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Repopulation of ovarian cancer cells after chemotherapy

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Abstract

The high mortality rate caused by ovarian cancer has not changed for the past thirty years. Although most patients diagnosed with this disease respond to cytoreductive surgery and platinum-based chemotherapy and undergo remission, foci of cells almost always escape therapy, manage to survive, and acquire the capacity to repopulate the tumor. Repopulation of ovarian cancer cells that escape front-line chemotherapy, however, is a poorly understood phenomenon. Here I analyze cancer-initiating cells, transitory senescence, reverse ploidy, and cellular dormancy as putative players in ovarian cancer cell repopulation. Under standard of care, ovarian cancer patients do not receive treatment between primary cytotoxic therapy and clinical relapse; understanding the mechanisms driving cellular escape from chemotherapy should lead to the development of low toxicity, chronic treatment approaches that can be initiated right after primary therapy to interrupt cell repopulation and disease relapse by keeping it dormant and, therefore, subclinical.

Chemotherapy in ovarian cancer has limited efficacy

Despite vast research efforts made over the past fifty years, the war against cancer remains to be won. Most of the improvement in overall patient survival is mainly a consequence of early diagnosis rather than due to better treatment approaches. We have made great progress in understanding the mechanisms driving carcinogenesis and cancer progression at the molecular level, which brought about the concept of targeted therapy designed to disengage a particular pathway, unique and essential for the survival of the cancer cells. Targeted therapy seemed ideal for eradicating cancer; however, its success in the clinic has been limited[1].

Hence in the treatment front, the war against cancer is still fought mainly with highly cytotoxic chemotherapeutic drugs that do not spare rapidly dividing non-cancer cells. Due to their toxicity, the amount of drug to be administered to patients is limited to the so-called patient-specific maximal tolerated dose. The drugs also have to be spaced to allow bone marrow recovery. Overall, removal of the tumor cells is not guaranteed, with many cancers recurring sooner or later, and the patients becoming cancer survivors rather than cancer cured.

Prospects are particularly disheartening in ovarian cancer. The disease is rare; yet, it represents the most deadly gynecologic malignancy with a five-year survival rate that has only improved nine percent in the past thirty years and a dismal overall survival rate that has remained stagnant for over fifty years (reviewed in[2–7]). Due to a lack of efficient early diagnostic tools, most patients are diagnosed when already symptomatic, with the disease progressing within the peritoneal cavity and beyond[8]. Patients undergo cytoreductive

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surgery, but due to the nature of the growths within the peritoneal cavity, it cannot guarantee total elimination of the disease since microscopic and sometimes even macroscopic residual tumors cannot be totally resected (reviewed in[9]). Surgery is followed by cycles of chemotherapy based on the combination of platinum and taxane agents[9,10]. Most patients respond favorably at first to this treatment, but the disease usually recurs within twelve to eighteen months with a platinum-resistant phenotype, leaving doctors with limited tools to maneuver within the available alternative chemotherapeutic armamentarium (reviewed in[2–4]).

Ovarian cancer cells escape chemotherapy

Platinum-derivatives are DNA cross-linking agents[11–14], whereas taxanes are microtubule stabilizers[15]. These drugs kill rapidly dividing ovarian cancer cells, and operate in a synergistic manner[16]; however, they also cause damage to normal tissues thus limiting their dosage. The main restraining factors for therapeutic dosage are renal toxicity, neurotoxicity, myelosuppression, and peripheral neuropathy (reviewed in[17,18]). To balance tumor-specific toxicity and unwanted side effects, the most common treatment regimen consists of six cycles, spaced every three weeks, of a taxane (e.g., paclitaxel) followed by a DNA platinating agent (e.g., cisplatin or carboplatin), which are given at the patient's specific maximal tolerated doses[9,10]. As a consequence of the required waiting periods between chemotherapeutic rounds, a largely overlooked phenomenon takes place: the repopulation of cancer cells between treatment intervals (reviewed in[19,20]).

The escape of cancer cells from chemotherapy was first attributed to the complexity of the circulation within the solid tumors, with an anarchic distribution of the newly-formed blood vessels, as a consequence of which drugs may not reach all cells within the tumor with an efficient toxic concentration[21]. The rationale given for in vivo repopulation, however, cannot explain why maximal tolerated doses and times of exposure of chemotherapeutic drugs tailored to treat monolayers of ovarian cancer cells in vitro do not kill the entire population of cells, leaving behind live cells with the capacity to recreate the culture[22,23]. The few cells that escape platinum-based therapy have the capacity to repopulate the culture at an accelerated pace[23], a concept known as accelerated repopulation[19]. Repopulation of cancer cells in culture cannot be attributed to the acquisition of resistance to platinum, because the cells need to be exposed to dose escalation for several months before developing the capacity to become refractory to clinically relevant doses of platinum[24].

Although the concept of cancer repopulation was coined from in vivo experience and involves solid tumor regrowth in between chemotherapy or radiotherapy intervals[19,25], it can be recreated in culture if cells in dishes are exposed to concentrations and exposure times reminiscent to those used in the clinic. Ovarian cancer patients are treated intravenously with a sequence of a taxane for three hours followed by a platinum-derivative for one hour. Under this regimen, the concentrations in circulation for the most standard taxane used, paclitaxel, do not reach beyond fifty to one-hundred nanomolar, whereas those for the canonical platinating agent cisplatin range between seven to ten micromolar[26–29]. Since the implementation in the clinic of platinum-taxane therapy, a large body of research uncovered the molecular mechanisms triggered by these drugs in terms of cell death and drug resistance (reviewed in[15,30]). Many such studies, however, did not take into consideration the dosage and/or the time of exposure, limiting the preclinical relevance of the results obtained.

To illustrate the feasibility of recreating repopulation of ovarian cancer cells following platinum chemotherapy, we utilized the cisplatin hyper-sensitive cell line OV2008, which is defective in the Fanconi anemia pathway required for repairing cisplatin-induced DNA

cross-links[31,32]. We exposed the cells to two-fold the clinically achievable concentration of cisplatin, but limited the time of exposure to one hour. Under these conditions, over eighty percent of the cells in culture die within four days of platinum removal. The few cells that remained in the dish were mostly giant, multinucleated and vacuolated, and managed to perpetuate the culture over time[23]. A similar phenomenon of repopulation took place when we exposed A2780, IGROV-1 and SK-OV-3 ovarian cancer cells to the combination cisplatin and paclitaxel at concentrations twice of what is clinically relevant (i.e., supra-pharmacological doses). We used this approach to maximize the cytotoxicity of the drugs, but tailored the time of exposure to those clinically relevant[22]. The combination cisplatin-paclitaxel was very efficient in killing the majority of the cells representing ovarian cancers of different genetic backgrounds; yet, there were cells escaping the therapy that with time repopulated the culture—albeit the drugs were utilized at higher doses than one could possibly achieve in vivo. These data suggest that escape from chemotherapy of otherwise chemosensitive ovarian cancer cells is an intrinsic phenomenon not related to long-term acquisition of resistance.

Potential molecular mechanism(s) driving ovarian cancer cellular escape from chemotherapy

There are several mechanisms that potentially clarify why and how a so called chemosensitive population of ovarian cancer cells escapes therapy and repopulate over time, thus most likely elucidating tumor relapse. However, mostly due to the scarcity of experimental model systems available, at present there is only partial, fragmented evidence to explain tumor cell repopulation after chemotherapy. The mechanisms proposed below may not be mutually exclusive and could share some components. Further evidences should be generated to support each mechanism proposed under the specific conditions of ovarian cancer patients recurring after being initially responsive to taxane-platinum therapy.

Cancer-initiating cells

One appealing explanation is that epithelial ovarian cancer cells are heterogeneous, having a hierarchy within a progeny. Within such hierarchy, the more differentiated cells might be efficiently killed by the chemotherapy, whereas the less differentiated cells with cancer-initiating properties (a.k.a. cancer progenitor cells or cancer stem cells)[33] survive and give rise to new transit-amplifying cells with the capacity to regenerate the culture. By definition, cancer initiating cells have a distinct molecular signature, the capacity to self-renew although at a very low rate, and the capacity to give rise to a more differentiated progeny. The low division rate makes these cells intrinsically resistant to chemotherapy (reviewed in[34,35]). In support of this theory, ovarian cancer cells with stemness properties have been successfully isolated from various ovarian cancer cell lines. A study showed ovarian cancer cells with stem-like properties expressing high levels of cell surface antigen CD44 (CD44+) and low levels of CD24 (CD24−)[36]. Another group reported CD44+ and aldehyde dehydrogenase positive (ALDH+) cells having enriched self-renewal and tumorigenic capacity[37], whereas two other reports agree in that ALDH defines a population of ovarian cancer stem cells that acquire more tumorigenic capacity if concurrently expressing CD133 (i.e. ALDH+/CD133+)[38,39]. According to the cancer-stem cell theory, these ovarian cancer progenitor cells also depict reduced sensitivity to platinum-taxane therapy[33,36–44]. The cancer initiating cell enrichment might be even higher after chemotherapy in the hypoxic conditions normally found within solid tumors[45].

Transitory senescence

A rare percentage of cancer cells can escape chemotherapy by undergoing a transient arrest passing through a senescence-like phenotype before regaining proliferation capacity. By

definition, senescence has been considered an irreversible phase in which the cell cycle is permanently arrested as a consequence of telomere shortening (replicative senescence). The senescent cell has a particular phenotype characterized by flat morphology; expression of senescence-associated beta galactosidase, consequence of the enhancement of the perinuclear lysosome compartment; chromatin remodeling, causing formation of heterochromatic foci; and a characteristic secretory phenotype (reviewed in[46–48]). Senescence, however, can be induced by drugs (drug-induced senescence), and its irreversibility has been challenged. For instance, senescent cells with low expression of $p16^{Ink4}$ resume growth if p53 is inactivated[49], p53 negative lung cancer cells can escape drug-induced senescence[50], and colon cancer cells undergoing senescence after exposure to doxorubicin regain proliferation capacity[51]. Furthermore, a study showed reversibility of senescence in melanoma cells upon overexpression of the inhibitor of apoptosis molecule, survivin[52]. Finally, breast cancer cell cultures exposed to conventional chemotherapy display an emerging population of surviving cells with stem cell-like properties that escaped drug's toxicities by transitioning towards a short-term reversible, senescent-like non-cycling stage[53]. The escape cells expressed the stem cell markers CD133 and Oct-4, exhibited low abundance of radical oxygen species (ROS), and elevated antioxidant enzymes[53]. In agreement, non-small cell lung cancer cells exposed to lethal doses of epidermal growth factor receptor-tyrosine kinase inhibitor displayed escape cells enriched with the cancer initiating marker C133[54].

Drug-induced senescence is highly associated with formation of polyploid cells, some of which may escape senescence forming an aneuploidy progeny with the capacity to proliferate, thus limiting the efficacy of chemotherapy[55]. Accordingly, after cisplatin or cisplatin/paclitaxel treatments, we observed the accumulation of giant flat multinucleated polyploid cells, that tend to disappear with time in culture, parallel to an increase in the number of smaller cells with high proliferation capacity and morphology similar to that of untreated cells[22,23]. Whether the polyploid ovarian cancer cells that escape cisplatin-paclitaxel therapy in our studies undergo transient senescence and/or express antigens characteristic of cancer initiating cells, remains to be studied.

Reverse ploidy

When a culture of ovarian cancer cells is exposed to cytotoxic therapy, the majority of cells die; yet, the few surviving cells appear mostly degenerated, giant, and multinucleated[23]. Formation of giant multi-nucleated cells can be the consequence of a genotoxic insult followed by mitotic catastrophe in which cells undergo cycles of DNA synthesis without cell division (endoreplication)[56]. After few endomitotic cycles, these cells mostly die as a consequence of mitotic disarray (mitotic death)[57] using a pathway of apoptosis or necrosis[58]. However, a scarce number of giant cells survive and adapt to the genotoxic environmental pressure. This survival occurs via a process termed depolyploidization[59] or reversible polyploidy[60], which was proposed earlier as a different modality of cell division or 'neosis'[61,62]. Mechanistically, the giant cells give rise to a progeny with a near diploid number of chromosomes (paradiploid) that is compatible with survival and division. This process of reverse ploidy associates with the activation of genes normally expressed during reduction division (meiosis)[63,64]. Furthermore, evidence shows that, following chemotherapy, the remainder of the giant cellular content, including extra-DNA and cytoplasmic material, seems to be cleared by autophagy[65].

Arising from cellular dormancy

Following chemotherapy there is a possibility of the persistence of cells in a dormant quiescent state with the capacity to regrow when environmental cues are appropriated ([66,67] and references therein). One mechanism for single-cell dormancy in ovarian cancer was

unveiled by the controlled expression of the tumor suppression gene aplasia Ras homolog member I (ARHI), leading to cell survival upon activation of autophagy in the presence of favorable growth factors within the tumor microenvironment[68]. These cells surviving the stress via autophagy-mediated dormancy may then emerge from such status and reenter the cell cycle causing tumor relapse. Though the genetic and/or epigenetic factors that control how and when escape from dormancy takes place remain to be determined, these appear to be related to the dialogue between the microenvironment, the cellular adhesion pathways, and the intracellular cell cycle machinery[69].

Abrogation of ovarian cancer cellular escape from chemotherapy

Upon cytoreductive surgery and chemotherapy, ovarian cancer patients do not receive any other treatment while in remission until the disease actually recurs[70–72]. Thus, patients have been without any treatment for very prolonged period of time—twelve to eighteen months in the standard responder—where cells that escaped initial chemotherapy had the time to adapt to and hijack the microenvironment to repopulate and advance the disease again to a symptomatic state with the added hurdle of likely having acquired a chemotherapy resistant phenotype. It is imperative to take advantage of the time the patient is in remission to attack escape cancer cells by disengaging their repopulation capacity. Evidence suggests the feasibility of this consolidation therapeutic approach using cytostatic agents. For instance, we successfully prevented repopulation of escape ovarian cancer cells after platinum or platinum-taxane chemotherapy using steroids with antiprogestin and antiglucocorticoid activities[22,23]. Likewise others used antiestrogens[73] or inhibitors of the mammalian target of rapamycin (mTOR)[74] to abrogate, respectively, escape of breast and prostate cancer cells from standard chemotherapy.

Despite the fact that improvement in chemotherapy to tackle ovarian cancer has been slim in the past decades, a better understanding of how cells escape clinical relevant doses of chemotherapy, together with the understanding of the mechanisms whereby cytostatic agents such as antiprogestins and antiglucocorticoids block cancer cell escape, should provide tools to discover new drugs capable of targeting more effectively the repopulation mechanism. Blocking tumor repopulation may be a promising way to conquer ovarian cancer not by eliminating the disease in its entirety, but by keeping it chronically dormant and subclinical.

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