

S014 Replication-associated homologous recombination as a target in cancer therapy

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Homologous recombination (HR) is an important pathway by which replication-associated lesions are repaired. It often permits the survival of cancer cells, despite the presence of DNA damage that is produced either endogenously, or during chemotherapy. Here, several distinct pathways for HR will be presented and their relevance in repair of replication lesions. It will be shown that replication lesions, similar to those produced during anti-cancer therapy, are commonly associated with cancer aetiology. DNA replication lesions are present in cancer cells owing to oncogene expression, hypoxia or defects in the DNA damage response or DNA repair. Here, we show how novel therapies can exploit endogenous replication lesions in cancer cells and convert them to toxic lesions. The aim of these therapies is to produce similar lesions as those produced by DNA damaging anti-cancer drugs. The difference is that the lesions will be cancer-specific and produce milder side-effects in non-cancerous cells. Tumour development can be associated with perturbed DNA damage response and repair pathways. This perturbation results in reduced DNA repair capacity and increased genetic instability in tumour cells. Defects in one DNA repair pathway can be compensated for by other pathways. Such compensating pathways can be identified in synthetic lethality screens and then specifically targeted for treatment of DNA repair-defective tumours, as being tested in phase II trials where patients with breast or ovarian cancers defective in homologous recombination are being treated with a poly(ADP-ribose) polymerase (PARP) inhibitor.