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10-gene biomarker panel: a new hope for ovarian cancer?

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Summary

The recent publication of a 10-gene biomarker panel generates new hope for the prognostication and personalization of therapy in ovarian cancer. Expression of the 10 biomarker genes (AEBP1, COL11A1, COL5A1, COL6A2, LOX, POSTN, SNAI2, THBS2, TIMP3, VCAN) in primary ovarian tumors correlates with metastasis, recurrence and poor survival. Importantly, the utility of the 10-gene panel extends beyond biomarkers since most of these genes play key roles in tumor progression and some have already been shown to be effective therapeutic targets in pre-clinical models.

Keywords

ovarian cancer; 10-gene biomarker; stroma; collagen; poor prognosis; metastasis

Current challenge in ovarian cancer management

Survival rates for advanced stage ovarian cancer have not changed significantly over the past 40 years and ovarian cancer remains the most lethal gynecologic cancer in women. The most common type of ovarian cancer, and the one that accounts for the majority of deaths from ovarian cancer, is serous papillary carcinoma. Approximately 20% of patients with this ovarian cancer subtype are intrinsically resistant to chemotherapy or develop chemoresistant disease within one year from initial treatment. Currently, ovarian cancer surveillance and subsequent therapies are implemented on a “watch-and-wait” basis because there is no diagnostic tool that identifies patients who have a high likelihood of recurrence. A reliable method to identify these poor prognosis patients would facilitate their inclusion into clinical trials or personalized treatment strategies at an earlier point. One successful example of such approach is the development and validation of the Oncotype DX[®] and MammaPrint[®] assays for breast cancer [1, 2], which have become the standard of care for individualized treatment decision-making in breast cancer. Unlike in breast cancer, a fully-validated and clinically-

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applied test that guides treatment decisions in the management of ovarian cancer patients does not exist.

Identification of the 10-gene biomarker panel

The lack of reliable prognostic markers and curative treatment strategies for ovarian cancer has prompted several research groups to utilize expression profile data to develop biomarker panels that predict clinical outcomes. Although each panel has a certain predictive ability, the biomarker panels described to date exhibit little overlap and lack apparent biological relevance to poor outcome. In addition, the mechanisms by which individual genes or groups of genes contribute to poor clinical outcome have not been well understood.

A recent study reported by Cheon et al. [3] identified a 10-gene biomarker panel that is strongly correlated with poor prognosis in ovarian cancer patients. They analyzed three large microarray datasets, including the Cancer Genome Atlas (TCGA) dataset [4], the GSE26712 dataset [5], and their own GSE51088 dataset [6], to identify “common” molecular abnormalities that contribute to poor overall survival in ovarian cancer. The three datasets included a total of 710 high-grade, advanced-stage serous ovarian cancer samples, which is the largest sample size used to date for the discovery and validation of a gene biomarker panel. They identified a 10-gene biomarker panel (AEBP1, COL11A1, COL5A1, COL6A2, LOX, POSTN, SNAI2, THBS2, TIMP3, VCAN) that correlates with poor patient survival in multiple ovarian cancer studies. Several genes in this panel are known markers of metastatic progression and adverse outcome in diverse types of solid cancers, including cancers of the ovary [6-10], breast [10, 11], colon [10, 12], prostate, pancreas [10] and lung [13], indicating that the expression of these genes may represent aggressive behavior across cancer types. To identify the underlying biological mechanism that could explain the observed association of poor survival with high expression of the biomarker genes, Cheon et al. evaluated the expression levels of the 10 genes in normal ovaries, primary ovarian cancers, metastatic ovarian cancers, and recurrent ovarian cancers. They observed that most of the 10 biomarker genes were not expressed in normal ovaries but their expression was detectable in primary ovarian cancers, enriched in metastases, and even further enriched in recurrent metastases [3]. This observation suggests that during tumor progression, the cell population expressing the biomarker genes is enriched or the process resulting in the expression of the signature genes is intensified. The majority of the biomarker genes are known to play roles in tumor microenvironment remodeling, such as collagen cross-linking, myofibroblast activation, desmoplasia, fibrosis, epithelial-mesenchymal transition, and acquisition of a stem cell phenotype. It remains inconclusive if the biomarker genes are upregulated in malignant cancer cells or non-malignant desmoplastic stroma. However, based on the observation that the 10-gene biomarker panel is associated with poor outcome in multiple tumor types, the panel appears to be either specific to a certain cell type present in diverse tumor types or specific to a common biological process occurring during progression of solid malignancies.

Tumor-stroma interaction: Achilles heel of ovarian cancer?

It is now known that tumors are complex ‘organs’ consisting of cancer cells, blood vessels, and many other cell types [14, 15], which are typically lumped together as tumor ‘stroma’

because their individual characteristics and roles in tumor progression and metastasis are not well defined. Desmoplastic stroma is universally found in malignant tumors and pathologists use the abundance and density of stroma to predict poor prognosis. Despite its universal presence and wide clinical use as a prognostic marker, dynamic bi-directional interaction between cancer cells and stroma is not well understood. It is becoming increasingly apparent that the stroma can modify the aggressiveness of tumor cells and that tumor cells re-program the stroma to generate a nurturing microenvironment that is crucial for tumor survival, progression, and metastasis [14-16]. The stroma also severely compromises the efficacy of chemotherapy delivery by increasing interstitial pressure, impeding the diffusion of large molecular weight drugs, or sequestering drugs [15]. Furthermore, current chemotherapeutic agents are largely selected for their ability to destroy rapidly dividing cancer cells rather than the tumor infrastructure that protects the rare specialized cells that drive tumor recurrence and chemoresistance [16]. This might explain why tumor response does not necessarily translate into increased patient survival. Because of the prominent role of stroma in most aspects of tumor progression, it is believed that rational anti-cancer therapy design should not only target the cancer cells but also the stroma. Therefore, a better understanding of cancer-stroma interaction and the identification of molecular events whose disruption may undermine tumor progression are required steps toward successful anti-cancer therapy.

The advantage of the 10-gene biomarker panel is that several genes in the panel are not only predictors of poor prognosis (metastatic progression, cancer recurrence, and poor patient survival) but also integral players in tumor progression. These genes form a molecular network required to maintain the three-dimensional structure of the tumor. Their inhibition may impede tumor progression or even completely incapacitate the tumor. Such genes could serve as therapeutic targets. Indeed, Cheon et al. showed that inhibition of one of the biomarker panel genes, COL11A1, is effective in reducing ovarian tumor growth in mouse models [3]. Other biomarker panel genes have also been shown to be relatively effective therapeutic targets in cancer models [8, 17-19]. A better understanding of the components of the underlying infrastructure that drives ovarian cancer progression could reveal the “Achilles heel” of the tumor and thus have a major impact on the development of therapies that target tumor microenvironment.

Future perspective and conclusion

The ultimate goal of the basic science discovery of the 10-gene biomarker panel is the translation into a new, clinically-applicable assay for the identification of patients who are likely to experience recurrence on standard chemotherapy and should be triaged to alternative treatments or clinical trials at disease onset. Toward this goal, it is essential to optimize and validate the biomarker panel in a large patient cohort to satisfy the required clinical performance criteria. Development of an assay that can quantify the biomarker genes in paraffin-embedded tumor tissues could facilitate the use of the biomarker panel in clinical setting. Additionally, it is important to identify and validate the key therapeutic targets in patients who express the poor prognosis genes since their current therapeutic options are limited. It must be demonstrated which target genes and which therapeutic agents show the best efficacy in pre-clinical models [20] as single agents or in combination

with standard chemotherapy. Such pre-clinical studies and models are an important step toward initiating clinical trials in ovarian cancer patients.

Does the 10-gene biomarker panel provide real hope? It is too early to draw any conclusions. However, an increasing number of studies demonstrate that the stroma is a crucial player promoting cancer progression and metastasis not only in ovarian cancer but also in many other cancer types. The 10-gene biomarker panel has strong predictive value, biological relevance, and translational potential. Ideally, application of this panel for the prediction of early recurrence would spare the patients from unnecessary toxicity from ineffective therapy and facilitate their timely inclusion into clinical trials or targeted treatment strategies. It would also assist clinicians in the management of ovarian cancer patients in a similar way to commercially available gene signature tests for breast cancer, such as Oncotype DX[®] and Mammaprint[®]. Such guided personalized treatment decisions in ovarian cancer should result in improved patient outcome and quality of life. Furthermore, a better understanding of how the stroma drives ovarian cancer progression could reveal the vulnerabilities of the tumor and thus have a major impact on the development of novel therapeutic strategies that effectively disrupt the interaction between the tumor cells and their microenvironment. We still have a long way to go but the trail of the 10-gene biomarker panel is leading us in the right direction toward better cancer management.

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