THE ROLE OF NUCLEOTIDE EXCISION REPAIR FACTORS IN RESISTANCE TO NUCLEOSIDE ANALOGUES

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Abstract

The Nucleoside Analogue (NA) Gemcitabine (2', 2'-difluorodeoxycytidine; dFdC) is a clinically important cancer drug that is used in the treatment of solid tumours (including pancreatic, metastatic breast, ovarian and non-small cell lung cancer (Bergman, Pinedo, & Peters, 2002)). Gemcitabine is similar to deoxycytidine (the naturally occurring nucleotide), in that after phosphorylation to its triphosphate (TP) form, dFdCTP competes with dCTP for integration into DNA during DNA replication and acts as a elongating chain terminator, inhibiting further replication (Prakasha Gowda, Polizzi, Eckert, & Spratt, 2010). For a cell to survive treatment with this drug, the modified nucleotide needs to be removed from the DNA to allow replication restart. It remains largely unknown which DNA repair pathways are responsible for the removal of NAs from DNA. The nucleotide excision repair (NER) pathway may be one mechanism that is used for gemcitabine removal from the genome.

NER is responsible for removing bulky adducts from the DNA strand, particularly those caused by UV radiation, such as 6-4 photoproducts, or cyclopyrimidine dimers (Vermeulen, 2011). NER is an extremely orchestrated process which is carried out by no less than 30 proteins, with a core set of 7 proteins, termed XPA to G, that are responsible for the main mechanism. The whole NER mechanism can be broken down into the steps of recognition of damage, confirmation of damage, excision of the lesion, followed by repair and ligation of the strand. NER can be further categorised into global NER (GG-NER) where damage is recognised by surveillance of the whole genome, or transcription coupled NER (TC-NER) where the damage is detected by the stalling of polymerases, either in replication or transcription (Kamileri, Karakasilioti, & Garinis, 2012).

Genetic deficiency NER causes the condition termed Xeroderma Pigmentosum (XP). Patients with this condition have extreme sensitivity to UV light and have x1000 incidence of skin cancers (Ahmad & Hanaoka, 2008; Rezvani et al., 2010). Work here uses fibroblasts from patients with Xeroderma pigmentosum, to investigate the mechanisms within NER, in both structural and enzymatic requirements of each NER protein, to determine their role in the removal of nucleoside analogues from the DNA. The resistance of some cancers to chemotherapeutic attack is often a result of the work done by such DNA repair pathways, therefore understanding the repair pathway that offers resistance to various drugs is essential for optimising treatment for individual cancers.

REFERENCES


