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PARP inhibitor combination therapy

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ABSTRACT

In 2014, olaparib (Lynparza) became the first PARP (Poly(ADP-ribose) polymerase) inhibitor to be approved for the treatment of cancer. When used as single agents, PARP inhibitors can selectively target tumour cells with *BRCA1* or *BRCA2* tumour suppressor gene mutations through synthetic lethality. However, PARP inhibition also shows considerable promise when used together with other therapeutic agents. Here, we summarise both the pre-clinical and clinical evidence for the utility of such combinations and discuss the future prospects and challenges for PARP inhibitor combinatorial therapies.

1. Introduction

The PARP (Poly(ADP-ribose) polymerase) family of enzymes utilise beta nicotinamide adenine dinucleotide (β-NAD^+) to covalently add Poly(ADP-ribose) (PAR) chains onto target proteins, a

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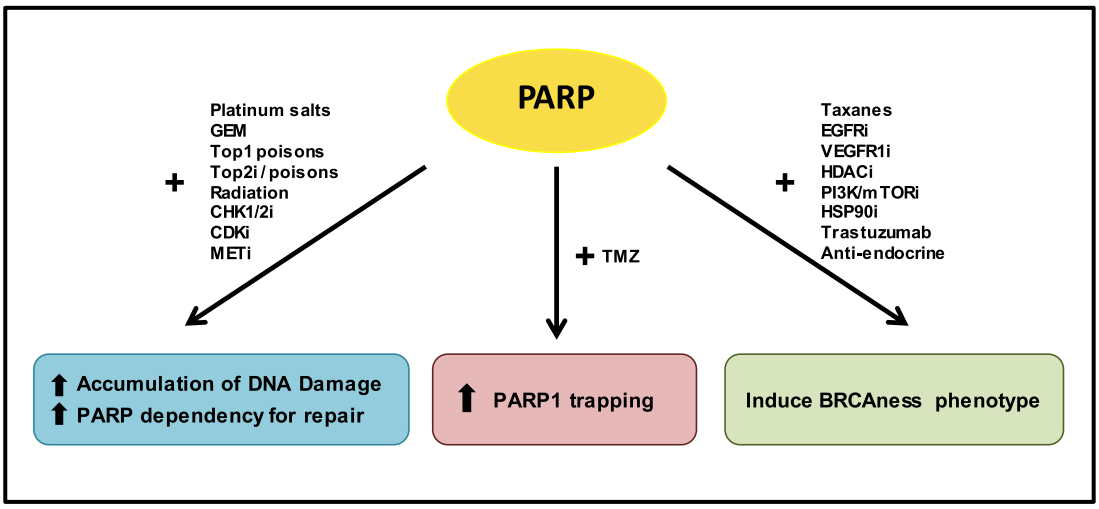

Fig. 1. Proposed mechanism for PARPi combinations therapy. Several agents are currently undergoing both preclinical and clinical evaluation in combination with PARPi. Combinatorial PARPi therapeutic rationale can be classified into three broad mechanisms: (1) increased accumulation of DNA damage and subsequent dependence on PARP-mediated DNA damage repair, (2) increased levels of trapped PARP-DNA complexes, and (3) induction of BRCAness phenotype to elicit PARPi/BRCAness synthetic lethality.

process termed PARylation (De Vos et al., 2012). This form of post-translational modification has the ability to alter the function of target proteins and has been found to be involved in a diverse set of cellular processes including chromatin modification, transcription regulation, the control of cell division, Wnt signalling and the maintenance of telomeres (Gibson and Kraus, 2012). The best-studied PARP enzyme is PARP1, which has a well-established role in the repair of damaged DNA (reviewed in (De Vos et al., 2012)). As part of this role, PARP1 is involved in the repair of single stranded DNA breaks (Woodhouse et al., 2008), but has also been implicated in the repair of other DNA lesions (Krishnakumar and Kraus, 2010). PARP1 binds to damaged DNA via a series of Zinc finger domains, and then PARylates a series of DNA repair effector proteins, releasing nicotinamide as a by product (Krishnakumar and Kraus, 2010). Subsequently, PARP1 autoPARylation causes the release of the protein from DNA (De Vos et al., 2012).

The role of PARP1 and the related enzyme PARP2, in DNA repair, prompted the development of potent small molecule PARP1/2 inhibitors (PARPi) (reviewed in (Zaremba and Curtin, 2007)). Their original proposed use was as chemo- or radiosensitizing agents. Indeed, as early as the 1980s, a toolbox PARP superfamily inhibitor, 3-aminobenzamide (3AB), was shown to enhance the cytotoxic effect of the DNA methylating agent, dimethyl sulphate (Purnell and Whish, 1980). Classical structure activity relationship-based drug discovery efforts led to the discovery of the first set of clinical PARPi to enter clinical trials; rucaparib (AG014699, PF-01367338/Pfizer), veliparib (ABT-888/Abbott Pharmaceuticals), olaparib (AZD2281, KuDOS/AstraZeneca, now marketed as Lynparza), and niraparib (MK-4827, Merck/Tesaro) (recently reviewed in (Lord et al., 2015)). In general, these inhibitors tend to have PARP1 IC_{50} (the drug concentration needed to kill 50% of a cell population) values in the nanomolar range, but more recently, a second generation of more potent PARPi with picomolar PARP1 IC_{50} values, such as talazoparib (BMN 673, Biomarin/Medivation) have been developed (Shen et al., 2013). Each of these small molecule inhibitors impairs the catalytic activity of PARP1 by interacting with the β-NAD^+ binding catalytic domain. However, there are distinct differences in other aspects of their function. For example, recent work has suggested that the cytotoxicity caused by PARPi is in part caused by PARP1 being "trapped" on DNA by PARPi (Murai et al., 2012), a likely consequence of impairing PARP1 autoPARylation. It seems that whereas

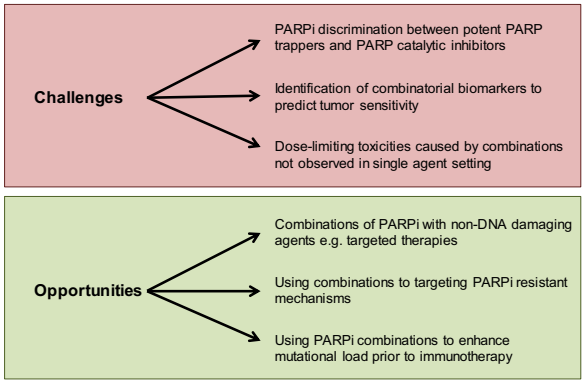

Fig. 2. Challenges and opportunities for PARPi combinations. Though PARPi therapy holds enormous potential as a targeted therapy, challenges for optimising its use within a combination context remain. Principally, these challenges are reclassification of PARPi agents to distinguish between PARPi trappers and PARP catalytic inhibitors, identification of predictive biomarkers for each combinatorial approach, and avoidance of creating conditions for new DLTs. That being said, if these challenges are met, enormous opportunities remain for PARPi combinations to generate a profound and sustained anti-tumour response within the clinical setting.

drugs such as talazoparib and olaparib are effective PARP1 trapping agents, veliparib has considerably less trapping activity (Murai et al., 2012, 2014b) (Figs. 1 and 2)

Although clinical PARPi were developed with a chemo- or radiosensitisation role in mind, their utility as single agents has overtaken this effort. PARP1/2 inhibitors can selectively target tumour cells with defects in either the *BRCA1* or *BRCA2* tumour suppressor genes that normally maintain the integrity of the genome by mediating a DNA repair process, known as homologous recombination (HR) (recently reviewed in (Lord et al., 2015)). This "synthetic lethal" effect of PARPi is likely caused by PARPi causing a persistent DNA lesion that is normally repaired by HR; in the absence of BRCA gene function and HR, tumour cells seem unable to effectively repair these DNA lesions and die, whilst normal (non-tumour) cells are unaffected (Bryant et al., 2005; Farmer et al., 2005). The effectiveness of PARPi in being able to selectively target BRCA mutant tumour cells in pre-clinical model systems (tumour cell lines and animal models) was reflected in clinical trials where significant and sustained anti-tumour responses were observed in