Editorial

Personalised treatment for prostate cancer patients: are we there yet?

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Prostate cancer (PCa) is an extremely heterogeneous disease—a small proportion of patients present with rapidly progressing, aggressive disease, referred to as unfavourable-risk PCa; whilst more commonly the disease progresses far more slowly and does not present an immediate health risk (1). This latter category, known as favourable-risk PCa, is not typically treated through intervention—instead, the recommendation for favourable-risk patients is monitoring via active surveillance (AS) (2). Generally, AS strategies are effective (3), although long-term surveillance studies have demonstrated PCa progression, in the form of disease grade reclassification (GR), in around 25% of cases by 10 years post-diagnosis (4,5). This GR risk is increased further in those of African-American race or advanced age (5,6). This propensity for PCa to progress during AS in some patients but not others, and particularly the association of GR with a particular ethnic group, suggests that underlying genetic factors may be important in disease progression, even in favourable-risk cases. Interrogating this heterogeneity provides a promising route to further stratify patients by their risk of disease progression, to better inform clinical assessment and lead to personalised treatment options.

ATM (ataxia-telangiectasia mutated), *BRCA1* (breast cancer 1) and *BRCA2* (breast cancer 2) are core components of the homology-directed repair pathway, one component of the DNA damage response—a simplified depiction is provided in *Figure 1*. ATM, a serine/threonine kinase, detects DNA damage and co-ordinates the cellular response by enabling numerous key damage-response pathways such as apoptosis and homology-directed repair (*Figure 1A*) (7-9). BRCA1 activates processes of homologous repair by recruiting effectors such as MRN and PALB2/BRCA2 (*Figure 1B*) (8,10). BRCA2 is a DNA-binding protein which contains a number of RAD51-binding repeats, allowing RAD51 localisation and filament formation for strand invasion (*Figure 1C*) (8,11).

As one may predict given their importance in genome stability, *ATM*, *BRCA1* and *BRCA2* are known tumour suppressor genes, and their involvement with PCa is well supported (12-14). Particularly notable when considering sources of PCa heterogeneity, germline mutations in this three-gene panel have been specifically linked to aggressive and castration-resistance PCa cases and most recently by Na *et al.* (14), who demonstrated that germline mutational status was predictive not only of disease aggression, but also age of PCa-specific death and time to death after diagnosis.

Utilising this three gene panel, Carter *et al.* (4) set out to investigate whether it was possible to predict progression in favourable-risk PCa patients during AS. A cohort of 1,211 patients total was assembled, from the Johns Hopkins and North Shore Health Systems. Over the course of the study, on average 4 years at follow-up, GR was observed in 289 (23.9%) patients. *BRCA2* mutation was significantly (P=0.03) associated with GR in six of eleven carriers. Neither *ATM* (P>0.99) not *BRCA1* (P=0.3) mutational status alone significantly associated with GR. When analysing the data in terms of a three gene panel, mutation in any one gene was associated with GR occurrence (P=0.04). Relative risk estimates calculated that patients carrying a germline mutation in either *ATM*, *BRCA* or *BRCA2* are

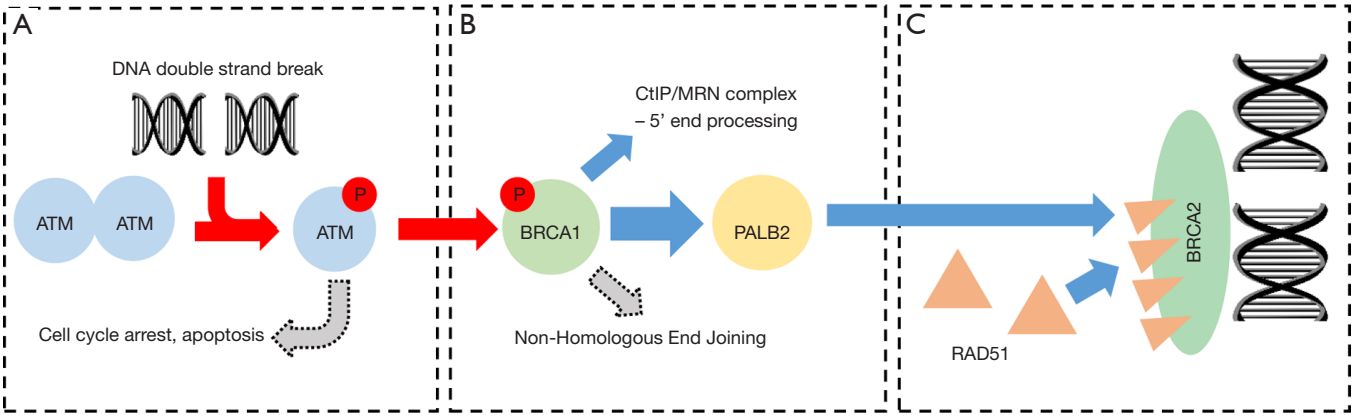

Figure 1 The role of ATM, BRCA1 and BRCA2 in homology-driven DNA damage repair. (A) Upon detection of a double strand break in DNA, multimerised ATM is autophosphorylated, triggering dissociation. In the active monomer state, ATM phosphorylates numerous effector proteins for differing damage responses (7); (B) phosphorylated BRCA1 recruits effector proteins to the DNA. In particular, the MRN complex is recruited to resect the 5' end of DNA at the break site, while PALB2 (Partner and Localizer of BRCA2) recruits BRCA2 (8). Alternately, BRCA1 may activate Non-homologous end joining to repair damage via an alternate pathway; (C) PALB2 recruits BRCA2 to the site of the DNA break. BRCA2 contains eight RAD51 binding sites, facilitating large numbers of RAD51 monomers to be brought to the site. This creates an environment which promotes RAD51 filament formation and strand invasion to complete homology-driven recombination (8). Red arrows, phosphorylation events. Blue arrows, recruitment. Grey arrows, alternate pathways. P, phosphate groups.

approximately twice as likely to undergo GR during AS.

The conclusion drawn by Carter *et al.* is that mutations in the three gene panel are predictive of GR in patients during AS, and indeed this is supported by the data presented. That said, an alternative interpretation is that *BRCA2* germline mutations alone are associated with GR, as the other members of the panel do not appear to be more frequently mutated in reclassified patients. It is important to point out that one limitation of the study, as noted by the authors, is the small number of carriers of mutations—only 26 patients carried a germline mutation in any of the selected genes. It is possible that these low numbers influenced results, as only five and ten patients carried mutations in ATM and BRCA1 respectively. To build on the groundwork laid by this study for understanding GR in patients, it will be important to expand the patient base considered to confirm specific mutational backgrounds facilitating progression.

Interestingly, *BRCA2* mutation was also significantly (P=0.01) associated specifically with severe changes in grade group (from group 1 to group 3 or higher). Indeed, patients carrying a *BRCA2* mutation were at a five-fold greater risk of severe GR versus non-carriers. In comparison, severe GR was only 2.5 times more likely in patients carrying a germline mutation in the three-gene panel versus the general population. As such, one could conclude that, while the three gene panel is associated with GR during AS, *BRCA2* in particular is associated with larger scale GR. This is in agreement with current thinking on the role of *BRCA2* in PCa, as studies have previously shown a link between *BRCA2* mutation, earlier age of PCa diagnosis (15), and rapid disease progression (16,17).

Given the evidence presented both by Carter *et al.* and in other recent studies (14), there is a firm rationale for screening PCa patients before advising AS, especially those from at-risk populations with a family history of known or suspected *BRCA2* mutation. Not only would screening patients allow for better stratification to predict clinical outcomes, but it opens a clear window for the application of personalised medicine. In particular, the loss of DNA repair capacity creates the possibility of creating synthetic lethality in rapidly dividing cancer cells by inducing DNA damage. Traditionally, platinum-based compounds have been used to this effect—platinum forms adducts with DNA, distorting the double helix and triggering damage response (18). More recently, PARP inhibitors, which cause double strand break accumulation, have emerged as an alternative. Indeed, PCa patients carrying mutations in DNA damage genes have been shown to respond more favourably to treatment with Olaparib (a PARP inhibitor) in a phase 2 clinical trial (19). In particular, all patients who carried a *BRCA2* mutation responded well to treatment. Further, Olaparib has been FDA approved for treatment of ovarian and breast cancer

patients with germline BRCA mutations (20). Clearly, induction of DNA damage represents a viable strategy for precision targeting of cancers in which DNA repair genes are mutated.

A secondary objective of Carter *et al.* was to investigate germline mutations in 51 other DNA repair genes, of which none were found to significantly associate with GR. Once more however, this result may have been impacted by low number of carriers investigated. Potentially interesting genes such as *MSH2* and *MSH6*, both vital in DNA mismatch repair and reportedly present in 12% of patient tumours, have no germline mutations represented in the Carter *et al.* patient population (20). Another promising candidate progression-related gene is *XPC*, which is part of the nucleotide excision repair pathway, and variants of which are related to PCa risk (21). Here, *XPC* is only mutated in two patients, but both presented GR. It is fair to say, then, that DNA repair pathways outside of homology-directed repair have not been conclusively proven not to associate with progression in AS patients. As such, while screening for the three gene panel proposed here may provide clinical utility, it would be a worthwhile endeavour to re-investigate alternate DNA repair pathways in a larger cohort.

Carter *et al.* take some notable steps towards addressing the presently unanswered question of why PCa presents so differently in different patients. Indeed, the authors provide compelling evidence of an association between their three-gene panel, in particular *BRCA2*, with GR during surveillance. This has potentially important clinical impact, as it adds weight to the growing suggestion that screening for underlying DNA repair mutations could assist in making informed therapeutic decisions to best address the needs of each specific patient. So, while we may not have arrived yet at a personalised approach for diagnosing and treating PCa patients, the study by Carter *et al.* and related recent studies on mutations in DNA repair genes shows a clear direction of travel going forward.

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Footnote

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