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PARP inhibitors: staying on target?

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Successful Phase III trials with Poly-ADPribose (PARP) inhibitors will have implications for stratified cancer therapy. In the current issue, Knezevic et al demonstrate that the existing collection of PARP inhibitors each display distinctive protein interaction profiles, reaching beyond their intended therapeutic target, with implications for metabolic and other disease.

The contest to provide efficacious and tolerable inhibition of Poly-ADPribose-transferases (PARPs) within the oncology setting is gaining momentum. PARP inhibitors, such as olaparib and veliparib, are either FDA approved for monotherapy against breast cancer or are currently in Phase III trials. However, PARP inhibitors may also be useful in the fight against other cancers including those affecting the ovary and prostate, since they block DNA repair to induce synthetic lethality in rapidly-dividing tumor cells. Just as not all cancer cells are equal, the same can be said it seems for PARP inhibitors. On Pages **XXX-XXX** of this issue, Knezevic et al (1) demonstrate that PARP inhibitors display additional effects beyond their simple blockade of PARP. By hitting secondary protein targets in a range of organelles, PARP inhibitors may provoke metabolic responses, influencing a wide range of homeostatic cell functions and potentially whole body metabolism (**Figure 1**).

First identified in 1963 (2) PARP enzymes were largely overlooked until the turn of the last century when their potential value in the treatment of BRCA1/2 breast and prostate cancers emerged (3). Upon DNA damage, PARPs catalyze ADP-ribose transfer to nuclear proteins, using nicotinamide adenine dinucleotide (NAD⁺) as a substrate. This highlights areas of damaged DNA, leading to recruitment of DNA repair complexes vital for sustaining cell viability.

PARP inhibitors represent a class of chemotherapeutics derived from nicotinamide analogues, the building blocks for NAD⁺, which in addition to DNA repair is also involved in hundreds of biochemical reactions as a co-enzyme. Thus, highly mobile small molecules with nicotinamide binding capacity, such as the emerging PARP inhibitors, may exhibit a broad range of effects and interactions, each one personalised and mediated by their alternative chemistries. Perhaps unsurprisingly, PARP inhibitors have shown variable responses in clinical trials, with some being more effective than others depending on the breast cancer subtype (often referred to as 'BRCAness').

Although PARP inhibitors share similar efficacy towards PARP1/2, there is clear disparity between their effects upon cell viability and sensitivity to DNA damage. Existing methodologies such as *in vitro* shift assays have shown limited ability to derive information on novel PARP inhibitor-protein interactions. To truly get to the

bottom of these *in vivo* observations, and inform human therapeutic use, Knezevic et al have employed unbiased LC-MS/MS based proteomic approaches to capture a global picture of the 'PARP inhibitor interactome' for each of the main inhibitors (niraparib, olaparib, rucaparib and veliparib). Through peptide analysis, they identified in excess of 1,200 proteins as potential PARP inhibitor binding partners. Future utilisation of this methodology may reveal the components of PARP multi-protein complex formation in differing models of oncogenic progression.

Importantly, these interactomes provide unique insight into the divergent effects of the PARP inhibitors. Rucaparib exemplifies PARPi interaction diversity by binding the endoplasmic reticulum (ER) luminal NADP⁺ dependent Hexose-6-Phosphate Dehydrogenase (H6PDH) and the cytoplasmic NAD⁺ dependent Inosine-5'-monophosphate dehydrogenase 2 (IMPDH2). Indeed, IMPDH2 was bound by all four PARP inhibitors examined, whereas H6PDH bound only one. Along similar lines, niraparib binds the mitochondrial enzyme ferrochelatase (FECH) and deoxycytidine kinase (DCK), a nuclear enzyme important for guanine synthesis. Indeed, the interaction of niraparib with DCK is the first identification of a kinase being inhibited by a PARPi.

The interaction of rucaparib with H6PDH is of particular relevance to both cancer and metabolism research. H6PDH has been shown to be an enzyme intimately linked to ER redox regulation and glucocorticoid metabolism and activation as part of an ER-specific pentose phosphate pathway. Mice lacking H6PDH display abnormalities in glucocorticoid metabolism in many tissues, as well as a progressive skeletal myopathy that is associated with the induction of ER stress, unfolded protein responses and apoptotic signals in glycolytic type IIb fibres (4,5). To date, the mechanistic link between sarcoplasmic reticulum stress and H6PDH has not been fully reconciled, but insight can be garnered through the present studies. The take home message from this is that H6PDH inhibition may be a useful target to limit cellular proliferation, as silencing H6PDH in CAL-51 breast cancer cells can induce apoptosis, further sensitizing cells to PARP inhibition. Any potential side effects would be offset by the benefits of sensitization to the PARPi.

Clearly, there is a propensity for PARP inhibitors to interact with a range of NAD(P)(H) binding proteins. Indeed, PARP inhibition could have the effect of influencing cellular NAD⁺ and ATP levels, impacting upon mitochondrial oxidative phosphorylation and whole body energy metabolism, though what this means for the cancer cell *versus* the non-cancer cell are unclear (**Figure 1**). PARP inhibitors do not directly interact with NAD⁺-dependent sirtuins, important sensors of a cells metabolic set point, that when activated by NAD⁺ can augment energy metabolism through

post-translational protein deacetylation and activation of adaptive transcriptional programs. However, this does not necessarily preclude an indirect effect of PARP inhibitors on sirtuin expression and activity. Indeed, PARPs have a high affinity for NAD⁺ and modulation of their activity may plausibly influence sirtuin access to the co-enzyme. IN support of this previous by Bai *et al* demonstrated that PARP inhibition increases NAD⁺ availability, enhancing sirtuin 1 activity and PGC1 α -mediated mitochondrial biogenesis (6). Notably, different members of the sirtuin family display both oncogenic and tumor suppressive features. By virtue of sparing NAD⁺, PPAR inhibitors could therefore have far-reaching effects on cell function, extending beyond each PARP inhibitor-interactome and into organelles beyond the nucleus.

The identification of extra-nuclear interactions creates new opportunities for human therapy with the PARP inhibitors, but also raises a new set of questions regarding the exact mechanisms underlying their activity, particularly when used as anti-cancer drugs. While specificity is a desirable attribute, many drugs demonstrate off-target effects that can either be useful or harmful. Drug safety and efficacy requires that we first understand molecular targets and any impact upon the cellular compartment they are localized to. Indeed, the enzymes shown here to interact with PARP inhibitors may prove to be fruitful future treatment targets for other cancers and metabolic diseases. Thus, the present work establishes PARP inhibitor-specific interactomes. These require detailed scrutiny when considering the utility of these PARP inhibitors in ‘targeted’ treatment of cancer and other diseases.

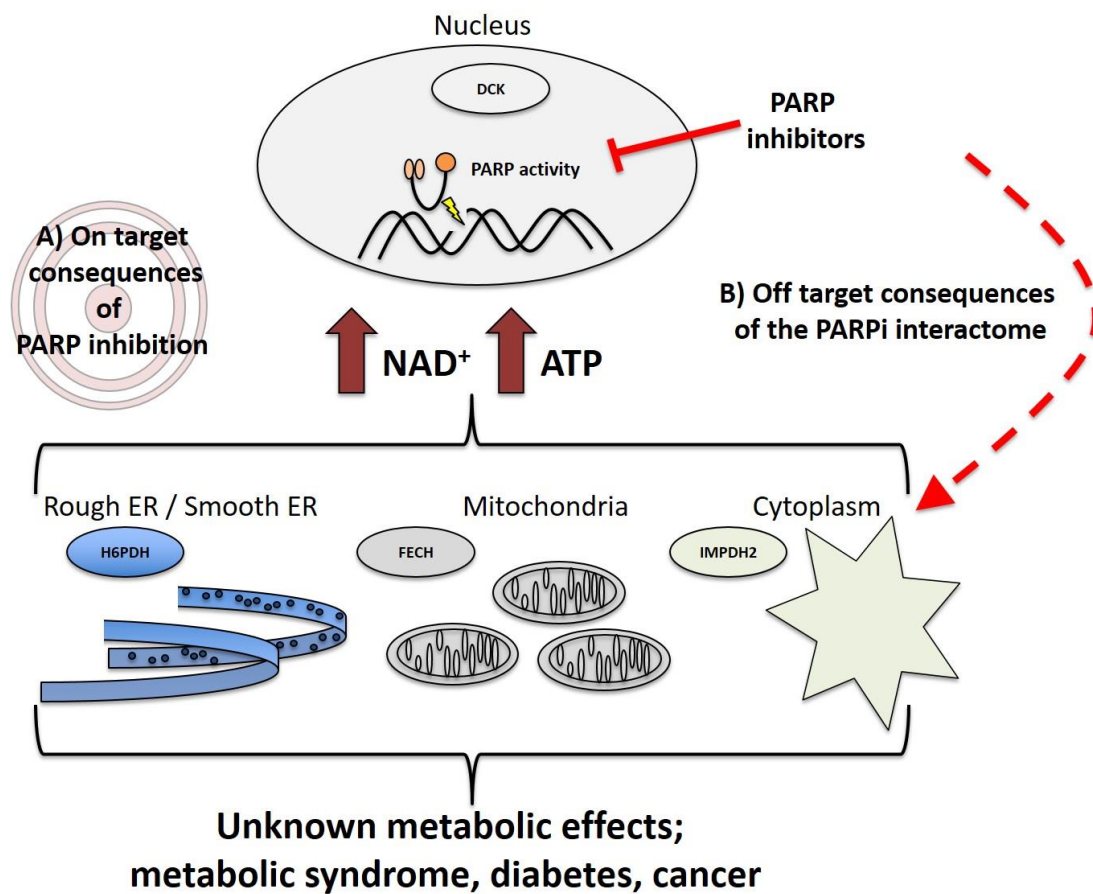


Figure 1. PARP inhibition staying on target? : PARP inhibition may have far reaching effects. A) Inhibition of PARPs increases cellular NAD^+ and ATP, resulting in changes in glycolysis, lipolytic and TCA cycle rates. B) The PARP inhibitors rucaparib and niraparib have their own individual interactomes with proteins outside the nucleus.

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