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Commentary

Pyroptosis in combinatorial treatment to improve cancer patients' outcome, is that what we want?

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The search to improve cancer treatment therapy is getting more and more attention from scientist year by year. Indeed, during the last decade, a big effort have been made to improve cancer patients' prognosis. One of the most frequent explored strategies in cancer is drugs combination. The appropriate drugs combination can improved significantly cell sensitivity to anticancer compounds helping to overcome therapeutic resistance in cancer. By combining two or more drugs the doses needed of each compound to effectively treat cancer can be reduce which can help to diminish undesired side effect and contribute to overcome cancer cell acquire resistance.

Drugs combination need to be well design because the interaction between compounds may not always be synergic, and in some cases it may compromise patients' safety [1]. In this context, in the last couple of year some software's have been developed to predict how drugs are going to interact when combined together [2]. Furthermore, commonly use cancer drugs have recently been tested in combination to others compounds in the intent to enhance its efficacy in causing tumor regression. Moreover, many new drugs have been developed and tested as new options for cancer therapy. Many of the recently discover anticancer drugs aimed to target proteins that are directly related to cell proliferation, such as Polo like kinase 1 (PLK1). PLK1 is a protein with kinase activity that play a role during cell cycle progression by regulating several step on mitosis. Due to its roles, many studies have explored the effect of PLK1 inhibition in cancer, and it is proved by now that lack of PLK1 function cause mitotic arrest and lead to cell death [3].

In an article published in *EBioMedicine,* Wu and colleagues showed that the combination of BI2536, a potent PLK1 inhibitor, is efficient to sensitize oesophageal squamous cell carcinoma (ESCC) cells to cisplatin (DDP) treatment [4]. They showed that the co-treatment of BI2536 and DDP causes a greater decrease on cell viability, G2/M arrest and cell death *in vitro*. The anti-proliferative and pro-apoptotic effect of BI2536 and DDP combination it is explain by them as consequences of an increase in DNA damage and an inhibition on DNA-damage repair. Moreover, the anti-cancer effect of the combinatorial treatment it was also proved efficient *in vivo* by a significant slower tumor growth. The molecular justification of the improved anti-tumor effect it is the triggering of pyroptosis, an inflammatory cell necrosis activated *via* BAX/caspase-3/GSDME. Indeed, Wu and colleagues showed an increased on cleaved caspase-3 when cells were co-treated with BI2536 and DDP, leading to an accumulation of GSDME around the cytoplasm that can be a direct cause for pyroptosis in ESCC cells. In addition, they showed that GSDME overexpression in ESCC samples is associated to patients' better prognosis and pointed out that PLK1 inhibition can strengthening DDP anticancer effect in those specific patients. This article point out the importance of drugs combination, and the results showed by them could have an impact on clinical practice in the near future.

BI2536 and DDP co-treatment have been previously shown by others in merkel cell carcinoma [5], medulloblastoma [6], gastric cancer cells [7] and balder cancer [8], however the molecular mechanism of action has never been shown before. One of most important challenges of BI2536 treatment is to control hematological toxicity, which has been the main reason to its limits use on the clinic, however its combination with other drugs allow a dose reduction which probably will decrease the undesired side effects. Furthermore, others PLK1 inhibitors have shown reduce side effect on patients' and similar anti-tumor effects when in combination to commonly use anti-cancer drugs such as DDP [6–8].

Although cancer cell death is one of the main goals of treatment, the mechanism of death must be considered once it will have implication on cancer patients' outcome. One of major challenge of BI2536 and DDP co-treatment is to understand the biological consequences on cells and the implication on patients` safety. According to Wu and colleague BI2536 and DDP combination in ESCC cause pyroptosis, which is a pro-inflammatory cell death type. The process of pyroptosis activation involves cellular swelling, the formation of pores on the cell membrane, membrane rupture, DNA fragmentation, and the release of cellular contents inducting an inflammatory response and causing toxicity to adjacent healthy cells leading to further cell death [9]. This cell death mechanism may not be the best for cancer patients, once that inflammation may contribute to the development and progression of malignancies [10]. Perhaps the amount of inflammation cause by pyroptosis activation by anticancer treatment is not great enough to induce cancer progression; however, the *in vivo* consequences for this cell's mechanism must be verify to predict if BI2536 and DPP co-treatment is an efficient option for cancer patients.

Several others studies are searching alternative way to improved cancer treatment, and many of them are exploring combination

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therapies. The biggest obstacle to find the perfect strategy for cancer treatment is to understand the interaction between drugs in a specific cell type to guarantee patient's safety and therapy eficiency. A big effort must still be made to fully exploit better ways to overcome cancer therapy limitation and to be able to predict precisely the consequences of drugs interactions.

Disclosure

The author declared no conflicts of interest.

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