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Reflexión

PARP1: a mechanism of resistance to drugs in pancreatic cancer

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Pancreatic cancer, the seventh leading cause of cancer death in both males and females in the world, shows only a 5% survival rate five years after diagnosis (1). This high mortality rate is due to the absence of symptoms that allow detecting cancer early, as well as to the absence of specific pancreatic cancer biomarkers. In fact, 50% of the patients develop metastasis, a clinical phase in which the chemotherapy is ineffective and the tumor rescission is limited (2,3). The drug most used in the clinical setting for several years has been Gemcitabine, although the survival rate is still maintained too low. Thus, other formulations that use several drugs to treat this type of cancer, such as FOLFIRINOX, the combination of nab-paclitaxel an gemcitabine or even the use of cisplatin and capecitabine, are being introduced into healthcare systems worldwide since it is able to increase the survival time in patients who are in advanced stages of cancer (4–6).However, there are many patients who are unable to benefit of the chemotherapy due to the rapid development of resistance on the part of the tumor cells (7). More than 165 genes related to drug resistance in pancreatic cancer has been identified which indicate the complexity of the problem. These genes are related to important processes such as the regulation of cellular antioxidant activity, apoptosis, cycle control and cell signaling (8). In addition, it is necessary to include the non-coding transcripts (ncRNA) possessing important regulatory functions in the cells. Within ncRNA, the miRNAs stand out which c are able to regulate 90% of the cell's gene expression, influencing such important processes as cell cycle regulation, invasion or tumor metastasis (9).Resistance phenomena in pancreatic cancer frequently trigger its recurrence by which the tumor reappearance after its elimination. This process may be associated with the presence of tumor stem cells (CSCs) which have a high capacity to withstand the treatments and are able to re-establish the tumor population. This new tumor is usually more resistant to pharmacological treatment and more invasive, ending normally with the life of patient (10). Although there are several mechanisms by which these cells have a high chemoresistance, three routes three ways have been highlighted: overexpression of ABC transporters, detoxifying enzymes and regulatory proteins of the apoptosis (11). This last pathway is related to a family of proteins called PARP.
Poly (ADP-ribose) polymerases (PARPs) are a family of proteins formed by 18 members that possess a conserved catalytic domain. Its enzymatic activity is based on the transfer of several units of ADP-ribose to certain objective proteins, which are related to processes at the cellular level such as the regulation of cell proliferation and programmed cell death. In addition, its two

main members (PARP 1/2) intervene in the process of DNA repair through the modification through its catalytic activity of factors responsible for the recruitment of proteins involved in the DNA repair process (12). Its structure is constituted by an N-terminal domain of DNA binding by Zinc fingers, a C-terminal domain that possesses catalytic activity and a central domain of self-regulation, capable of regulating enzymatic activity (13). Thus, during death Due to excess DNA damage, PARP1 is specifically proteolyzed by caspases to prevent PARP1-mediated rescue of the cell through efficient repair of the genetic material (14). In addition, PARP1 is overexpressed in pluripotent cells (such as tumor stem cells) and its correct expression is fundamental for the maintenance of the characteristics that they possess. Its operating mechanism is based on the use of NAD ^+ as a substrate to carry out the union of several units of ADP-ribose formed a chain called PAR (poly ADP-ribose) that can contain up to 200 units (15).

Given the great importance of PARP1 / 2 enzymes in the process of repair of DNA damage, several inhibitors have been designed capable of limiting their enzymatic activity. These could be used as possible methods to be used against not only with pancreatic cancer but different types of tumors (from liver, lung, hepatocarcinoma, ovary, skin, endometrium, etc.) where overexpression has been detected (16). Among these drugs, Olaparib, an inhibitor of PARP1 and PARP2 that induce cell cycle arrest (between S and G2 / M phases), has been used. It was approved by the FDA in 2014 for patients with ovarian cancer and mutations in BRCA1 and BRCA2 (17). Olaparib application in pancreatic cancer allows improve of the pharmacological effect of other drugs. In the clinical setting it has already begun to be stipulated as a possible alternative that allows an increase in the survival of patients suffering from pancreatic cancer. In fact, pancreatic cancer with BRCA1 and/or BRCA2 mutations (10% -12%) show a high activity of PARP for DNA repair (18). In these cases, PARP inhibitors can improve treatments. In fact, Olaparib administered to 23 patients with mutations BRCA1/2 after treatment with gemcitabine induced partial or complete response (21.7%) and stable disease (35%) in pancreatic cancer patients (19). However, other resistance mechanisms so could avoid damage caused by cytotoxic agents. There are many doubts about the usefulness of these agents for the treatment of pancreatic cancer (20). Meanwhile, new PARP inhibitors are undergoing treatment (niraparib, veliparib and rucaparib). The knowledge of the structure and action of PARP1 and PARP2 inhibitors may be one of the most promising ways to design new strategies for the treatment of pancreatic cancer.

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