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The DNA damage induced immune response: Implications for cancer therapy

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ABSTRACT

Genomic instability is a hallmark of tumourigenesis, influencing tumour development and progression. In particular, defects in the DNA damage response (DDR) have been extensively investigated and are known to shape therapeutic response. Since immune checkpoint blockade (ICB) therapy has been approved for treatment of tumours with defective mismatch repair the interplay between DDR pathway deficiency and the immune system has been of particular interest. The cGAS/STING signalling pathway has recently emerged as a key mediator of inflammation in response to DNA damage. This was identified through transcriptional profiling of BRCA1/2 deficient breast cancers and Fanconi Anaemia (FA) patient bone marrow, revealing a common transcriptional subgroup associated with BRCA1/2 and FA deficiency characterised by upregulation of innate immune signalling genes. Additionally, it is now apparent that the DNA damage arising from a multitude of DNA repair defects and DNA damage induced by some classical chemotherapies/radiation also has the ability to induce an innate immune response mediated by cGAS/STING activation. Here we review the role of intrinsic and extrinsic DNA damage in mediating immune activation and its context within tumourigenesis, as well as the potential therapeutic opportunities it represents for the treatment of cancer, such as combining DNA damaging agents with immunotherapies.

1. Introduction

1.1. DNA repair deficiency driven immune responses

The immune system is a powerful network of cells and proteins that function to protect the body against illness and infection caused by pathogens such as virus or bacteria. Equally, it acts as a constant surveillance system, ensuring that damaged/abnormal cells are destroyed and cleared to maintain physiological homeostasis. In the context of tumourigenesis, the concept of cancer immunosurveillance has been extensively debated since it was first proposed in the late 50’s, but it is now recognised that the immune system can indeed function to recognise and prevent primary tumour formation and contribute to the selection of immune evasive cancers through immune editing [1,2]. More recently, the complexity of the interaction between the tumour and the immune system, and the importance of the tumour microenvironment (TME), has become evident and it is now acknowledged that immune cells and inflammation play roles in tumour proliferation, migration and survival, representing a key hallmark of cancer [3].

The tumour microenvironment is infiltrated with several types of immune cells, such as B cells, T cells and NK cells; and the immune response against tumour formation and progression is a result of competing inhibitory and stimulatory signalling pathways. Under normal circumstances, the immune system ensures that cells are protected against infection and tumour development, however tumour cells have evolved many strategies to evade immune surveillance. One of these strategies, is to upregulate the activity of inhibitory pathways by promoting the expression of negative regulators of the immune system, such as CTLA-4, PD-1/PDL-1, LAG3, TIM-3 and TIGIT, whilst inhibiting pathways/molecules that are responsible for stimulating the immune response, such as OX40, GITR, ICOS and CD40 [4]. Importantly, from a therapeutic perspective, as these regulators are surface molecules, their activity can be easily inhibited through the use of antibodies that prevent ligand-receptor interactions, which has led to the development of several immune checkpoint blockade (ICB) therapies. However, despite usually leading to more durable responses than classical therapies, it is now apparent that ICB therapy alone has a low response rate in most cancers and understanding the dynamic nature of checkpoint biology

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will be essential to develop the next generation of therapies [5].

Another hallmark of cancer, genomic instability, is tightly linked with immune surveillance and editing, with the high frequency of coding mutations occurring in genomically unstable tumours leading to the production of proteins that are not normally expressed. These potentially serve as novel antigens (neoantigens) that may be detected by the immune system [6]. Such neoantigens can be derived from single nucleotide variants (SNVs), insertions and deletions (Indels), gene fusions, frameshift mutations and structural variants, and can be presented on the tumour cell surface, and/or by dendritic cells, via MHC complexes, following cancer cell death, driving immune activation (Fig. 1) [7]. Although tumour cells widely express neoantigens through major histocompatibility complex I (MHC-I), it has more recently been appreciated that expression of MHC-II restricted neoantigens, more commonly found on professional antigen-presenting cells, also play a key role in the anti-tumour response, as well as impact immunotherapy responses [8,9]. Some of the first studies to demonstrate the causality between neoantigen presentation and an improved clinical response to immune checkpoint inhibitors targeting CTLA-4, PD-1 and PDL-1, were conducted in melanoma, non-small cell lung cancer and urothelial carcinoma, all tumours that harbour a high mutational burden [10–12].

Given the promising results obtained with immunotherapy in certain patients/tumour types, a plethora of studies have continued to focus on identifying reliable predictive biomarkers for response to immune checkpoint blockade therapy. PD-L1 expression on tumour epithelial cells and/or tumour-associated immune cells was among the first suggested biomarkers of response, with several studies indicating that its expression is predictive of response to anti-PD-1 therapy [13–15]. However, other studies have not found PD-L1 to be a reliable biomarker, as patients with no observed tumoural/immune PD-L1 expression can also benefit from anti-PD-1 therapy and vice versa [16–19]. Another widely assessed biomarker of ICB response is tumour mutational burden (TMB). Despite showing initial promising results in several tumour types, such as melanoma, lung cancer and urothelial carcinoma, subsequent studies have shown that in isolation TMB is not a reliable biomarker, as much like PD-L1 expression, many patients with a high

![Fig. 1. DNA repair deficiency driven sensitivity to immune checkpoint inhibitor therapy.](https://example.com/fig1.png)

Defects in DNA repair pathways, such as those in BER, MMR, HR/NHEJ and NER, may lead to accumulation of mutations within the cancer cell genome. A proportion of these mutations occur within coding regions and may be expressed as mutant proteins. Mutant proteins may be processed via the MHC-I antigen presentation pathway leading to presentation of neoantigens on the cancer cell surface. Additionally, defects in these DNA repair pathways may also lead to accumulation of cytosolic and/or micronuclear DNA fragments leading to cGAS/STING pathway activation (summarised in Fig. 2). This results in a Type I interferon response resulting in cytokine driven immune cell recruitment and inflammation. Simultaneously, Type I interferon responses also result in upregulation of immune checkpoint proteins such as PD-L1, resulting in inhibition of T-cell mediated cancer cell killing. However, in response to immune checkpoint inhibition, e.g. α-PD-L1 therapy, concurrent activation of the cGAS/STING pathway and neoantigen presentation may lead to enhanced T-cell mediated cancer cell death.
TMB do not benefit from ICB therapy and vice versa [12,18,20–24]. Whilst other biomarkers, such as high levels of microsatellite instability (MSI), density of tumour infiltrating lymphocytes (TILs) and mutations in certain genes have been linked with response to ICB, the majority of these markers alone remain insufficient to stratify patients for therapy [25–30].

In addition to promoting tumourigenesis, DNA repair deficiencies can also represent a therapeutic opportunity to target cancer cells. The use of PARP inhibitors in homologous recombination (HR) defective tumours is an excellent example of how such defects can be exploited therapeutically [31,32]. Similarly, patients with mismatch repair (MMR) deficient colorectal tumours were the first to be shown to have significantly improved responses to an anti-PD1 antibody (Pembrolizumab) [29]. Once established that other solid tumours with microsatellite instability/defective MMR were also susceptible to PD-1 inhibitors, the US Food and Drug Administration (FDA) approved the use of anti-PD1 therapy based on this biomarker, regardless of the histologic origin of the tumour, leading the way towards a treatment based on molecular profiling rather than tumour type [33]. Since then, DNA repair deficiencies have been extensively studied to identify possible associations between the DNA damage response (DDR) and response to immunotherapies. HR defects, particularly mutations in BRCA1/BRCA2, have been associated with increased sensitivity to ICB therapy in several tumour types, such as pancreatic, prostate and melanoma [34–37]. Additionally, mutations in these key HR genes were shown to result in elevated neoantigen load, higher levels of TILs and increased expression of PD-1/PDL1 in ovarian cancer [38]. Furthermore, mutations in DNA polymerases POLE and POLD1, which have essential roles in DNA replication, DNA synthesis during nucleotide and base excision repair, and cell cycle control, have shown promising results as predictive biomarkers of ICB therapy and ongoing trials are now recruiting patients whose tumours harbour mutations in these genes in order to further confirm their potential [39,40]. Mutations in other DNA damage signalling pathway components have also been linked to ICB response. Mutations in ATM, for example, have been reported in bladder and endometrial cancers, whereby the treatment of these patients with ICB resulted in increased overall survival (OS) compared to patients with ATM wild-type tumours [41,42]. This is suggested to be a result of a higher tumour mutational burden and neoantigen load, as well as increased immunogenicity [41,42].

Taken together, these observations suggest that tumours with deficiencies in DNA damage response pathways may be more susceptible to ICB therapy (Fig. 1) [43]. Nevertheless, there is a clear need to understand the mechanisms through which DNA repair defects contribute to this enhanced response to immunotherapies and to identify reliable biomarkers to stratify patients for appropriate treatment selection.

1.2. DNA damage induced cGAS/STING activation

Understanding the underpinning biology driving immunogenicity in cancer will be essential to unlock the full potential of immune checkpoint blockade therapies. In addition to the increased neoantigen load/TMB and TIL levels associated with DNA repair deficient tumours, the identification of a gene expression based molecular subtype of breast cancers, in which double strand break repair (DSBR) deficient tumours (enriched for BRCA1/2 mutant tumours) showed activation of the innate immune response, has shed light on an additional mechanism through which DDR deficiency (DDRD) may contribute to immune activation and response to ICB therapies [44]. This study, which aimed to identify a gene expression based molecular classifier for DNA repair deficient breast cancers, found that BRCA1/2 mutant breast tumours, as well as bone marrow from Fanconi Anaemia (FA) patients (harbouring mutations within various FA genes), could be identified via upregulation of innate immune signalling pathways, particularly genes classically associated with response to viral infection [44]. Importantly, upon investigating the key pathways driving the upregulation of the immune-related genes in cell line models, it was noted that loss of DNA repair genes e.g. BRCA1/2 could activate an innate immune response, characterised by upregulation of type I interferon response genes, such as CXCL10, CCL5 and IFNγ, independently of immune infiltration or neoantigen production [45]. Further investigation uncovered that S-phase specific DNA damage was responsible for driving this pheno-type, and that this response is dependent on the cGAS-/STING/TBK1/IRF3 anti-viral response pathway [45,46]. Within this anti-viral response, cytoplasmic dsDNA is bound by cGAS, which leads to the production of 2’3’ cyclic GMP-AMP (cGAMP), which in turn activates STING through induction of a conformational change [47]. Following this, STING is trafficked from the endoplasmic reticulum (ER) to the Golgi apparatus, where it recruits and interacts with TANK-binding kinase 1 (TBK1), which is responsible for activation of the interferon regulatory factor 3 (IRF3) transcription factor [48,49]. Activated IRF3 is then translocated to the nucleus where it induces the transcription of interferon stimulated genes (ISGs) and type I IFNs, leading to the production of cytokines, such as CXCL10 and CCL5 [50]. In the context of an intact immune system, induction of a type I IFN response also leads to the production of IFNγ by NK and T cells, consequently enhancing the production of cytokines such as CXCL10 and promoting an enhanced immune response. In turn, these cytokines drive the migration of circulating lymphocytes, in particular dendritic cells (DCs), B-cells, CD4+Th1 cells and CD8+ T effector cells, as well as tumour associated macrophages (TAMs) to the tissue (Fig. 2). As a consequence of this pathway’s activation, the microenvironment becomes infiltrated with immune cells, in order to mount an effective antiviral response. Another consequence of the type I interferon response is upregulation of immune checkpoint genes including PD-1, CTLA-4, LAG3, particularly on immune cells, to prevent auto-immune cell killing.

Interestingly, we and others have shown that in HR defective tumour cells, e.g. BRCA1/2 deficient cells, fragments of dsDNA, thought to be by-products of replication fork instability in a HR defective background, are exported to the cytoplasm, where they act as substrates for cGAS, leading to STING dependent innate immune activation [51–53]. Additionally, it has been shown that large chromosomal fragments induced either directly by DNA damage, or missegregated during mitosis as a result of persistent/unrepaired DNA damage, are encapsulated within micronuclei when the nuclear envelope reassembles after mitosis. cGAS accumulates within these micronuclei, leading to potent cGAS and subsequent STING activation upon micronuclei rupture, which can occur spontaneously or during a second round of mitosis [51–53]. In this context, intrinsic genomic instability leads to activation of the cGAS/STING pathway (Fig. 2). Additionally, cGAS/STING activation, and the associated interferon response, also leads to upregulation of immune checkpoint genes such as PD-L1, resulting in evasion of immune mediated tumour cell killing [5,53,54]. In addition to BRCA1/2, mutations in ATM, a key DNA repair protein, which results in Ataxia Telan-giectasia (AT), have also been shown to induce a type I interferon response, which is also due to cytoplasmic dsDNA mediated activation of the cGAS/STING pathway [55]. Additionally, ATM inhibition has been shown to promote cytoplasmic leakage of mitochondrial DNA, leading to activation of the cGAS/STING pathway, highlighting how different mechanisms can equally result in immune activation [56]. In a similar manner, mutations in SAVH1D1, which is responsible for maintaining centromeric DNA degradation at replication forks, have been shown to promote cGAS/STING activation and chronic inflammation, leading to the autoimmune disorder AGS (Aicardi-Goutieres syndrome) [57–60]. These and other studies, suggest that efficient DNA repair and replication fork protection appear to be essential, in order to prevent aberrant DNA processing and consequent export of DNA fragments into the cytoplasm, leading to persistent innate immune activation.

In addition to mutations in DNA repair genes that can cause abnormal repair and lead to the accumulation of cytosolic DNA that can
trigger cGAS activation, other endogenous mechanisms of activation of this pathway have been described, including mutations in STING itself, which have been observed in lupus-like syndromes and autoinflammatory disease SAVI (STING associated vasculopathy in infancy) [61].

In order to prevent a disproportionate inflammatory response and avoid chronic inflammation, cells have evolved several mechanisms of protection. The most apparent and simple of these, is the containment of self-DNA within the nucleus, which prevents cytosolic cGAS from accessing and binding DNA and from consequently activating the inflammatory pathway. Nevertheless, it has recently been shown that cGAS can also be found in the nucleus [62]. In order to prevent cGAS activation by self-DNA in the nucleus and during mitosis when the nuclear membrane is degraded, several groups have demonstrated that cGAS binds tightly to histones 2A and 2B, which prevents its interaction with nucleosomal DNA and therefore inhibits its catalytic activity [63–65]. Additionally, it has been suggested that cGAS can also suppress DNA repair within the nucleus and promote tumour development, so it is possible that cGAS nuclear function might also modulate the innate immune system, however this requires further investigation [66,67]. More sophisticated mechanisms to prevent erroneous activation of the cGAS/STING pathway and protect self-DNA have also been described. RPA and RAD51 have well-established functions in DNA replication and repair, binding ssDNA directly, promoting DNA repair and preventing excessive DNA degradation and export to the cytosol. In fact, it has been shown that RPA or RAD51 depletion alone enhances the accumulation of ssDNA in the cytosol, resulting in cGAS activation and driving a type I interferon response [68]. Additionally, RAD51 protects replication forks from excessive DNA degradation by Mre11, ensuring the process is tightly regulated in order to avoid DNA accumulation in the cytosol. Interestingly, as mentioned above, mutations in SAMHD1 can result in the production of type I interferons, which is driven by Mre11 exonuclease activity on stalled forks, highlighting the importance of keeping these processes finely tuned in order to avoid an abnormal proinflammatory signal [60]. Mre11 is not the only DNA nuclease with the ability to process nascent DNA at replication forks. Indeed, other fork processing nucleases, such as MUS81 have also been linked with cGAS/STING activation during tumourigenic transformation, leading to immune editing of earlier stage CINII prostate cancers [69]. Strikingly, in gastric cancer cells, it has been reported that MUS81 can indirectly promote the activation of the immune response through modulation of Wee1 expression via deubiquitination, a process that is still dependent on its enzymatic activity [70].

Inevitably, when ssDNA/dsDNA/mtDNA is generated, either as part of a cellular process or as a result of abnormal processing and it becomes accessible in the cytoplasm, the 3’–5’ activity of the nuclease TREX1 is responsible for its swift degradation, before cGAS activation occurs. In keeping with its major role in DNA degradation in the cytosol, mutations in TREX1 have been associated with many autoimmune diseases, such AGS and SLE (systemic lupus erythematosus) [71–73]. In mice, TREX1...
depletion has also been shown to result in an autoinflammatory phenotype, even in the absence of infection, reinforcing the important role of this nuclease in protecting the cell from erroneous innate immune activation [74–76]. In a similar fashion to TREX1, DNaseI also plays a role in preventing inappropriate innate immune signalling. DNA generated through apoptosis and the phagocytosis of maturing erythroblast nuclei, for example, is processed via DNaseI and in DNAseII deficient mice, the accumulation of self-DNA promotes the expression of cytokines and other immune genes in a STING dependent manner [77]. More recently, mutations in DNAseII that result in loss of its endonuclease activity, have also been reported in humans and have been shown to result in enhanced interferon signalling, suggesting this enzyme might also have an important role in protecting the cell from erroneously activating the inflammatory response [78].

Besides the tight regulation of processes involved in the generation and clearance of cGAS activating DNA, cGAS expression itself is controlled by different mechanisms, which include regulation by transcription factors, epigenetic modulators and miRNAs. Additionally, several post-translational modifications have been described in the literature, which have the ability to modulate cGAS activation/function, including ubiquitination, SUMOylation, phosphorylation and others, which are described in detail in a review by Liu et al. [79].

Taked together, these data highlight the extreme importance of recognising and adequately processing self-DNA to avoid over-stimulation of the immune system and prevent autoimmune disease.

1.3. cGAS/STING mediated immune activation through therapy induced DNA damage

Whilst the immune response via the cGAS/STING pathway to pathogens and intrinsic DNA damage has been relatively well characterised, only more recently has it become apparent that therapy induced DNA damage may also play a key role in the activation of the innate immune response. Indeed, early observations found that S-phase specific DNA damaging agents, such as cisplatin, could activate the cGAS/STING pathway through the generation of cytoplasmic dsDNA fragments [45]. Following this, it was noted that cGAS localises to micronuclei after exogenous exposure to DNA damage [51,53]. These micronuclei can be formed following induction of DNA double strand breaks, mitotic progression in the presence of unrepaired DNA, or chromosomal mis-segregation of DNA during cell division [51,52]. Once the cell cycle progresses through mitosis, these fragments of DNA are encapsulated within their own nuclear membrane, which, when ruptured, leads to exposure of the DNA to the cytosol, rapid accumulation and activation of cGAS and a STING dependent proinflammatory response [51–53] (Fig. 2). Subsequent studies are now focusing on elucidating the mechanisms linking therapy mediated DNA damage to cGAS/STING activation, as these will clearly impact future therapeutic strategies and potentially provide a rationale for combination therapies of specific DNA damaging agents and immune checkpoint inhibitors in tumours that do not respond to ICB therapy alone. Below, we will discuss some of the milestones achieved so far in more detail.

In 2012, a case report noted that a patient with melanoma showed regression of metastatic cancer at a distance from the irradiated site, following treatment with ipilimumab (a CTLA-4 inhibitor) and radiotherapy [80]. Further investigations revealed that this abscopal effect was accompanied by immune transformations, such as changes in peripheral-blood immune cells and increases in antibody responses to other antigens, suggesting that the addition of radiotherapy to treatment had the ability to induce global immune changes that may influence the response to immunotherapy [80]. Following this, a phase I clinical trial in metastatic melanoma evaluated the combination of radiotherapy and CTLA-4 inhibition showing major tumour regressions in a subset of patients, which could be recapitulated in a mouse model [81]. However, acquired therapeutic resistance was commonly observed and mainly attributed to high expression of PD-L1, highlighting how complex the interplay between tumour and tumour microenvironment can be [81]. Although several preclinical studies have evaluated different combinations of immunotherapy and radiotherapy, contrasting results have been reported. More data is therefore needed to determine what conditions promote a beneficial activation of the immune system, without concurrently triggering immunosuppressive mechanisms.

When classical chemotherapies were developed, it was not appreciated that the interplay between the immune system and the therapy in question could influence the patient’s response to these agents. However, it is now clear, at least in mouse models, that the presence of a functional immune system translates into a superior outcome in response to different chemotherapies [82]. The effects a chemotherapeutic agent can have in relation to the immune system can be broadly divided into three categories: 1) on target effects on cancer cells; 2) off target effects on immune cell populations; or 3) more broad alterations in body physiology that alter the immunosurveillance process. These effects have been discussed in greater detail by Kroemer et al. [83].

In some tumours, such as melanoma, NSCLC and renal cell carcinoma, highly encouraging results have been reported with the use of immune checkpoint blockade in isolation. However, in other tumours, which may be regarded as less immunogenic, such as breast cancer, the results of ICB alone have not been so positive. There has, therefore, been great clinical interest in combining cytotoxic regimens with ICB in an attempt to mediate conversion of immune “cold” tumours into “hot” tumours and thus potentiate the effects of ICB. The use of chemotherapy to induce sensitivity to ICB therapies has been observed in a variety of mouse models and positive results have now been observed in clinical studies as well [84]. There are now a large number of trials investigating such combinations in a number of diseases. However, many therapeutic combinations appear to have been selected somewhat arbitrarily, and perhaps pre-date our improved understanding of the ability of DNA damaging agents to activate immune pathways. Thus, in breast cancer, initial interest has focused on combinations of taxane-based chemotherapy with ICB, as seen in IMPassion130, which demonstrated a progression-free survival benefit for the combination treatment in metastatic TNBC compared with chemotherapy alone [85]. However, data from the TONIC trial, also in advanced TNBC suggested that anthracyclines may be the optimal agent for immune priming, as the best objective response to nivolumab was seen in patients pre-treated with doxorubicin compared to other agents including platinum agents [86]. This data is borne out in the early breast cancer setting by a number of trials which have evaluated the use of ICB in combination with chemotherapy in the neoadjuvant setting. Several studies, including KEYNOTE522 and Impassion031 have shown improved pathological complete response rates achieved by combining ICB with anthracycline-containing chemotherapy regimens [87,88]. In contrast, NeoTRIP, where the neoadjuvant chemotherapy did not contain anthracyclines, did not show an improved pCR rate where ICB was added to the chemotherapy backbone [89]. Taken together, these studies suggest that there remains a need to define optimal DNA damaging drugs, dosing schedules and agent sequences in the clinical setting to maximise the benefits of ICB. Furthermore, it is clear that improved predictive biomarkers are required to define patient populations likely to benefit from addition of ICB to their treatment regimens, as it has repeatedly been demonstrated in breast cancer that similar improvements in pCR rates with the addition of ICB are seen in both PD-L1 positive and negative patients (KEYNOTE522, Impassion031).

These studies, as well as ongoing studies in other tumour sites, show great promise for the development of new combination therapies that will enhance patient outcomes. However, as outlined above there remain some considerations to be addressed in a number of areas to maximise patient benefits.
2. Conclusion and future perspectives

It is now apparent there is a clear link between cellular DNA damage responses and the activation of the immune system. DNA repair deficiencies in pathways such as HR, as well as replication fork processing, have been shown to result in accumulation of cytotoxic DNA, triggering activation of the CGAS/STING pathway and promoting an inflammatory response. In addition, mounting preclinical and clinical evidence indicates that both radiotherapy and chemotherapy also have the ability to induce the immune system and promote pro-inflammatory responses, suggesting that the products of DNA lesions and lack of repair are the drivers of the immune phenotype observed. More importantly, if DDR inhibition and conventional therapies are capable of inducing an immune response in tumour suppressive microenvironments, then it is reasonable to infer that combination with ICB could drive a synergy capable of enhancing treatment efficacy, whilst minimising immunosuppression, overall improving patient outcomes.

Ongoing studies are continuing to evaluate the use of ICB with a number of combination therapies. However, as noted, there remains substantial work to be done in order to determine optimal choice of agents, dosing and scheduling to induce and maximise immune responses, and to identify validated biomarkers with clinical utility in the IO setting. This will be even more pressing in the face of the development of both novel immunotherapeutic drugs and new inhibitors of the DDR [90]. Furthermore, it is becoming clear that it is perhaps insufficient to evaluate the immunological effects of classical therapies in peripheral blood, as it is possible that intratumoral factors (such as the presence of utumoural factors) may in fact be more relevant in promoting the desired response. The design and development of clinical trials in this context will need to be underpinned by a sound biological rationale and incorporate significant translational science to enable the evaluation of both tissue and peripheral blood samples and allow a more comprehensive understanding of the tumour immune microenvironment during therapy. Such approaches will leverage the ongoing development and availability of more powerful tools, such as single cell omics.

In conclusion, it is anticipated that the incorporation of classical DNA damaging agents and novel DNA repair inhibitors in immunotherapy regimens will not only more frequently deployed in the clinic but will also be based on an improved understanding of tumour and immune biology, allowing a more precise and personalized medicine approach to cancer treatment.

CRediT authorship contribution statement

Eliana Barros: Writing – original draft preparation, Writing – review & editing. Stuart McIntosh: Supervision, Writing – original draft preparation, Writing – review & editing. Kianan Savage: Conceptualization, Visualization, Supervision, Project administration, Funding acquisition, Writing – review & editing.

Conflict of interest

The authors declare that there are no conflicts of interest.

Data Availability

No data was used for the research described in the article.

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References
