Editorial
Volume 7:3, 2022

Journal of Molecular Histology and Medical Physiology

ISSN: 2684-494X

Open Access

Signaling of Synthetic Lethality in Human Cells

Tomas Korski*

School of Medicine, Temple University, Philadelphia, Pennsylvania, USA

Editorial

The potential for this phenomena to be an efficient but also safe anti-cancer chemotherapy agent is what drives research investigations on synthetic lethality (SL) in human cells. Those involved in DNA repair appear to be the most pertinent of the variables that are targets for the induction of the synthetic lethality effect. Specifically, the alternative routes may present a promising target for the removal of aberrant cells when mutation in one of the conventional DNA double-strand break (DSB) repair pathways occurs, which is a frequent event in cancer cells. The current potential target for causing the effect of synthetic lethality is blocking RAD52 and/or PARP1 in tumour cells that are lacking in the canonical repair pathways. Unfortunately, the biggest challenge to developing a successful treatment strategy is the emergence of resistance to routinely used PARP1 inhibitors (PARPi). The POLQ gene's DNA polymerase theta (Pol) protein is essential for theta-mediated end joining, a different method of DSB repair (TMEJ). Because its blockage can cause SL, it is a prospective target in the treatment of malignancies with defects in homologous recombination repair (HRR). The authors of this review talk about the present understanding of Pol as a possible target for synthetic lethality-based cancer treatments.

Nearly a century ago, the phenomenon of synthetic lethality (SL) was initially identified and reported in Drosophila melanogaster [1]. Synthetic lethality can be defined as the ability of a redundant pathway B to maintain cell viability in the absence of process A. In cells lacking pathway A, pathway B can be inactivated or blocked, rendering both pathways inoperative and causing cell death. It took 85 years for it to be used for the first time in targeted cancer therapy [2,3]. The process of transforming it into a successful treatment programme took time. The Food and Drug Administration (FDA) has currently approved a number of commercially available medications that make use of this mechanism, including olaparib, rucaparib, niraparib, and talazoparib [4]. These are all poly (ADP-ribose) polymerase 1 inhibitors (PARPi), and their use in therapy has been successfully translated, mostly in conjunction with homologous recombination deficient (HRD) tumours, including both cancers with BRCA mutations and those that mimic them, known as BRCA-associated or BRCAness. It's interesting to note that there have also been a number of cases of ovarian cancer patients who relapsed after receiving PARPi but did not have these mutations. The downside of this approach is that cancer cells may become resistant to PARPi as a result of the reinstatement of the homologous recombination repair mechanism [4]. In order to find new synthetic lethal interactions that can be utilised to treat cancer that is resistant to treatment, scientists are continuing their study.

Recent research suggests that the POLQ gene, which encodes DNA polymerase theta (Pol), may be important in alternative DNA double-strand breaks (DSBs) repair pathways [5]. Pol is therefore thought to keep the genome stable, although its activity is linked to the development of cancer. As a result, cancer cells have increased Pol expression, which aids in their survival. However, the level of Pol expression in normal cells is either very low or nonexistent. The link between the HR and Pol genes is also synthetically deadly, as shown by silencing Pol in HR-deficient cells. Additionally, Pol depletion makes tumour cells more susceptible to conventional therapies like chemotherapy or radiation. Due to this Pol characteristic and its likely involvement in tumour PARPi resistance mechanisms, Pol is destined to become a new target in personalised cancer treatment.

The authors of this review focused on synthetic lethality in the context of anticancer medicines and described Pol and its function in DSB repair pathways. The authors underline Pol's potential as a target of this type of treatment in their concluding paragraph.

The most pertinent articles (published up until March 2022) on polymerase theta's function in synthetic lethality and prospective anticancer therapy were reviewed using Google Scholar and Indexed at. The in vivo and in vitro investigations on human and animal subjects, together with the clinical trials, were taken into consideration by the writers. Following keywords were used: Synthetic lethality, dual synthetic lethality, homologous recombination repair, anticancer therapy, microhomology-mediated end joining, DNA damage response, helicase, polymerase, DNA repair, and polymerase theta-mediated end joining (TMEJ).

Personalized anticancer therapy has the potential to improve therapeutic efficacy while reducing side effects. To do this, a therapeutic model based on the molecular biology of cancer as well as the clinical signs of a particular neoplastic disease is required. It remains a significant difficulty for both academics and doctors to pinpoint the components that a tailored therapy will focus on in various types of cancer. A promising strategy for treating human solid tumours with personalised medicine involves the use of carefully chosen inhibitors of DNA double-strand break repair proteins with the goal of inducing cell death based on the phenomena of synthetic lethality.

Initial success with PARP inhibitors like Lynparza has shown a promising course of treatment for some patients with cancers with BRCA1/2 mutations. Additionally, it has produced data that backs up the idea of DSB repair by causing synthetic lethality. However, these cancer forms inevitably develop medication resistance over time. Recent research has showed that cells lacking BRCA1, BRCA2, or Ku70, which are necessary for the classical DSB repair pathway, become dependent on Pol, indicating that Pol-dependent DNA repair processes serve as a backup. This discovery has increased interest in Pol as a potential new therapeutic target. New genes recognised as synthetic lethality partners for Pol include those involved in DNA damage repair, chromatin structure maintenance, and DNA metabolism. The pharmacological inhibition of Pol is expected to specifically kill TMEJ-dependent cancer cells. Furthermore, new research suggests that the activity of TMEJ with Pol mediation is the cause of secondary mutations that restore the function of BRCA1/2. In this instance, inhibiting Pol may stop the emergence of PARPi resistance. Beginning at the end of 2021, clinical trials for an anticancer medication from the class of Pol inhibitors will be conducted.

Conflict of Interest

None.

References

1. Beagan, Kelly, Robin L Armstrong, Alice Witsell, and Upasana Roy, et al. "Drosophila DNA polymerase theta utilizes both helicase-like and polymerase

***Address for Correspondence:** Tomas Korski, School of Medicine, Temple University, Philadelphia, Pennsylvania, USA, E-mail: Tomas_korski@temple.edu*

Date of Submission: 05 May, 2022; Manuscript No: jmhmp-22-73990; **Editor assigned:** 07 May, 2022, PreQC No: P-73990; **Reviewed:** 18 May, 2022, QC No: Q-73990; **Revised:** 25 May, 2022, Manuscript No: R-73990; **Published:** 31 May, 2022, DOI: 10.37421/2684-494X.2022.7.39.

domains during microhomology-mediated end joining and interstrand crosslink repair." *PLoS Genetics* 13 (2017):e1006813.

2. Dobzhansky, Th. "Genetics of natural populations. XIII. Recombination and variability in populations of *Drosophila pseudoobscura*." *Genetics* 31 (1946): 269.
3. Han, Kyuho, Edwin E. Jeng, Gaelen T. Hess, and David W. Morgens, et al. "Synergistic drug combinations for cancer identified in a CRISPR screen for pairwise genetic interactions." *Nat Biotechnol* 35 (2017): 463-474.
4. Lord, Christopher J and Alan Ashworth. "Mechanisms of resistance to therapies targeting BRCA-mutant cancers." *Nat Med* 19 (2013):1381-1388.
5. Wang, Zi, Yadong Song, Shibo Li, and Sunil Kurian, et al. "DNA polymerase θ (POLQ) is important for repair of DNA double-strand breaks caused by fork collapse." *J Biol Chem* 294 (2019):3909-3919.

How to cite this article: Korski, Tomas. "Signaling of Synthetic Lethality in Human Cells." J Mol Hist Med Phys, 7 (2022): 39.