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REVIEW ARTICLE

Origin of Ovarian Cancer: Molecular Profiling

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Abstract This is a review on the transition from our empirical approach to treat ovarian cancer to a specific treatment based on molecular signature. We have reviewed not only the evidence-based medicine focused on the origin and tumor morphology of ovarian cancer but also the molecular signature era based on molecular phenotyping of the tumor and its microenvironment, which influences the direct targeted therapy. Evidence-based medicine has shown that the targeted therapy studies are mainly biomarker driven, more focused, and hence treat only those patients who have the underlying molecular abnormality. This molecular abnormality is the target of the drug, leading to higher rates of response. These findings will carry important implications for screening, detection, and treatment of ovarian cancer in the future.

Keywords Ovarian cancer · Molecular profiling · Targeted therapy

Introduction

With the turn of the century, we are witnessing the transition from our empiric approach to cancer treatment to the new paradigm of personalized medicine, based on the molecular signature of individual cancers (Table 1). Evidence-based medicine has focused on the organ of origin and tumor morphology, whereas in the molecular signature age, molecular phenotyping of the tumor and its microenvironment directed the therapeutic decision [1]. Until recently, our treatments resulted from large randomized trials comparing new therapies to the "gold standard." These costly studies were slow in accrual and because of the mixture of various tumor types originating in the same organ, e.g., the ovary, the results were limited. Targeted therapy studies are biomarker driven, more focused, and would treat only those patients who have the underlying molecular abnormality that is the target of the drug, yielding higher rates of response.

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Time-Honored Concepts

Ovarian cancer was believed to originate from the invagination, metaplasia, and malignant transformation of the surface epithelium of the ovary. This is a unicellular layer of mesothelium similar to the peritoneum that was thought to undergo metaplasia in the inclusion cysts following ovulation. The cancerous cells would then expand, reach the surface, and extend to the peritoneal surfaces. This view had important implications on the efforts for screening and early detection, search of new chemotherapy regimens, and routes of delivery of chemotherapy. These time-honored concepts led to large randomized trials in which

Table 1 Paradigm shift from "evidence based" medicine to "personalized" medicine

Evidence-based era	Personalized molecular signature era
Based on organ of origin and tumor morphology	Based on molecular phenotyping of the tumor and microenvironment
Randomized studies: comparing the study drug to "the gold standard"	Targeted therapy: biomarker driven
Slow, mixture of tumor types, poor results, and restricted application	More focused so it becomes affordable

all patients with ovarian cancer were placed on trial irrespective of histology, mixing endometrioid, clear-cell, mucinous, and serous cancers alike. Since the introduction of platinum compounds in the early 1980s, combination chemotherapy regimens improved the length of survival of patients with ovarian cancer, but did not impact cure rates that have remained below 30 % over the last 40 years.

Implication of the Molecular Analysis of Ovarian Cancers

Recent evidence suggests that ovarian cancers can be segregated into two major types similar to endometrial cancer (Table 2). Type II ovarian cancers form a majority of cancers and include high-grade papillary serous tumors and high-grade endometrioid cancers, including the carcinosarcomas. Overall, these aggressive tumors represent ~75 % of ovarian cancers and have a poor outcome. Type I ovarian cancers include the low-grade cancers that have indolent courses and usually present at a low stage. Frequently, areas of borderline tumors are visible in the vicinity of these cancers, and there appears to be a continuum of histologically progressive lesions from dysplasia to low-grade neoplasia.

Table 2 Differences between Type I and Type II ovarian cancer

Type I ovarian cancer	Type II ovarian cancer
LOW-GRADE serous, endometrioid, clear-cell, and mucinous cancers	HIGH-GRADE serous, Endometrioid, and undiff., carcinosarcomas (responsible for 3/4 ovarian cancers)
Usually Indolent	Poor outcome
Usually low stage	Highly aggressive
Shared lineage with borderline tumors	Papillary, glandular, and solid patterns

Low-grade serous tumors are characterized by K-ras (30 %), B-raf (30 %), or erb-b2 (5 %) mutations (Fig. 1) [2]. These are mutually exclusive. Therefore, mutations in any of the genes are detected in about two-thirds of micropapillary serous carcinomas and atypical proliferative serous tumors. In contrast, these genes are not mutated in high-grade serous cancers [2, 3]. Mutations of K-ras and B-raf seem to occur very early in the development of low-grade micropapillary serous carcinomas, as evidenced by the demonstration that the same K-ras and B-raf mutations detected in borderline tumors are detected in the cystadenoma epithelium adjacent to these borderline tumors [4]. On the other hand, no increase in BRCA mutations was detected in patients with borderline tumors [5].

Low-grade endometrioid tumors have a similar molecular profile as their endometrial counterparts (Compare with Fig. 2). In addition, endometrioid carcinomas of the ovary are associated with HNPCC [6] and coexist with their endometrial counterparts relatively frequently (up to 20 % of cases of endometrioid carcinoma of the ovary are associated with synchronous atypical hyperplasia or endometrioid adenocarcinoma of the endometrium [7]). The favorable outcome of such cases suggests that these are independent primaries and also suggests a role of hormonal environment.

Clear-cell carcinomas seem to form a subgroup of non-hormonally dependent cancers with a low mitotic index [8], which may be related to their reduced response to platinum-based chemotherapy [9]. They resemble renal clear-cell cancers, and microarray analysis has recently been shown to predict their response to sorafenib [10].

Mucinous tumors are a relatively rare subtype of ovarian cancer. K-ras mutations are frequently found in these tumors [11]. HER2 amplification with overexpression of the protein on the surface of the tumor cells is present in 15–20 % of mucinous ovarian cancers [12]. No data are yet available on the response rate of this small group of tumors to Trastuzumab (Herceptin) therapy.

High-grade cancers of the ovary on the other hand are associated with p53 mutations and cyclin-associated abnormalities (Fig. 3). Cyclins, as their name indicates, contribute to the temporal coordination of each mitotic event [13]. Abnormalities result in chromosome instability and thus may contribute to tumorigenesis (ref).

Based on the above-indicated molecular changes, it becomes apparent that each type of ovarian cancer can be targeted differently and that the response to presently available chemotherapies will vary in function of the underlying mutations, explaining the spectrum of responses seen in large randomized trials. Personalized therapies resulting from specific mutation analysis of the particular tumor and the evaluation of the surrounding tissues in a specific patient are expected to yield higher response rates

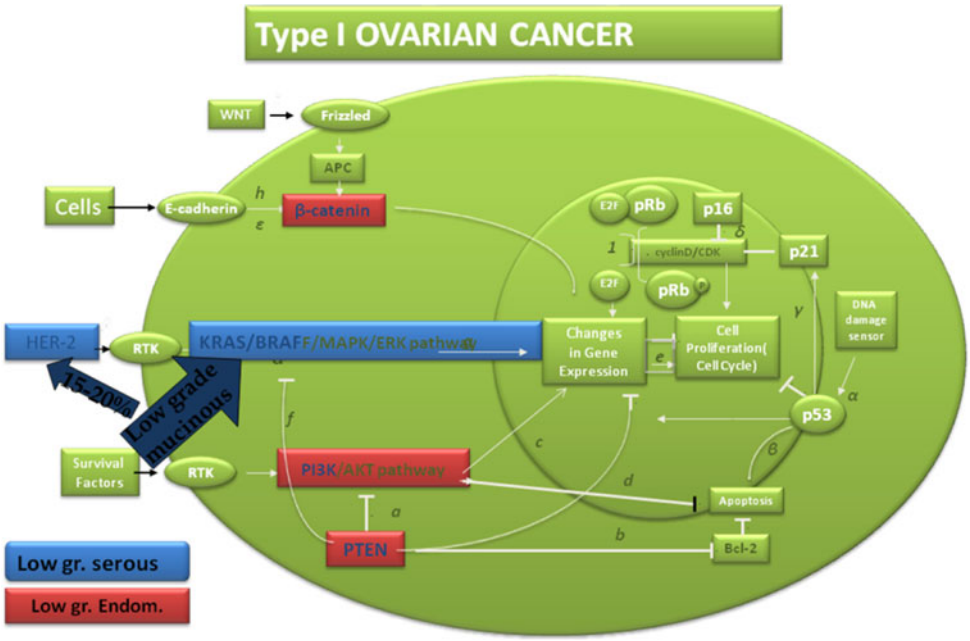

Fig. 1 Type I ovarian cancer

than presently observed and ultimately result in potential cures.

Differences in Genetic Profiles Segregate Between Low-Grade and High-Grade Serous Cancers

Based on whole genome expression profiling using thousands of probe sets, the authors have reproducibly been able to document that borderline ovarian tumors were indistinguishable from low-grade ovarian cancers, but were completely distinct from high-grade cancers [14–16]. In addition, none of these had any common clusters compared to ovarian surface epithelium, indicating that ovarian tumors do not arise from the surface epithelium. This has important implications for screening strategies. Low-grade cancers, that for the most part are early stage, represent different molecular entities compared to advanced-stage

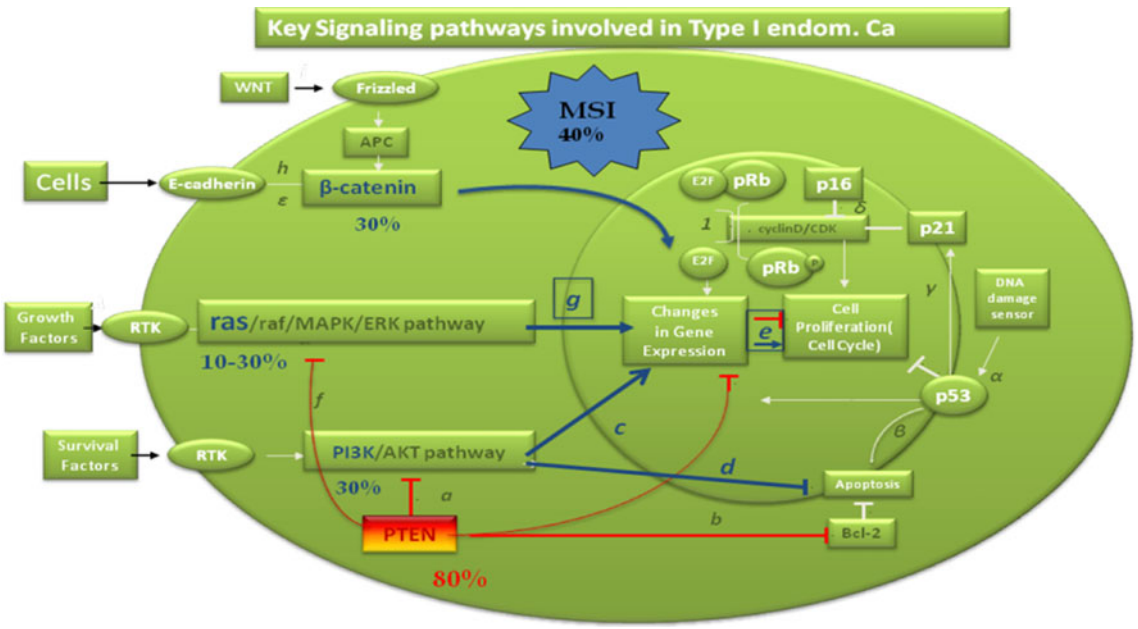

Fig. 2 Key signaling pathways involved in Type I endom. Ca

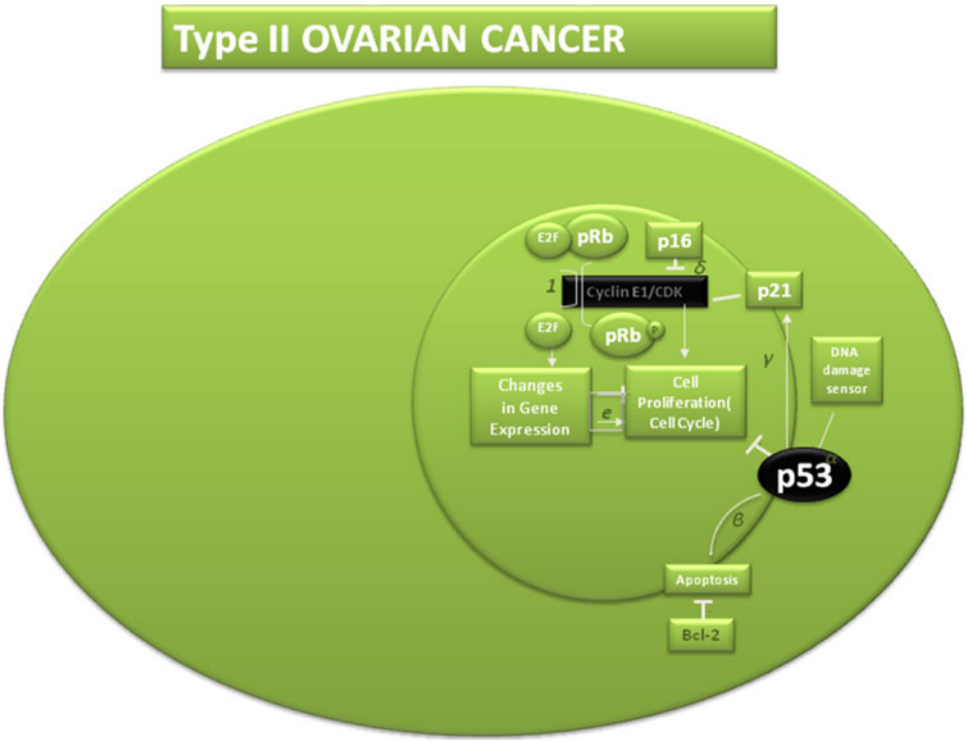

Fig. 3 Type II ovarian cancer

high-grade cancers. Finding these early low-grade cancers by presently available screening tools or early detection means will have no impact on the survival of the high-grade cancers which represent the cancers that carry the poor prognosis. Only screening for molecular markers specific to high-grade cancers might influence the detection of these cancers and impact their outcome.

On the Cell of Origin of Ovarian Cancers

An important shift in our understanding of the origin of ovarian cancers came when unexpected incidental fallopian tube cancers were detected at the time when prophylactic salpingo-oophorectomies were performed on BRCA mutation carriers [17]. Some authors started to speculate that the epithelial

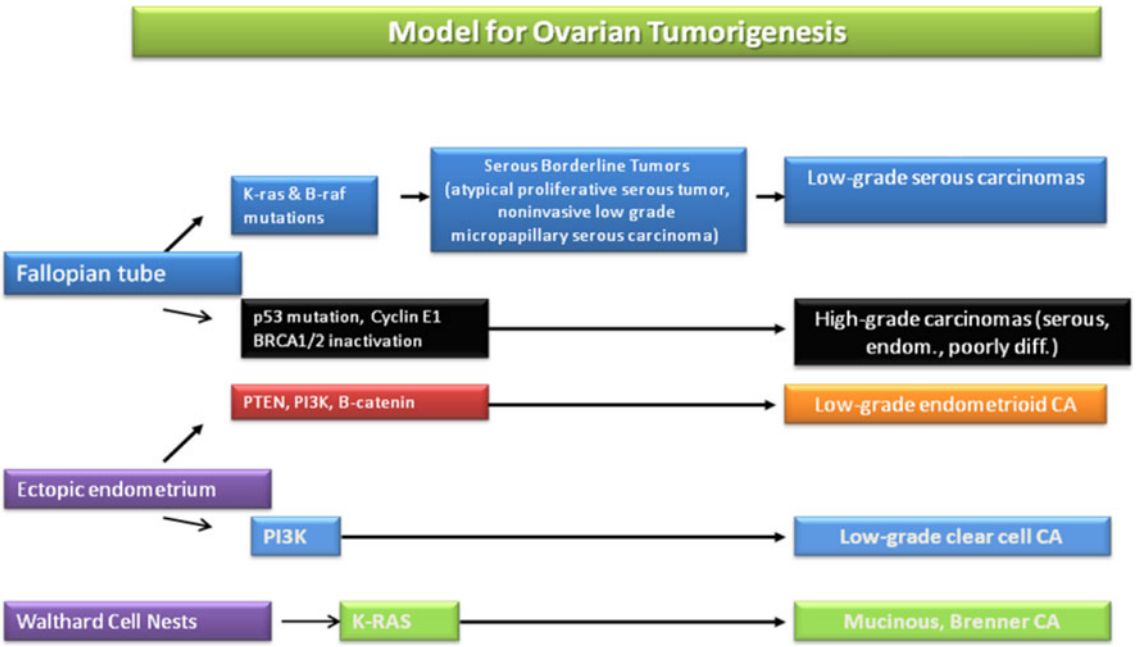

Fig. 4 Model for ovarian tumorigenesis

serous cancer cells found on ovaries and throughout the peritoneal cavity might arise from shedding of cells from the epithelium of the fallopian tube, rather than from the metaplasia and malignant transformation of the single layer of mesothelial cells surrounding the ovary [18]. Further investigating this hypothesis, areas of strong p53 immunostaining were identified in normal secretory cells from the fimbriated end of the fallopian tube of BRCA-positive patients [17] as well as the foci of tubal intra-epithelial carcinoma [19]. These areas, referred to as TIC, expressed identical mutations as the associated quote ovarian cancers [20]. If confirmed, risk-reducing surgery might focus on the fallopian tube rather than the ovary. A recent effort initiated in the third quarter of 2010, led by the cancer agency in British Columbia (Canada), promoted salpingectomies rather than tubal ligations performed for birth control as well as at the time of hysterectomy for benign causes (www.ovcare.ca). The authors of this initiative hope to decrease the development of ovarian cancers in these women in the future. In addition, Marquez et al. [21] had shown in 2005 that clear-cell cancers and endometrioid cancers of the ovary resembled normal endometrial tissue, serous cancers resembled normal fallopian tube cells, and mucinous cancers resembled normal colon epithelium. Moreover, none of the cancer profiles resembled ovarian surface epithelium. It is presently believed that serous tumors originate in the fimbriated end of the fallopian tube [22]. Other authors [23] further hypothesize that if the K-ras/B-raf pathways become altered in the cells from the fimbria, these cells evolve via a morphologic continuum including low malignant potential and low-grade cancers. On the other hand, if p53 mutations occur, these cells produce high-grade aggressive-behaving cancers. In addition, they speculate that clear-cell cancers and endometrioid cancers migrate from the endometrium. This is supported by the protection obtained from tubal ligation only on clear-cell (OR, 0.32; 95 % CI, 0.006–2.50) and endometrioid cancers (OR, 0.20; 95 % CI, 0.046–1.46) [24]. Mucinous cancers and Brenner tumors would originate from Walthard cell nests [23].

These findings (Fig. 4) carry important implications for screening, detection, and treatment of ovarian cancer, which will necessitate a complete reappraisal and adjustment of our present practices. Gene expression profiling of individual cancers and their microenvironment, in the context of host factors, represents the cornerstones of personalized medicine and will predict the response to chemotherapy and prognosis for the specific patient being evaluated [25].

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