription factor IIH; TOPBP1, topoisomerase II binding protein 1; TOPOIII, DNA topoisomerase 3; Ub, ubiquitin; USP1, ubiquitin-specific peptidase 1; XLF, XRCC4-like factor; XP, xeroderma pigmentosum, complementation group; XRCC, X-ray repair complementing defective repair in Chinese hamster cells.

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