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Mini-review

Nucleotide excision repair: Why is it not used to predict response to platinum-based chemotherapy?

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ABSTRACT

Platinum based therapy is one of the most effectively used chemotherapeutic treatments for cancer. The mechanism of action of platinum compounds is to damage DNA and drive cells into apoptosis. The most commonly used platinum containing agents are cis-diammine-dichloroplatinum (II)], more commonly known as cisplatin, its analogue carboplatin, and oxaliplatin. Cisplatin is used to treat a wide variety of tumours such as ovarian, testicular, head and neck and non-small cell lung cancers (NSCLCs). In addition, it forms the basis of most combined treatment regimes. Despite this, cisplatin and its analogues are extremely toxic and although some patients benefit substantially from treatment, a large proportion suffer the toxic side effects without any therapeutic benefit. Nucleotide excision repair (NER) is a versatile DNA repair system that recognises DNA damage induced by platinum based therapy. For many years the components of the NER pathway have been studied to determine mRNA and protein expression levels in response or resistance to cisplatin in many forms of cancer; particularly testicular, ovarian and NSCLCs. Despite the consistent finding that over or under expression of subsets of NER proteins and mRNA highly correlate with response to cisplatin, the translation of these findings into the clinical setting has not been forthcoming. This review summarises the results of previous investigations into NER in cisplatin response and clinical trials where the expression of NER proteins were compared to the response to platinum therapies in treatment.

1. Introduction

Platinum based therapy is one of the most effectively used chemotherapeutic treatments for cancer. The mechanism of action of platinum compounds is to damage DNA, primarily by formation of monoadducts followed by intra and inter-strand crosslinks, which consequently distort the DNA helix, inhibit DNA replication and drive cells into apoptosis [1–4]. The first discovered and most commonly used platinum containing agent is cis-diammine-dichloroplatinum (II)], more commonly known as cisplatin [5]. Cisplatin and its analogue, carboplatin form the same platinum–DNA intrastrand crosslinks. The final platinum compound commonly used is oxaliplatin, which produces a slightly different form of intrastrand cross-link, which may account in part for its different spectrum of activity. Cisplatin is commonly used to treat a wide variety of tumours such as ovarian, testicular, head and neck and NSCLCs [1]. In addition, it is often called the scaffolding of chemotherapy as it forms the basis of most combined treatment regimes. The downside to cisplatin and its analogues is that they are extremely toxic and although some patients benefit substantially from treatment, a large proportion suffer the toxic side effects without any therapeutic benefit [6].

Testicular and ovarian tumours have a very high response rate to platinum therapies, but various other forms of solid tumours such as lung, colorectal, breast and skin cancers have a high level of resistance. Tumour resistance to platinum therapies can occur by 3 different mechanisms: Loss of apoptotic signalling after damage has occurred; DNA repair/removal of the damage or tolerance of the damage [7]. The hypersensitivity of testicular cancer to cisplatin appears to be due to DNA-repair deficiency [8]. Additionally, cisplatin-resistant ovarian cell lines have been shown to have increased DNA-repair capacity, indicated by the number of DNA adducts present compared to the cisplatin-sensitive parental cell line [9]. Lung cancer cell lines also have increased DNA-repair capacity when cisplatin resistant.

In early clinical studies investigating the role of DNA repair in cisplatin resistance, elevated DNA repair capacity (DRC) was associated with resistance to cisplatin in lung cancer cell lines [10]. DRC

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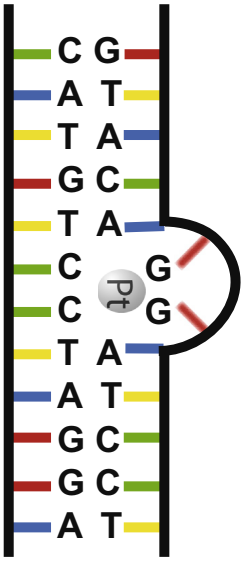

Fig. 1. Cross-links between guanine bases induced by platinum-based therapy. Cisplatin and carboplatin cause the same cross-link but oxaliplatin causes a structurally distinct adduct containing a bulky 1,2-diaminocyclohexane group. The damage caused by all these platinum compounds is helix distorting.

is a direct measurement of the repair capability of cells after treatment with a DNA damaging agent or after transfection with a reporter plasmid that has undergone DNA damage. A recent study has shown DRC in peripheral lymphocytes from patients with NSCLCs treated with first-line platinum-based therapies was an independent predictor of survival [11].

Cross-links between guanine bases are induced by cisplatin, carboplatin and oxaliplatin (Fig. 1). Cisplatin and carboplatin cause the same cross-link but oxaliplatin causes a structurally distinct adduct containing a bulky 1,2-diaminocyclohexane group [12]. The damage caused by all these platinum compounds is helix distorting, therefore it is recognised and repaired by the distinct DNA repair pathway known as nucleotide excision repair (reviewed in [13]). The first reports that NER is involved in the repair of cisplatin-induced DNA damage was in the late 1980s, when Hansson and colleagues confirmed involvement of several NER proteins [14,15]. Since then studies have investigated the mRNA and protein expression levels and genetic variation in almost every component of the NER pathway in relation to cisplatin response and resistance.

2. Nucleotide excision repair (NER)

NER is a versatile DNA repair system that eradicates a range of lesions that all have one commonality: distortion of the helical structure of DNA. The majority of insults that result in DNA distorting lesions are persistently present in our daily lives. For example: in food (e.g. nitrosamines), the air (e.g. benzo[a]pyrenes from cigarette smoke) and the environment (e.g. cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6–4) pyrimidine photoproducts (6–4PPs) from sunlight) [16–18].

The mechanistic actions of NER have been well characterised and have been thoroughly reviewed [19–21]. To summarise these actions (Fig. 2), NER removes lesions via four steps: (a) recognition of the DNA lesion, (b) DNA unwinding, (c) incision of the DNA upstream and downstream of the lesion by endonucleases and (d) DNA resynthesis and ligation [22,23]. There are two damage recognition arms of the NER pathway, global genome repair (GGR) and transcription coupled repair (TCR). GGR encompasses damage recognition in the non-coding parts of the genome, in silent genes, and in the non-transcribed strand of active genes [19]. TCR ensures that the transcribed strand of active genes is repaired with higher priority than the rest of the genome, by using stalled RNA polymerase II (RNAPII) as a lesion sensor [19,24]. Prolonged stalling of RNA polymerases at lesion sites results in p53-dependent and -independent apoptosis, and are thus highly cytotoxic if the damage is not repaired [25–28]. Once the damage is recognised via one of these processes the remainder of the repair process follows a convergent pathway (Fig. 2).

2.1. Disorders directly associated with NER

The importance of the NER pathway is very evident in the rare autosomal recessive disease xeroderma pigmentosum (XP). Individuals with XP have diminished NER activity, which results in up to 1000 times greater susceptibility to develop uniformly distributed melanomas and nonmelanoma skin cancers (NMSCs) [29,30]. XP consists of seven distinct subgroups, named XPA through to XPG. Each complementation group refers to the presence of a causative mutation in one of the XP genes involved in NER (depicted in Fig. 2) and has a differing level of NER activity. Treatment options for XP patients with malignancies are very limited. Platinum-based therapies rarely show any response and are not usually administered, the exact cause of this resistance is currently not known but there is recent evidence that altered NER may play a role [31–33].

2.2. NER and platinum-therapy resistance

Due to the integral role NER plays in detecting and initiating a response to platinum-based DNA damage, many studies have focused on quantifying each individual NER protein in relation to cisplatin sensitivity and/or resistance. The majority of studies have quantified mRNA or protein levels of NER components in relation to cisplatin response in a variety of tumour types, whilst cell lines deficient in NER proteins have also been utilised to achieve this goal with surprising results. Clinical trials investigating the clinical utility of NER protein levels, particularly ERCC1, for predicting cisplatin response have produced variable results. The current understanding of each NER protein in cisplatin sensitivity and resistance in carcinomas is outlined below and summarised in Table 1. The NER pathway can be split into DNA damage recognition (global genome repair, transcription coupled repair), DNA unwinding and DNA incision. The components of all these have been investigated in cisplatin response studies, as outlined below.

3. DNA damage recognition

3.1. Global genome repair

GGR is responsible for recognising helix-distorting DNA damage on the non-transcribed strand of actively transcribed genes and inert non-coding regions of the genome. It is particularly important for detecting replication forks blocked by DNA damage which result in mutations and chromosomal aberrations [34]. GGR is comprised of several proteins that work in concert to detect DNA damage and initiate the remainder of the NER pathway. XPC initially recognises the damage [35], then the damaged DNA binding (DDB) complex consisting of DDB1 and DDB2, are recruited to facilitate binding of XPC to the site of damage and recruitment of the TFIIH complex [36–38] (discussed in detail below).

Several studies have identified a strong correlation between reduced XPC mRNA and protein levels and increased resistance of cancer cells to cisplatin treatment [31,39–41]. The most important