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Do we have enough knowledge to win the fight against ovarian cancer?

Kenny Chitcholtan

WHAT IS OVARIAN CANCER?

Epithelial ovarian cancer is a malignancy of the ovaries. The exact origin of ovarian cancer cells is still under ongoing scientific debate. Early detection is very crucial for a favorable prognosis in ovarian cancer patients, and that will increase the chance of survival by 90% [1]. However, it is uncommon for patients to be diagnosed at the early stage of the disease because the signs and symptoms are easily dismissed. As a result, most patients has been presented at the advanced stage 3 or stage 4 ovarian cancer. At these stages, patients will have a slim survival rate below 30% [1]. Ovarian cancer at stages 3 and 4 displays an extensive spread of cancer cells within the abdominal cavity, and tumor nodules reside on the internal organs [2]. The choice of chemotherapy is very limited to treat advanced ovarian cancer. There are several cytotoxic agents used in the treatment of other cancers which potentially slow down tumor growth, but we cannot predict the efficacy of these agents in advanced ovarian cancer because selective clinical trials showed ineffectiveness of some of these agents and variation in patient's responses [3].

WHAT KNOWLEDGE DO WE HAVE SO FAR?

Ovarian cancers are derived from epithelial cells in the ovary, but there are different subtypes of ovarian cancer

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which are notable. This may suggest that the origin of each ovarian cancer subtype may be from a different location of the ovaries [4]. Ovarian tumors are classified entirely based on tumor cell morphology. There are four major subtypes of ovarian tumors; serous, endometrial, clear cells and mucinous [5, 6]. These subtypes can be subdivided, based on tumor differentiation, into low grade and high grade. In general, the low grade ovarian tumor shows slow growth potential and does not respond well to common used cytotoxic agents. High grade ovarian tumors, on the other hand, grow rapidly but show rapid growth reduction after cycles of taxane and platinum drugs [7]. The high grade serous ovarian tumors are highly prevalent in the advanced stage.

High grade serous cancer is genetically distinctive from low grade serous cancer. For example, TP53 gene is frequently mutated in high grade serous tumors but this mutation is rarely observed in low grade serous tumors [8, 9]. There is strong evidence to suggest that the mutation of TP53 occurs in the early stages of serous carcinoma pathogenesis. Mutations of KRAS and BRAF genes are more prevalent in low grade tumors than high grade tumors [5]. The mutation of these two genes constitutively activates the MAPK pathways found in a majority of low grade serous tumors. However, the activation of the MAPK pathway in ovarian tumors without the KRAS and BRAF mutations is also noted in patient samples and ovarian cancer cell lines activated by growth factors [10–14]. This may suggest that the microenvironment within the tumor's niche could elicit the MAPK activation independently from the activation of KRAS and BRAF mutations.

Analyzed global DNA copy number alterations in high grade and low grade serous tumors revealed higher levels of chromosomal instability in high grade than low grade serous tumors [12]. Gene amplifications were found in CCNE1 (cyclin E1), AKT2, NOTCH3 and PI3K loci [14, 15]. These gene amplifications may have a critical impact on the diagnostic evaluation and subsequently the selective treatment with advanced ovarian cancers. However, in the current clinical practice, the prediction and the use of protein signaling molecular profiles associating with chemotherapeutic resistance have been ignored in the routine treatment of ovarian cancer.

Endometrioid low grade and high grade of the ovary share common features with the uterus endometrioid cancer. Furthermore, these two cancers share genetic fingerprints in common. Both endometrioid carcinoma of the ovaries and the uterus have significant numbers of the PTEN tumor suppressor gene mutation [16]. The concomitant PIK3CA and PTEN mutations in ovarian endometrioid carcinoma are also noted [17]. Interestingly, the β-catenin mutation co-exists with the mutation of PI3K/PTEN, and these are present in low-grade and low-stage ovarian endometrioid tumors [17, 18]. The P53 mutations are also common in ovarian endometrioid carcinomas. These mutations are used to divide ovarian endometrioid carcinoma into low-grade, where tumor cells have no P53 mutations and high-grade for tumors with P53 mutations [19–21].

Clear cell and mucinous ovarian carcinomas are rare tumors, and their molecular changes have not been investigated in great detail. However, there are a few studies that have looked at molecular alteration in the pathogenesis of these two subtypes. Mutations of P53, KRAS and BRAF are not prevalent in clear cell carcinomas. However, PI3KCA mutations are reasonably evident at 20–25%. In primary ovarian mucinous carcinomas, the mutation of KRAS is a very common event. Gene expression analyses of clear cell carcinoma are quite distinct from the other subtypes of ovarian cancer. The most prominent expression is hepatocyte nuclear factor-1 beta (HNF-1β), which is responsible for the metabolism of glucose and glycogen. The cytological feature of clear cell carcinoma is based on the presence of the glycogen-rich, clear-appearing cytoplasm. Napsin A, an aspartic protease, is a protein marker also associating with the ovarian clear cell carcinoma. The gene expression of mucinous carcinomas is largely different from other subtypes. Proteins of various mucin families are highly expressed in mucinous carcinoma. Furthermore, intestinal type differentiation genes, including the caudal type homeobox transcription factor CDX2 which is present in an intestinal cell surface, are found in mucinous carcinomas [22–31].

WHAT KNOWLEDGE ARE WE STILL LACKING?

Heterogeneity of ovarian cancer cells in tumor tissue

The heterogeneity of cells in tumor tissue associating with the progression of solid tumors is an ongoing problematic issue regarding its role in sensitivity towards anti-cancer drugs. This hurdle is also notable in the field of ovarian tumor research. So far, we acknowledge that not only malignant cells are present in tumor tissue but also non-cancerous cells including immune cells, stromal cells and the composition of extracellular matrix (ECM), which play an important role in the dynamic turnover of the microenvironment [32–34]. We are facing great challenges to understand behavior of tumor cells in vivo because cancer at primary and secondary sites may be surrounded with various types of bystander cells. For instance, metastatic ovarian cancer cells residing at the omentum may encounter large numbers of adipose cells or fat cells, which secrete various adipokines that can have cancer cell growth promoting effects which is distinctive from cancer cells at the primary sites [35]. Therefore, it is scientifically sound to assume that gene and protein expressions of cancer cells at the primary and secondary nodules must have differential expressions and functions due to a specific microenvironment.

Investigating and understanding the profiles of gene expressions, and importantly the functions of protein products in ovarian cancer that are regulated by the modulation of microenvironment, will be a forefront research avenue. This is very crucial to advance our understanding to ensure our proper use of effective chemotherapy that will be targeting the bystander non-cancerous cells. Recent findings in some solid tumors suggest that a small population of cancer cells' genotypical and phenotypical profiles mimic normal stem cell behavior and may be responsible for tumor relapse [36, 37]. This idea is increasingly becoming recognized in ovarian cancer research [38, 39]. However, the research in the cancer stem cells in ovarian cancer is still early to know whether these cancer-like stem cells are the primary source of cancer cells that have ability to acquire resistance to chemotherapy. Therefore, the first priority now is that we should study and understand the hallmark of molecular and biological landscapes of these cancer-like stem cells by using an advanced analysis tool that accurately pinpoints the cells that are responsible for a relapse and for the recurrence of the disease. A single cell analysis may provide us with the answer to identify cancer stem cells in ovarian tumors. This concept can be implemented using sophisticated cell biology techniques including a flow cytometry and immunofluorescence to identify the stem cell protein markers.

Tumor subtypes

The other ongoing challenge that we are encountering today in the clinical end is the identification and classification of ovarian cancer subtypes. The routine examination of ovarian cancer subtypes is based on a pathologist's expertise using morphological features of tumor cells and on attempting to decide the subtype of tumor. Unfortunately, morphological appearance does not reflect the genetic and proteomic footprints of ovarian tumors given that a primary tumor might be different from a metastatic counterpart. And even though, using tumor morphology as a rapid clinical tool to differentiate tumor subtypes and subsequently provide appropriate chemotherapy for patients after the primary diagnosis, this does not suggest that all patients should receive a similar chemotherapy. Some patients might not receive

any chemotherapy if, for instance, a low grade ovarian cancer is diagnosed; a low grade ovarian cancer may grow very slowly. Cytotoxic drugs working on proliferative cells will not work in this subtype of tumor. These challenges will not be solved quickly overnight but it may be transiently improved if more knowledge regarding the molecular profiles of ovarian tumors is available for a clinician to help with decision making prior to delivery of an appropriate chemotherapy for each patient.

Tumor resistant phenomenon

Chemotherapeutic regimens, including taxane and carboplatin, are common cytotoxic drugs available for ovarian cancer patients [40, 41]. The rationale using these agents is to slow down tumor growth and induce cell death; both necrosis and apoptosis. However, a relapse is very common in patients who receive the regimen, and we still do not know the possible cause of the tumor being resistant to commonly used anticancer drugs. Clearly, it is a complicated event that is happening within tumor cells when they are exposed to these drugs. Cancer cells may use various cellular activities to overcome the cytotoxic insult from these drugs. Furthermore, the autocrine and paracrine axis in the microenvironment may play a pivotal role in an induced drug resistance. Questions are: Do we know how cancer can adapt to the toxicity of anticancer drugs?

How can we overcome drug resistance in tumor cells?

How can we select an alternative chemotherapeutic drug if patients fail to respond to the first choice of anti-cancer drugs?

This makes it very clear that an oncologist and cancer scientists must not ignore these questions when relapse patients are treated. Again as aforementioned, if we know the profile of gene and protein expressions of cancer cells in drug resistant patients we may be able to utilize chemotherapy that is tailored specifically to the individual proteins in a well-designed and controlled fashion.

Epigenetic modification in ovarian cancer

So far, we think that genetic aberrations, such as mutations of tumor suppressor genes and oncogenes, have largely attributed to the onset and progression of ovarian cancer, and we know that each subtype of ovarian cancers possesses unique molecular alterations. Each patient may have varying degrees of mutations and alterations, and the magnitude of disease progression and prognosis is shown with a broad variation among patients. So the question is what is the crucial factor(s) to determine the different disease progression if patients have identical genetic mutations? Do we overlook other factors that may contribute to the disease progression apart from the genetic mutations and aberrations?

Post modification of DNA or epigenetic alteration of DNA is an important step that can regulate the function of cell behavior. Epigenetic modification is caused by the processes of DNA methylation, histone modification, and non-coding microRNAs (miRNAs). Methylation of DNA is the most widely studied epigenetic event in recent years. DNA methylation occurs in cytosine-guanine (CpG) rich regions refereed to as "CpG islands" [42]. In cancer cells, DNA hypermethylation is associated with gene silencing and DNA hypomethylation with gene expression [42]. DNA hypermethylation is usually associated with the silencing tumor suppressor genes [43]. On the other hand, DNA hypomethylation associated with unsilenced oncogenes becomes transcriptional active [43]. The post-modification of DNA is a reversible process and is regulated by environments, including diets, chemotherapy, and tumor tissue microenvironment [44]. If these factors are amended for any reasons, then these will affect the outcome of tumor progression. It is worth mentioning that diets can play an important role in the onset and progression of cancers [44]. All available anti-cancer drugs used today are designed to inhibit a machinery of cell division and proteins that are involved in cell signaling pathways. Research that is searching for a novel drug that regulates DNA modification will be an exciting area and it is needed to be explored so that an optional chemotherapy may be available for selected women with ovarian cancer.

Functions of Proteins: Post-modifications of proteins are the fuel engine of cells

We always think that a tumor is a disease associated with the fundamental dysfunction of genomic expressions, and it is not surprising that the genomic research into cancers has been expanding at a rapid pace. The cancer genetic has provided us with useful and meaningful information that has been exploited to explain the biological activity of cancers. Many questions still deserve to have definite answers which will address whether the onset and the progression of cancers strongly correlate with either the genomic aberration, or functions of proteins that are the end products of those genes or the combination of both. Can the genomic expression and the alteration predict the expression and the function of their proteins? There is some evidence to suggest that the levels of transcription of mRNA are not entirely correlated with the levels of proteins [45–48].

Every cell in man comprises similar genetic materials, but there are various types of cells in various tissues that regulate the human body to function in a proper manner. This suggests that the local environment in tissues has a unique way to command specific gene expressions that trigger for specific tissues to function properly. All cells in the human body can function properly due to protein functions, and these functions are regulated by the post-modification of proteins. These include protein-protein interactions [49–51], protein phosphorylations [52–54], protein degradation [55–57], protein glycosylation

[58–61], and the endocytosis pathway [62–65]. These processes are absolutely not dependent on the gene expression. The post-modifications of proteins are very crucial in the fundamental basis of tumor growth, survival and metastasis, and subsequently will determine the fate of disease. It is encouraging that the most important factor that regulates the function, expression and activation of proteins is the cancer tissue microenvironment.

Ascitic fluid: Is it a key component in the progression of advanced ovarian cancer?

Women in the advanced stage of ovarian cancers often show signs of the accumulation of body fluid in the abdominal cavity, a medical term known as ascites. In normal physiological conditions, body fluid is absorbed from the abdominal cavity into the vascular network lying beneath the abdominal wall [66]. In the case of advanced ovarian cancer patients, normal and tumor cells secrete vascular endothelial growth factor (VEGF) and that subsequently disrupts the vascular endothelial cell integrity of blood vessels beneath the abdominal wall, leading to increased leakage of fluid from the vascular and lymphatic systems into the abdominal cavity [67]. Patients associated with ascites have a poor prognosis. Blocking the VEGF activity can restore the function of blood and lymphatic vessels, and can diminish ascites, suggesting the VEGF is a key factor in ascites [68].

Ascitic fluid is the carrier of ovarian malignant cells and allows these cells to circulate within the abdominal cavity and subsequently increase the chance of cancer cell metastases. Patients with ascitic fluid always display the spread of cancer into various internal organs, suggesting ascitic fluid plays an important role in the contribution to the secondary growth of ovarian cancer. Current ovarian cancer research is mainly focused on the studies of tumors at the primary and metastatic sites, but is largely ignore the importance of ascitic fluids being a valuable biological clinical sample which is routinely obtained from patients and discarded during the clinical procedure. Ascitic fluids are comprised an heterogeneity of growth factors, cytokines, chemokines, bioactive fatty acids, immune cells, mesenchymal stem cells, and ovarian cancer cells [69]. The levels of these mixture components are varied among ovarian cancer patients suggesting the biological activity of the tumor microenvironment may be unique in individual patients [70]. Little is known about the mechanisms underlying ovarian cancer progression from the primary to the peritoneal seeding. Furthermore, the biological profiles of cancer cells during the exposure to the ascitic fluid are not discernible to target cancer cells with novel intervention chemotherapy. More importantly, we do not yet understand the effects of ascitic fluids during chemotherapy, via intravenous (IV) and intraperitoneal (IP), in ovarian cancer patients. It is very tempting to speculate that ovarian cancer cells in women in the advanced stage have acquired resistance to commonly used cytotoxic agents, carboplatin and taxol due to the presence of ascitic fluids.

Certainly, there is an urgent need for a preclinical study to conduct the hypothesis: "ascitic fluid can decrease the efficacy of chemotherapy". There are a few targeted agents that have been trialing in advanced ovarian cancer, and most of these agents show a lack of clinical activity except for bevacizumab, an antibody scavenger VEGF and subsequently reducing its levels causes ascites to be reduced dramatically. Studying specific protein activation following the exposure of cancer cells to ascetic fluid is also a very exciting area and may potentially provide us with a mechanistic basis which can be used to treat ovarian cancer with any potential targeted agents in a well-designed randomized trial. In preclinical studies, there are some reports showing that the ascitic fluid induces the activation of Erk, Akt, focal adhesion kinase (FAK) and integrin engagement in ovarian cancer cell lines [71–74]. Understanding the unique signaling proteomic profiles of tumor cells in each patient is very crucial for the clinical evaluation, as the devised targeted chemotherapy can be given to each patient and that will tailor patient disease in a control manner.

CONCLUSION

Advanced ovarian cancer is very difficult to treat because the tumor quickly develops drug resistance. There is limited success achieved by the use of targeted agents in this type of tumor. We are lacking the knowledge to understand the tumor biology of advanced ovarian cancer. Ascitic fluids are the major source of metastatic malignant cells, and nutrients that support cancer cells viability in the peritoneal cavity. To successfully eradicate and effectively treat patients in the advanced stage, we must understand the mechanism underlying ascitic fluids and how they support the progression of advanced ovarian cancer. There is research opportunity to discover the signaling protein cascades activated by ascitic fluids. Clearly, the possibility of biologically targeted agents is emerging at a rapid pace and this class of drug will be in the forefront of weapons to fight the war against ovarian cancer.

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Author Contributions

Kenny Chitcholtan – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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