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Commentary

A strike against indolent neuroblastoma

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Neuroblastoma has extraordinary diversity in its presentation and clinical course, and prognosis is often associated with age of diagnosis. Younger children tend to have better outcomes, where spontaneous regression can be observed without any therapeutic intervention [1]. In contrast, indolent or chronic neuroblastoma in older children and adolescents is characterized by protracted disease that is refractory to chemotherapy [2]. Alterations of the chromatin remodeler ATRX are the most common recurrent event in this indolent clinical subtype, which is associated with overall poor survival and lacks effective therapies [3,4]. In this article of EBioMedicine, George et al. utilize an isogenic cellular system to screen for compounds that target ATRX-deficient neuroblastoma [5]. Their study sheds light on a promising therapeutic strategy consisting of a combination of olaparib (a PARP inhibitor) and irinotecan (a topoisomerase I inhibitor), both clinical compounds.

ATRX mutations were first identified in neuroblastoma in 2012 through genome sequencing efforts [3,4]. Approximately 30–40% of tumours in older children harbour ATRX alterations, half of which are point mutations leading to loss of ATRX product, and the other half comprise large deletions of the amino terminal chromatin binding modules creating an in-frame fusion protein [3,6]. ATRX plays a role in a myriad of nuclear processes, ranging from its role in histone variant deposition [7] to maintenance of genome stability. This includes the regulation of repetitive DNA such as pericentric and telomeric heterochromatin [7,8], G-quadruplex structures [9], and relevant to this study, various aspects of the DNA damage response [10].

To tease apart the specific impact of ATRX loss, George et al. undertook a strategy of generating an isogenic system whereby ATRX was knocked out by CRISPR-Cas9 genome editing in an ATRX wild type neuroblastoma cell line. While attempted knock out of ATRX alone failed to produce null clones (suggesting ATRX loss is detrimental in ATRX wild type neuroblastoma cells), removing TP53 concomitantly allowed the authors to create an isogenic cellular model for drug screening. Such a system is critical for studying ATRX-altered neuroblastoma, as the availability of ATRX mutant cell lines as well as patient samples remains limited. Furthermore, the use of an isogenic model ensures that effects of heterogeneous genetic backgrounds do not confound the output of a screen. With this tool in hand, the authors first demonstrated that ATRX deficiency results in increased DNA damage, defects in homologous recombination at telomeres, and impaired replication fork processivity. These findings are in keeping with previous reports in the developing forebrain where ATRX deletion leads to PARP and ATM activation upon the loss of replication fork protection by ATRX and subsequent cell death of neural progenitor cells [10].

With the characterized isogenic system in hand, George et al. performed a drug screen with a diverse set of over 400 compounds. Consistent with the above cellular phenotypes, they identified sensitivity of ATRX-deficient cells to ten compounds, five of which were DNA damage modulators, including each of the three clinical PARP inhibitors included in the screen. Sensitivity to PARP inhibition was further confirmed with siRNA knock down. Next, to explore drug combinations, the authors examined sensitivity to chemotherapy agents utilized in relapsed neuroblastoma patients and found that the combination of olaparib + irinotecan was more effective than single agent treatment in ATRX deficient cells, as well as in ATRX in-frame fusion neuroblastoma cells. This combination was further demonstrated to be effective *in vivo* through xenograft assays using an ATRX in-frame fusion PDX model.

Collectively, this study implicates a vulnerability of ATRX-altered neuroblastoma to defects in homologous recombination, revealing combination treatment of irinotecan and PARP inhibition as a potential new therapeutic approach that can be rapidly translated to the clinic. These findings are consistent with PARP inhibition as a synthetic lethality in other cancers with DNA damage repair defects, such as BRCA1/2-deficient tumours. Importantly, the combination of PARP inhibitor and irinotecan resulted in tumour regression and may be effective in other ATRX mutant paediatric cancers such as osteosarcoma and glioblastoma [7]. Whether this therapeutic combination would be beneficial for other indolent types of neuroblastoma, or in patients, remains to be seen. However, given the lack of therapies for ATRX-altered neuroblastoma patients who do not respond to chemotherapy, this study provides an alternative strategy that can be further explored clinically.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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