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Editorial

Red Wine Polyphenol Resveratrol Reduces Breast Cancer Progression and PARP Inhibitor Olaparib Efficiently Enhances its Anti-cancer Action

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Breast cancer is regarded as the most common type of malignancy affecting women worldwide. In 2020, it became the most commonly diagnosed cancer, surpassing lung and other types of cancer [1]. Currently, the different breast cancer treatment options include chemotherapy, radiotherapy, and hormone therapy. But the cancer cells have devised ways to bypass the therapeutic effects of these treatment strategies [2]. Moreover, the chemotherapeutic drugs have been found to exhibit certain adverse effects, including high cytotoxicity, off-target effect, development of chemoresistance, and reduced bioavailability [3]. Hence, it is now imperative for the cancer biologists to conduct extensive research and develop novel chemotherapeutic regimens that will minimize the side effects and also effectively kill the breast cancer cells.

Presently, in cancer research, a combinatorial approach is being undertaken to develop new anti-cancer therapeutic strategies. In our laboratory, we decided to expose the breast cancer cells to a combination of two chemical agents: first, the cancer cells are treated with a DNA damaging agent, followed by treatment with a DNA repair inhibitor. After treatment with a DNA damaging agent, the DNA repair pathways are activated to reverse the DNA damage. But, if these drug-treated cells are exposed to a DNA repair inhibitor, then the DNA lesions are not repaired, resulting in apoptosis and breast cancer cell death [4].

While choosing the DNA damaging agent, it was important to use a chemical agent, which will specifically affect the cancer cells and not harm the normal cells of the body. We also wanted to employ a chemical agent, which can induce a particular type of DNA damage called double-stranded breaks (DSBs) in the DNA of the cancer cells, accumulation of which is considered to be extremely harmful for a cell. Hence, we chose Resveratrol (*trans*-3,4',5-trihydroxystilbene) as the DNA damaging agent, which is present in plant sources, such as grapes, berries, peanuts, etc. [5]. This polyphenolic compound is also present in red wine [6]. Previous studies have reported that Resveratrol possesses anti-cancer, anti-inflammatory, and antioxidant properties [7]. It has also been found that Resveratrol can generate DSBs in cancer cells [8], and cause activation of DNA repair pathways [9]. Among the different DNA repair pathways, there are two signaling cascades that execute resolution of DSBs: (1) homologous recombination (HR), and (2) non-homologous end joining (NHEJ). Of the two pathways, the HR repair pathway has been found to be the main DSB repair cascade. Multiple studies have shown that a defective HR pathway can have lethal effects on the cancer cells [10].

Next, we decided to use Olaparib, an FDA-approved PARP inhibitor, to block the DNA repair pathways in the cancer cells after Resveratrol treatment. The reason for choosing a PARP inhibitor is that Poly(ADP-ribose) Polymerase-1 (PARP-1) protein has been found to sense DNA damage and activate the DNA repair pathways [11]. Hence, PARP-1 inhibition can effectively block the DNA repair processes in the cancer cells. Moreover, previous studies have also reported a strong relationship between PARP-1 inhibition and HR pathway deficiency. HR-deficient cancer cells have been found to be extremely sensitive to treatment with PARP inhibitors [12]. But it is important to realize that the HR-deficient cancer cells can be

easily killed because a defective HR pathway cannot repair the DNA lesions caused by the cytotoxic drugs, resulting in accumulation of DNA damage, apoptosis and cancer cell death. On the other hand, when the HR pathway is functional, the DNA lesions can be successfully repaired, leading to cell survival. This is the reason why it is extremely difficult to kill HR-proficient cancer cells. Till date, not much research has been carried out to develop therapies to treat HR-proficient breast cancer. Hence, we decided to conduct an investigation to find out if Resveratrol + Olaparib combination treatment can effectively kill the HR-proficient breast cancer cells.

We carried out multiple biochemical assays to elucidate the mechanism of action of Resveratrol + Olaparib combination in inhibiting the aggression and proliferation of HR-proficient breast cancer cells. While performing the assays, it was found that Resveratrol efficiently induced DSBs in the cancer cells and then Olaparib enhanced the DNA damage by downregulating the HR pathway proteins. The combination treatment also inhibited PARylation of PAPR1, blocked PARP1 from interacting with BRCA1, and trapped PARP-1 at the site containing the DNA lesion. As a result of this combined drug exposure, the cancer cells were arrested in the late S/G2 phases of cell cycle, suffered apoptosis and finally cell death. These results were then validated in mice xenograft model system and cancer cells derived from breast cancer patients.

In summary, our research conclusively showed that Resveratrol + Olaparib combination exposure caused apoptosis in breast cancer cells by inducing extensive DNA damage and also blocking the HR pathway. Our research findings were published in Experimental Cell Research, Elsevier in 2022 [13]. We hope that our research work will surely help in the development of a novel anti-cancer therapy to treat HR-proficient breast cancer.

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