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Gene Amplification in Ovarian Carcinomas: Lessons from Selected Amplified Gene Families

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1. Introduction

Ovarian cancer is the most malignant gynecologic cancer causing an estimated 140,000 deaths per year worldwide (Jemal et al 2011). In greater than 75% of incident cases, the disease is detected only after it has reached an advanced stage (stage III and IV) when standard therapy is unlikely to be curative. Even after maximal cytoreductive surgery followed by platinum-based chemotherapy, the survival rate at 5 years is only 15-30% (Kosary 1994). Epithelial ovarian cancer is a heterogeneous disease that can be subdivided into four histological categories: serous, clear cell, endometrial, and mucinous. The pathogenesis of the individual subtypes relies on different molecular and pathway aberrations and thus will likely respond with different sensitivities to systemic and targeted therapies (Kurman and Shih 2008). The identification of critical molecular and pathway aberrations specific to each subtype could provide key insights into the mechanisms driving tumorigenesis and direct efforts in the development of targeted therapies.

Tumors characteristically display alterations in gene expression that lead to the acquisition of the hallmark features of cancer: uncontrolled proliferation, evasion of growth suppression and of the immune system, resistance to death signals, unlimited replicative potential, development of a supportive microenvironment (including angiogenesis), and ability to invade and metastasize (Hanahan and Weinberg 2011). Aberrant gene expression is manifest through a number of different mechanisms including DNA copy number alterations (amplifications, deletions, gains and losses of whole chromosomes resulting in aneuploidy), epigenetic regulation via methylation or histone acetylation, fusion proteins and individual gene mutations. Amplifications that are critical to tumorigenesis likely are essential because they result in the overexpression of gene products on which the tumor is dependent. These are often referred to as “driver” genes, as dysregulated expression leads to the activation of oncogenic pathways, while other genes in the amplified region may or may not be overexpressed and instead are “passenger” genes. Analysis of individual amplifications have elucidated driver pathways of cancer and revealed potential targets for drug development. For example, amplification of the Her-2/neu gene occurs in 25-30% of breast cancers and is associated with a more aggressive phenotype (Slamon et al 1989). However, treatment with HER-2 targeted therapy, in particular trastuzumab, has dramatically improved the natural history of HER2-positive breast cancer (Ferretti et al 2007). Similarly,

non-small cell lung cancers with mutations in or amplification of the EGFR gene benefit from EGFR inhibitors. Several amplified genes have been identified in epithelial ovarian cancers. The Cancer Genome Atlas (TCGA) project recently published their results from a multicenter comprehensive effort to characterize the molecular abnormalities in high-grade serous ovarian carcinomas. In this study 489 clinically annotated stage II-IV high-grade serous ovarian cancer samples were analyzed for changes in mRNA expression, microRNA expression, DNA copy number, and DNA promoter methylation. Interestingly, the TCGA found a relatively low rate of recurrent mutations while copy number changes were relatively abundant(Cancer Genome Atlas Research Network, 2011). In light of the recent results of the TCGA, this chapter will discuss the major pathways (Figure 1) frequently amplified in ovarian cancers and review the clinical efficacy of therapeutic agents targeting these genes.

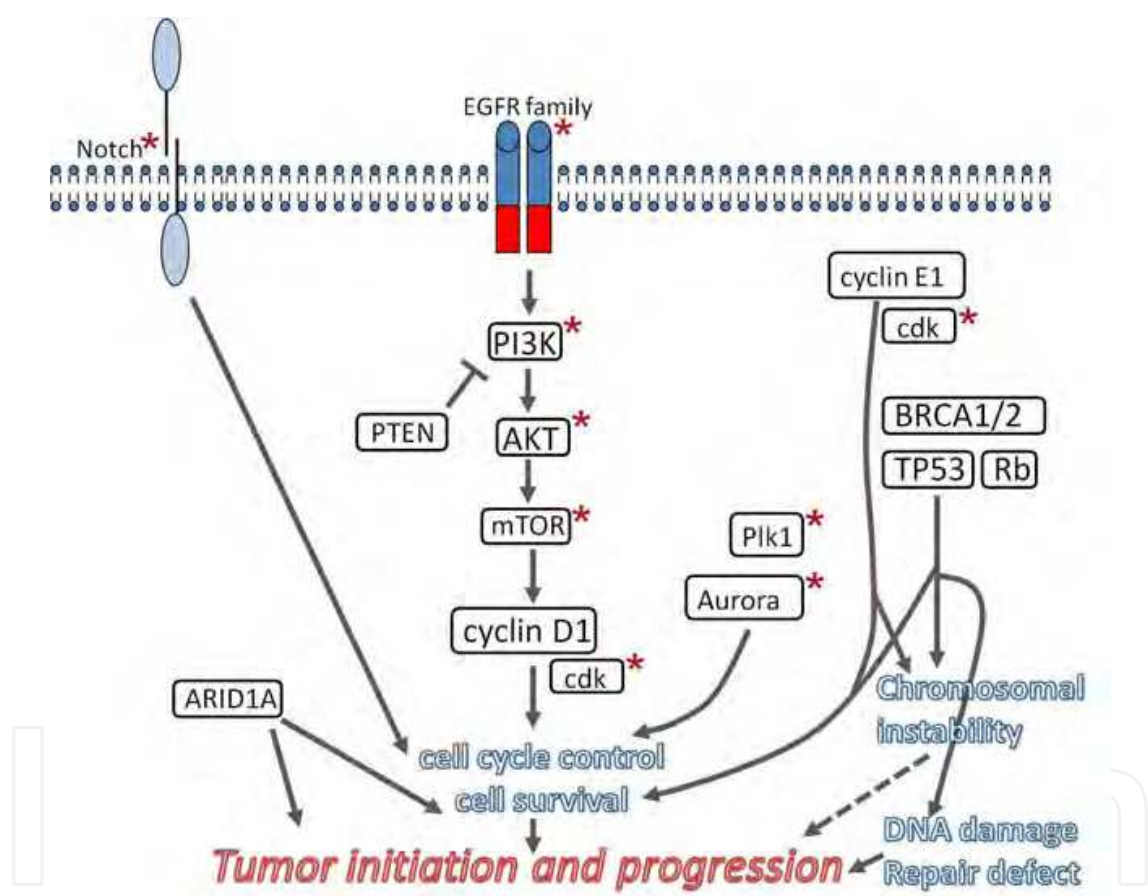


Fig. 1. Pathways amplified in epithelial ovarian cancer. *represents targetable pathways discussed in this chapter.

2. Global assessment of copy number variation in ovarian cancer

DNA copy number variations can be identified using several techniques including cytogenetics, fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH), and single nucleotide polymorphism (SNP) arrays. The latter two have the advantage of providing an unbiased genome wide assessment of copy number variation and have been widely used to characterize the complex genomic alterations attributable to

ovarian cancer and reveal it to be a heterogeneous group of diseases (Gorringe et al 2010, Meinhold-Heerlein et al 2005, Nakayama et al 2007, Staebler et al 2002). Recent studies of the genomic alterations between invasive serous carcinomas and low grade or borderline serous tumors have identified dramatic differences in DNA copy number changes (Meinhold-Heerlein et al 2005, Nakayama et al 2007, Staebler et al 2002). High-grade serous carcinomas uniformly exhibited more extensive DNA copy number variations than borderline tumors or low-grade serous carcinomas (Figure 2). The frequency and amplitude of changes was higher in invasive serous carcinomas and involve the majority of chromosomes through gain or loss of discrete subchromosomal regions, chromosome arms, or whole chromosomes. By contrast, low-grade tumors exhibit significantly fewer copy number gains and few chromosomal losses. The pervasive changes seen within the chromosomes of high-grade serous ovarian carcinomas suggest that significant genomic instability is a critical feature of this disease.

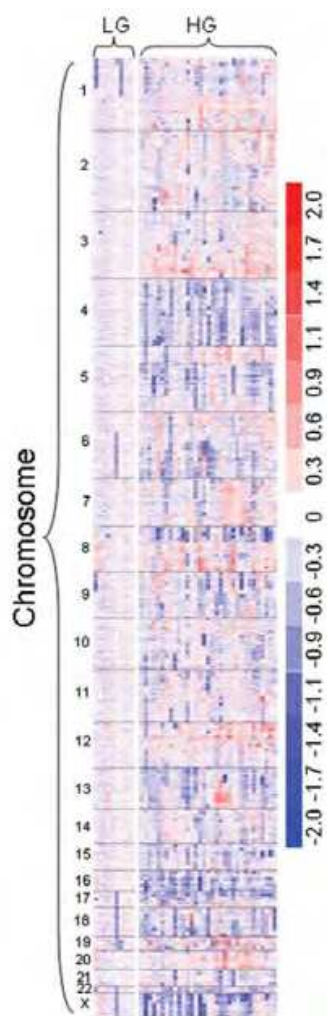


Fig. 2. Genome-wide distribution of DNA copy number changes in low-grade and high-grade ovarian serous carcinomas. Each column represents an individual tumor sample. DNA copy number changes are represented as pseudocolor gradients corresponding to the folds of increase (red boxes) and decrease (blue boxes), as compared to pooled normal samples. Reproduced with permission (Nakayama et al 2007).

Similar results were found in the TCGA analysis of the molecular aberrations in high-grade serous ovarian carcinomas. The project identified only 9 significant recurrently mutated genes, of which TP53, BRCA1, and BRCA2 were the most common (Cancer Genome Atlas Research Network, 2011). In contrast, copy number aberrations were abundant. One hundred and thirteen significant focal DNA copy number aberrations, including 8 regional recurrent gains, 22 regional recurrent losses, and 63 regions of focal amplification, were identified. Five of the regional gains were present in >50% of tumors. Analysis of the focal amplifications identified a number of genes that were highly amplified and potential therapeutic targets.

The results of these studies clearly highlight the complex molecular and genetic changes that are harbored by ovarian serous carcinomas. Copy number alteration alone, however, does not necessarily indicate that the region plays a causal role in tumorigenesis. One of the challenges with these studies is identifying the potential oncogenes or oncogenic pathways within the affected chromosomal regions that are likely to be responsible for the pathogenesis of ovarian cancer and/or should be a focus for drug development. In the following sections, we will discuss some of the candidate genes that have been identified and are being evaluated in clinical practice.

3. PIK3CA and AKT2

The phosphoinositide 3-kinase (PIK3)-AKT2 signaling pathway regulates diverse cellular functions including cellular proliferation, migration, metabolic homeostasis, apoptosis and survival, and the dysregulation of this pathway has been implicated in the tumorigenesis of a variety of cancers (Karakas et al 2006, Stokoe 2005). AKT2 is a serine/threonine protein kinase containing SH2-like (Src homology 2-like) domains and is a member of the AKT subfamily. It was originally identified as one of the putative human homologs of the v-akt oncogene of the retrovirus AKT8 (Staal 1987). AKT2 is activated by its upstream regulator PI3K. PIK3CA is the 110kD component of the catalytic subunit of PIK3 and aberrations in normal signaling of PIK3CA and AKT2 have been implicated in ovarian cancer pathogenesis making them potential targets for drug development (Cheng et al 1992, Dancey 2004, Hu et al 2005). Overexpression of activated PIK3CA results in phosphorylation of AKT and cellular transformation and inactivation of AKT by dominant negative mutants abrogates the survival advantage conferred by activated PI3K (Kang et al 2005, Link et al 2005). PTEN (phosphatase and tensin homologue deleted on chromosome 10) is a dual lipid and protein phosphatase that targets PIP3 (phosphatidylinositol-3,4,5- triphosphate), the target of PIK3. This pathway may be aberrantly activated by amplification or mutation of AKT2 or PIK3CA, or deletion, promoter methylation, or functional loss of PTEN which can lead to the excessive activation of downstream effectors, such as mTOR (Altomare et al 2004, Gao et al 2004, Mabuchi et al 2009).

AKT2 amplification has been reported in 5-29% of ovarian cancer cases (Bellacosa et al 1995, Cheng et al 1992, Courjal et al 1996, Nakayama et al 2006b, Park et al 2006). In comparison, AKT2 was not amplified in benign or borderline ovarian tumors (Bellacosa et al 1995, Nakayama et al 2006b). Similarly, low-level amplifications were present in PIK3CA in high-grade carcinomas but not in serous borderline tumors. Twenty seven percent of cases showed amplification in either gene emphasizing how frequently components of this pathway are amplified in ovarian cancer and coamplification of the two genes was seen in a small subset (Nakayama et al 2006b). The findings of this study also support the dualistic

model of ovarian serous carcinogenesis in which high-grade and low-grade ovarian serous tumors develop along distinctly different molecular pathways (Kurman and Shih 2008).

Pathway activation through PIK3CA can occur through either amplification or activating mutation of the catalytic subunit. Mutations of PIK3CA are typically associated with endometrioid and clear cell subtypes and are associated with lower tumor stage and grade (Campbell et al 2004, Kolasa et al 2009, Willner et al 2007). Amplifications, on the other hand, have been detected in all histological subtypes, though there was an association with poorer differentiation. PIK3CA amplification has been reported in 13-24% of ovarian carcinomas and is associated with increased expression of phosphorylated AKT indicating that amplification results in increased activation of the pathway (Campbell et al 2004, Kolasa et al 2009, Nakayama et al 2006b, Willner et al 2007, Woenckhaus et al 2007).

Clinical data is lacking in the majority of these studies and the prognostic role of AKT and mTOR in ovarian cancer is unclear. The median survival of patients with normal levels of AKT2 was longer than in patients whose tumors harbored AKT2 amplifications (45 versus 22 months, respectively), however the study was limited by the small number of patients for which survival data was available and did not reach statistical significance (Bellacosa et al 1995). The activation of AKT and increased downstream mTOR expression has been associated with more aggressive disease and shorter patient survival (Bunkholt Elstrand et al 2010). The effect of PIK3CA amplification on survival is also unclear with some studies showing no influence of amplification on overall survival while another showed that PIK3CA amplification was associated with shorter survival (Kolasa et al 2009, Willner et al 2007, Woenckhaus et al 2007).

PIK3-AKT2 pathway activation may affect response to therapy. PIK3CA amplification was identified more frequently in patients who were platinum resistant and in patients who did not achieve a complete remission to chemotherapy (Kolasa et al 2009). Disease recurrence was increased in the group with amplifications, however this study was limited by its small size and overall survival was not affected. Further studies in ovarian cancer cell lines with acquired cisplatin resistance shown that the cells harbor increased activation of the Akt/mTOR survival pathway and that inhibition of the pathway resensitizes the cells to cisplatin treatment (Lee et al 2005b, Peng et al 2010). However, whether they can be used as predictors of therapeutic response has not been established.

Given the relatively common activation of this pathway in tumorigenesis, there has been considerable interest in developing therapeutic drugs to target the PTEN/PIK3/AKT pathway for use in multiple cancers. The most successful approach thus far has been the development of mTOR inhibitors, which have been approved for use in renal cell carcinomas and pancreatic neuroendocrine tumors. Rapamycin, and its derivative inhibitors (temsirolimus, everolimus, and ridaforolimus) are currently in use in multiple clinical trials specifically evaluating their effectiveness for the treatment of advanced ovarian cancer. The current progress of the development of these drugs for ovarian cancer was the topic of a recent excellent review (Mabuchi et al 2011). Preclinical data suggest that these agents may be effective both as monotherapy as well as in combination with traditional cytotoxic chemotherapy and may even be effective as preventative agents. The majority of these studies are ongoing and have not completed recruitment, however the results of a few have been published (Table 1). In a phase I clinical trial designed to determine the recommended phase II dose of weekly temsirolimus and topotecan for the treatment of advanced and/or recurrent gynecologic malignancies, the toxicities of the combination were dose-limiting (Temkin et al 2010). Seven participants with ovarian cancer were enrolled in the study but

the authors do not report the best response for these participants; nine of the 11 evaluable participants on the study had stable disease. In a Phase I study of temsirolimus, carboplatin, and paclitaxel in patients with endometrial and ovarian cancers, the combination was well tolerated and a recommended phase II dose was established(Oza et al 2009). In addition, 22 of the 26 participants with follow-up data showed either partial response (38.5%) or stable disease (46%) for a median duration of 7 months. In a phase II trial combining targeted therapies, temsirolimus and bevacizumab, a monoclonal antibody targeting VEGF-A, were given to patients with recurrent epithelial ovarian cancer who had received ≤ 2 chemotherapy regimens for recurrent disease. This study met its first stage goal of 14 participants remaining progression free at 6 months and has been reopened for second stage accrual(Morgan et al 2011). Rapamycin and its analogues predominantly inhibit mTOR complex 1 (mTORC1) without affecting the activity of mTORC2. A novel ATP-competitive inhibitor of mTOR kinase activity, AZD8055, inhibits both the mTORC1/mTORC2 and prevents the feedback activation of AKT that is observed with the rapalogues and has completed phase I clinical trial in advanced solid malignancies(Banerji et al 2011, Chresta et al 2010).

Therapy	Phase	# Pts	Selection Criteria	Outcome	Comments
Temsirolimus + Topotecan (Temkin et al 2010)	I	15 (7 ovarian cancer)	advanced or recurrent gynecologic malignancy refractory to curative therapy	9/11 SD	Toxicities of the combination were dose limiting, intolerable in pts previously treated with radiation
Temsirolimus + Carboplatin + Paclitaxel (Oza et al 2009)	I	31	advanced solid malignancies suitable for carboplatin and paclitaxel chemotherapy who had not received more than 2 prior lines of chemotherapy	10/26 PR 12/26 SD	Median duration of response 7 months
Temsirolimus + Bevacizumab (Morgan et al 2011)	II	31	recurrent epithelial OC who had received ≤ 2 chemotherapy regimens for recurrent disease	3/25 PR 9/25 SD	Met first stage goal, reopened for second stage accrual (NCT01010126)

Table 1. Selected Clinical Trials of mTOR inhibitors in Ovarian Cancer.

Several other PI3K-AKT pathway inhibitors (Table 2) are in early clinical development. Of these, GDC-0941, an inhibitor of PIK3CA, has shown early signs of possible clinical efficacy in an ovarian cancer patient with a PTEN negative tumor(Moreno Garcia et al 2011). MK-

2206, an allosteric AKT inhibitor, showed preclinical efficacy in ovarian cancer cell lines with synergistic responses when combined with other cytotoxic agents such as doxorubicin, docetaxel, and carboplatin. It is currently under investigation in a phase II trial evaluating its efficacy as monotherapy specifically in ovarian cancers exhibiting defects in the PI3K/AKT pathway while several other phase I trials are evaluating its safety in combination with other chemotherapeutic agents(Hirai et al 2010). The results of these and other ongoing studies of PI3K-AKT pathway inhibitors are eagerly awaited.

Drug	Target	Comments
Everolimus	mTOR inhibitor	Under evaluation in Phase I and II trials for ovarian cancer
OSI-027	ATP-competitive mTOR inhibitor	
AZD-8055	ATP-competitive mTOR inhibitor	Dual mTORC1/mTORC2 inhibitor, prevents feedback activation of AKT observed with rapalogues
CH5132799	Selective class I PI3K inhibitor	Anti-tumor activity in vitro and in animal models
GDC-0941	PIK3CA inhibitor	One ovarian cancer patient (PTEN negative) showed 30% response by PET & 80% by CA-125, stayed on study for ~5 months(Moreno Garcia et al 2011)
BEZ235	Dual PI3K/mTOR inhibitor	Anti-tumor activity in mouse model, undergoing evaluation as monotherapy and in combination with cytotoxic chemotherapy
MK-2206	Allosteric AKT inhibitor	Currently being evaluated in recurrent Grade 2 or 3 ovarian, fallopian tube, or primary peritoneal cancer with evidence of a defect in the PI3K/ AKT pathway

Table 2. Other PI3K-AKT pathway inhibitors with pre-clinical efficacy in ovarian cancer.

4. Epidermal growth factor receptors

The epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases has been implicated in the oncogenic transformation of a number of cancers. This family of genes encodes for four transmembrane tyrosine kinase receptors commonly referred to as EGFR (HER1/erbB1), HER2/neu (erbB2), HER3 (erbB2) and HER4 (erbB4). They each consist of a ligand-binding extracellular domain, an intracellular kinase domain, and a C-terminal signaling tail. The receptors are activated by binding to one of more than 30 ligands that then allow the formation of homodimers or heterodimers; except HER2 has no known ligand but is able to form heterodimers with other ligand-bound EGFR family members. Interestingly, HER3 lacks intrinsic kinase activity and therefore must form a heterodimer to be active and its preferred binding partner is HER2/neu. Activated dimers recruit signaling molecules through a phosphorylated cytoplasmic domain that initiates a signaling cascade leading to the activation of downstream pathways such as PI3K-AKT and MAPK that

ultimately regulate cellular proliferation, migration, invasion, and apoptosis. Two recent excellent reviews have been published on the role of these receptors in ovarian cancer (Sheng and Liu 2011, Siwak et al 2010); herein we will focus on the clinical implications of EGFR, HER2/neu and HER3, the three receptors found to be amplified in ovarian cancers.

Amplification of the EGFR gene has been identified in 4-22% of ovarian cancers and, for the most part, amplification correlates with overexpression (Dimova et al 2006, Lassus et al 2006, Stadlmann et al 2006, Vermeij et al 2008). Some studies have delineated the level of amplification into high and low categories. While high level amplification occurs in a small percentage of tumors (4-12%), low level gain has been reported in as many as 43% of cases (Dimova et al 2006, Lassus et al 2006). High-level amplifications have been associated with malignant tumors and worse histologic grade. Results are mixed on the influence of EGFR overexpression on patient outcome. Several studies showed no association with survival, while EGFR overexpression was found to be a strong prognostic indicator in other studies (Baekelandt et al 1999, Elie et al 2004, Lassus et al 2006, Lee et al 2005a, Nicholson et al 2001). The discrepancy may be related to different methodologies used in staining and analysis.

Preclinical data suggests that targeting EGFR is an effective approach to treating ovarian cancer. Ovarian cancer cells treated with antisense RNA or dominant-negative approaches showed reduced proliferation, invasion, and tumorigenicity in a rat ovarian tumor model (Alper et al 2000, Alper et al 2001, Chan et al 2005). A human-mouse chimeric anti-EGFR monoclonal antibody (C225, cetuximab) resulted in decreased activity of cyclin dependent kinases and inhibition of ovarian cancer cellular proliferation by 40-50% and when combined with cytotoxic chemotherapy enhanced the efficacy of those agents (Ye et al 1999). However, the results have been inconsistent and targeting of EGFR with either gefitinib or cetuximab in several ovarian cancer cell lines showed minimal response (Bull Phelps et al 2008).

Two types of EGFR inhibitors are currently in clinical use: monoclonal antibodies (Table 3) and small molecule tyrosine kinase inhibitors (TKIs), and several have been evaluated for the treatment of ovarian cancer. The studies have taken different strategies, some requiring EGFR immunohistochemical positivity as an inclusion criterion, while others evaluated EGFR expression only after enrollment. Overall the results have been disappointing with some studies showing, at best, modest response. In the two studies using single agent EGFR monoclonal antibodies, cetuximab and matuzumab, overall response rates were 4% and 0%, respectively (Schilder et al 2009, Seiden et al 2007). There are five trials evaluating EGFR monoclonal antibodies in combination with cytotoxic chemotherapy, with three ongoing. Of the two involving cetuximab, a phase II trial of cetuximab in combination with carboplatin in recurrent, platinum-sensitive disease yielded an objective response rate of 34.6%, a rate that was too low to warrant further evaluation (Secord et al 2008). The other Phase II study that evaluated the combination of cetuximab, paclitaxel, and carboplatin in the initial treatment of advanced-stage ovarian, primary peritoneal, or fallopian tube cancers did not show an increase in progression free survival compared to historical controls (Konner et al 2008). Three separate phase II trials are evaluating panitumumab with cytotoxic chemotherapy; the results of these studies are not yet available but are eagerly awaited.

Small molecule tyrosine kinase inhibitors (TKI) targeting EGFR activity have been investigated in several trials specifically focused on ovarian cancer (Table 4). Single agent TKI did not show any substantial clinical benefit (0-9% for gefitinib (Posadas et al 2007,

Schilder et al 2005), 0% for CI-1033 an irreversible EGFR inhibitor(Campos et al 2005)). TKIs combined with cytotoxic chemotherapy, anti-angiogenic therapy, or hormonal therapy have also shown limited clinical efficacy and in some cases excessive toxicity(Campos et al 2010, Chambers et al 2010, Nimeiri et al 2008, Vasey et al 2008). The reason behind the relative failure of EGFR targeted therapies is not understood, but may be related to constitutive activation of downstream pathways, overexpression of ligands, or activation of alternative signaling pathways (reviewed in (Bianco et al 2007, Siwak et al 2010)). Despite the promising preclinical results based on the amplification data, these therapeutic agents cannot be recommended outside of a clinical trial setting for the treatment of ovarian cancer.

Therapy	Phase	# Pts	Selection Criteria	Outcome	Comments
Cetuximab (Schilder et al 2009)	II	25	Persistent/recurrent ovarian or primary peritoneal carcinoma	1/25 PR 9/25 SD	Median progression free survival 1.8 months
Matuzumab (Seiden et al 2007)	II	37	recurrent, EGFR-positive ovarian, or primary peritoneal cancer	6/37 SD	
Cetuximab + Carboplatin (Secord et al 2008)	II	28 (26 EGFR +)	relapsed platinum-sensitive ovarian or primary peritoneal carcinoma	3/28 CR 6/28 PR 8/28 SD	Did not meet criteria for a second stage of accrual
Cetuximab + Carboplatin + Paclitaxel (Konner et al 2008)	II	40	Initial treatment of stage III or IV, debulked tumor, EGFR positive by IHC	Median PFS 14.4 mths, PFS at 18 mths 38.8%	No prolongation of PFS when compared to historical data
Panitumumab + Gemcitabine	II		Persistent/recurrent platinum-resistant epithelial ovarian, primary peritoneal or fallopian tube cancer		Ongoing (NCT01296035)
Panitumumab + Pegylated Liposomal Doxorubicin	II		Platinum resistant epithelial primary ovarian, primary fallopian or primary peritoneal cancer		Ongoing (NCT00861120)
Panitumumab + Carboplatin + Pegylated Liposomal Doxorubicin	II		Platinum-sensitive recurrent epithelial ovarian cancer, primary peritoneal carcinomatosis or fallopian tube cancer, KRAS wild type		Opening soon (NCT01388621)

Table 3. Anti-EGFR monoclonal antibodies.

Therapy	Phase	# Pts	Selection Criteria	Outcome	Comments
CI-1033/ Canertinib (Campos et al 2005)	II	105	Persistent/recurrent epithelial ovarian cancer	18/52 SD at highest dose level	median PFS 2.2 mths, median OS 9.1 mths at highest dose level
Gefitinib (Posadas et al 2007)	II	24	Recurrent epithelial ovarian cancer	9/24 SD	EGFR and pEGFR levels decreased during therapy in >50%, however not associated with clinical benefit
Gefitinib (Schilder et al 2005)	II	27	Persistent/recurrent epithelial ovarian or primary peritoneal carcinoma	1/27 PR	4 pts with PFS ≥6 mths, trial did not continue to second stage, responder had activating EGFR mutation, trend towards response in EGFR positive pts
Gefitinib + Anastrozole (Krasner et al 2005)	II	35	Recurrent ovarian, peritoneal or tubal carcinoma, ER and/or PR positive by IHC	1/23 CR 14/23 SD	
Gefitinib + Tamoxifen (Wagner et al 2007)	II	56	Refractory, recurrent epithelial ovarian cancer	16/56 SD	Tumor did not need to be positive for ER or EGFR by IHC
Erlotinib (Gordon et al 2005)	II	34	Refractory, recurrent, ovarian cancer, EGFR positive by IHC	2/34 PR 15/34 SD	
Erlotinib + Carboplatin + Docetaxel (Vasey et al 2008)	Ib	45	Chemonaive	5/23 CR 7/23 PR	Objective response rate (52%) lower than in historical controls (59%), unselected for EGFR expression
Erlotinib + Bevacizumab (Chambers et al 2010)	II	40	Platinum resistant	1/39 CR 8/39 PR 10/39 SD	ORR not improved compared to historical controls of Bevacizumab alone
Erlotinib + Bevacizumab (Nimeiri et al 2008)	II	13	Recurrent ovarian, primary peritoneal or fallopian tube cancer	1/13 CR 1/13 PR 7/13 SD	Combination not superior to single-agent Bevacizumab, rate of GI perforation a concern

Table 4. Anti-EGFR small molecule inhibitors.

Expression and amplification levels of Her2/neu in ovarian cancer have been extensively evaluated, however the data is inconsistent and its significance is still controversial. Early studies showed amplification in 26% with corresponding overexpression and an analysis of the subset with available survival data showed a significantly longer median overall survival in women whose tumors did not exhibit Her2 amplification (1879, 959, and 243 days for women having one copy, 2-5 copies and >5 copies of Her2/neu gene, respectively, $p < 0.0001$) (Slamon et al 1989). In subsequent studies, observed rates of Her2/neu amplification in ovarian cancer has been reported in up to 66% of epithelial ovarian cancers with overexpression reported in up to 76% (Camilleri-Broet et al 2004, Press et al 1990, Ross et al 1999, Serrano-Olvera et al 2006, Slamon et al 1989, Tuefferd et al 2007, Vermeij et al 2008). Levels of amplification differ with low copy number amplification (<2) observed in as many as 79%, 3-5 copies in 14%, >5 copies in 6.8%, and >10 copies in 1.8% (Lassus et al 2004). The level of amplification in general has correlated with level of overexpression by IHC, however this too has been called into question (Lassus et al 2004, Mano et al 2004, Pegram et al 1997, Wu et al 2004) and may be reflective of other mechanisms responsible for overexpression other than amplification.

Several studies have shown an association between Her2/neu overexpression/amplification and poor response to therapy and prognosis, however more recent reports refute this association (Berchuck et al 1990, Bookman et al 2003, Farley et al 2009, Pegram et al 1997, Rubin et al 1994, Tuefferd et al 2007). In a recent Gynecologic Oncology Group study that evaluated Her2/neu amplification in 133 epithelial ovarian cancers, amplification (>2 copies) was only identified in 7% and was not an independent prognostic factor for progression free survival or overall survival (Farley et al 2009). A phase II trial evaluating the efficacy of trastuzumab, a monoclonal humanized anti-Her2 antibody, in patients with recurrent ovarian cancer showed that only 11% of tumor samples exhibited elevated expression of Her2 by immunohistochemistry. Of the participants treated with trastuzumab, the overall response rate was only 7% with a progression free interval of 2 months (Bookman et al 2003). Overall, it does not appear that Her2/neu amplification has predictive or prognostic value in epithelial ovarian cancer and the value of treatment with HER2 directed monotherapy is limited (Table 5). Despite, preclinical evidence of effectiveness (Gordon et al 2006), pertuzumab, a recombinant, humanized monoclonal antibody that binds the HER2 dimerization domain impeding dimerization of HER2 with other family members and thus prevents activation of downstream pathways, has shown similarly low response rates in clinical trials in the treatment of ovarian cancer. As a single agent, the response rate was only 4.3% and in a randomized phase II study the addition of pertuzumab to gemcitabine improved the objective response rate to 13.8% from 4.6% (Gordon et al 2006, Makhija et al 2010). Treatment response appeared to correlate with Her2 phosphorylation status in one study and low Her3 expression in another, however these markers have not yet been validated in further studies. Lapatinib, a dual EGFR/HER2 TKI, has also shown limited clinical response and excessive toxicity (Joly et al 2009, Kimball et al 2008). Preliminary results of a phase I/II trial combining lapatinib with carboplatin and paclitaxel showed promising preliminary results, but the final results of the trial have not been published (Rivkin et al 2008). Further studies will be necessary to determine whether lapatinib may be a useful agent in ovarian cancer.

Therapy	Phase	# Pts	Selection Criteria	Outcome	Comments
Trastuzumab (Bookman et al 2003)	II	41	persistent or recurrent epithelial ovarian cancer, 2/3+ HER2 by IHC	1/41 CR 2/41 PR 16/41 SD	serum HER2 was not associated with clinical outcome
Pertuzumab (Gordon et al 2006)	II	117	Recurrent epithelial ovarian cancer	5 PR 8 SD	Median PFS 6.6 wks, trend toward improved PFS for pts with pHER2+ disease
Pertuzumab + Gemcitabine vs Placebo + Gemcitabine (Makhija et al 2010)	II	65 (combo) 65 (placebo)	advanced, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	9/65 PR (combo) 3/65 PR (placebo)	Low HER3 mRNA expression may predict pertuzumab clinical benefit
Lapatinib + Topotecan (Joly et al 2009)	II	39 (37 ovarian cancer)	Ovarian cancer relapsed w/in 12 months	0/2 PR 7/9 SD	Prematurely stopped for lack of efficacy
Lapatinib + Carboplatin (Kimball et al 2008)	I	12	Recurrent platinum sensitive epithelial ovarian carcinoma	3/11 PR 3/11 SD	unacceptable toxicities, excessive treatment delays and limited clinical responses
Lapatinib + Carboplatin + Paclitaxel (Rivkin et al 2008)	I/II	25	Recurrent ovarian cancer	CR 21% PR 29% SD 29%	final results not published

Table 5. Selected Clinical Trials of HER2/neu Targeted Agents in Ovarian Cancer.

The roles of HER3 and HER4 in ovarian cancer have been less extensively studied(Sheng and Liu 2011). HER3 amplification and overexpression in ovarian cancer has been described and in one study was significantly associated with poor survival (median survival time 3.3 years vs. 1.8 years for patients with low vs. high HER3 expression)(Sheng and Liu 2011, Tanner et al 2006, Tsuda et al 2004). Antibodies directed against the extracellular domain of HER3 diminished HER2 activity and attenuated the activation of downstream effectors(van der Horst et al 2005). Compensatory overexpression of HER3 has also been implicated as a mechanism of resistance to other EGFR inhibitors(Sheng and Liu 2011). These data suggest that targeting HER3 may be an effective treatment strategy and three monoclonal antibodies that target HER3 are being tested in early phase clinical trials for advanced solid tumors (U3-1287, MM-121, and MM-111 which targets both HER2 and HER3). The expression of

HER4 has been variably reported in ovarian cancer, ranging from nearly absent to almost ubiquitously expressed (Sheng and Liu 2011). Interestingly, overexpression of HER4 in ovarian cancer was associated with a trend toward improved progression free and overall survival, an effect that has also been seen in breast cancer possibly by promoting differentiation (Pejovic et al 2009, Rajkumar et al 1996). However, these results have not been confirmed and the role of HER4 in ovarian cancer is still undefined.

5. Notch signaling pathway

The Notch signaling pathway is an evolutionarily conserved pathway that regulates cellular differentiation, proliferation, and apoptosis. The family of Notch receptors (Notch 1-4) are large transmembrane proteins that consist of an extracellular ligand binding domain, a transmembrane domain, and an intracellular domain. Activation of the receptors is a multi-step process consisting of an initial cleavage event allowing the extracellular domain to heterodimerize with transmembrane ligands (Delta-like 1, 3, 4 and Jagged 1 and 2). Following ligand binding a second cleavage event releases the Notch extracellular domain (ECD) causing the ECD and the ligand to be endocytosed. Cleavage by gamma secretase following endocytosis releases the active Notch intracellular domain (NICD) allowing for translocation to the nucleus and heterodimerization to transcription factors and recruitment of coactivators to form a functionally active transcriptional complex (Rose 2009). Of the Notch receptors, Notch1 and Notch3 have been implicated in ovarian cancer. Reports of Notch1 expression in ovarian cancer are inconsistent with some showing increased expression in carcinomas compared to benign tumor or normal ovarian surface epithelium, while others showed decreased mRNA expression in carcinomas (Hopfer et al 2005, Rose et al 2010, Wang et al 2010).

The association between Notch3 and ovarian cancer has been more extensively studied. High level Notch3 amplification has been observed in 7.8% of high-grade serous carcinomas (Nakayama et al 2007), while high level protein overexpression was found in 63% of serous carcinomas and was significantly correlated with advanced stage, likelihood of metastasis, chemoresistance and poor overall survival (Jung et al 2010). Overexpression of the Notch ligands, Jagged-1 and Jagged-2, has also been identified in ovarian tumor cells lending support that activation of the Notch pathway promotes ovarian cancer proliferation and that inhibition of this pathway may be a viable therapeutic approach (Choi et al 2008, Hopfer et al 2005). Similarly, the TCGA identified alterations in the Notch pathway in 22% of high-grade serous ovarian carcinoma samples, which included amplification/mutation of Notch3, amplification of Jagged-1 and Jagged-2, and amplification/mutation of MAML1-3, a family of Notch transcriptional coactivators (Cancer Genome Atlas Research Network, 2011). Inactivation of Notch signaling through targeting Jagged-1 or direct inhibition of Notch by preventing cleavage with a gamma-secretase inhibitor decreases the proliferative potential of and increases apoptosis in ovarian cancer cell lines and xenograft models (Park et al 2006, Steg et al 2011). Targeting Jagged-1 also resulted in decreased microvessel density in xenografts suggesting Notch signaling may play a role in angiogenesis.

Notch pathway inhibitors have recently moved into clinical trials. Early reports of a phase I clinical trial of RO4929097, a selective oral gamma-secretase inhibitor, showed prolonged

stable disease in 3 ovarian cancer patients (Table 6)(Tolcher et al 2010). Combination therapy is being evaluated in two ongoing early phase clinical trials in which RO4929097 is combined with either cediranib, a VEGF inhibitor, or GDC-0449, a hedgehog inhibitor. Whether this will be a useful agent in treating ovarian cancer remains to be seen.

Drug	Target	Comments
R04929097	Selective oral gamma-secretase inhibitor of Notch	Preliminary efficacy in 3 ovarian cancer patients(Tolcher et al 2010). Two early phase combination trials ongoing: NCT01131234 (+ cediranib), NCT01154452 (+ GDC-0449)
PD 0332991	CDK4/6 inhibitor	Current being tested in NCT01037790 which includes ovarian germ cell tumors
BMS-387032 (SNS-032)	CDK2 inhibitor	
Flavopiridol (Alvocidib)	Multi-CDK inhibitor	Ongoing phase II trial in combination with cisplatin in epithelial ovarian cancers (NCT00083122)
ON 01910.Na	Polo-Like Kinase 1 inhibitor	Durable response in a platinum-refractory ovarian cancer pt, maintained progression free for 24 months (Jimeno et al 2008)
MLN8237	Aurora A kinase inhibitor	Durable response (PR) in a pt with platinum-refractory ovarian cancer with continued treatment over 1.5 years(Dees et al 2010), ongoing phase II in combination with paclitaxel (NCT01091428)
ENMD-2076	Aurora kinase inhibitor	3/46 PR, 27/46 SD in preliminary report from phase II trial in platinum resistant ovarian cancer(Matulonis et al 2011)

Table 6. Other pathway inhibitors with pre-clinical efficacy in ovarian cancer.

6. Cell cycle regulatory proteins

Sustaining proliferative signaling through disruption of cell cycle regulatory checkpoints is one of the hallmarks of cancer(Hanahan and Weinberg 2011). Aberrant expression of cyclins, cyclin dependent kinases (Cdks), and cyclin-Cdk inhibitors has been linked to tumorigenesis in multiple cancer models(Deshpande et al 2005, Hwang and Clurman 2005). Studies in epithelial ovarian cancer have shown inconsistent associations between individual cell cycle regulatory protein expression and patient outcome (reviewed in Nam and Kim(Nam and Kim 2008)). Among the best studied in ovarian cancer is cyclin E. Amplification of the cyclin E gene occurs in 7-65% of ovarian cancers, typically resulting in overexpression of the cyclin E protein(Cancer Genome Atlas Research Network, 2011, Courjal et al 1996, Marone et al

1998, Mayr et al 2006, Nakayama et al 2007, Nakayama et al 2010, Park et al 2006, Schraml et al 2003a). Cyclin E expression has been found in as many as 97% of ovarian cancer/primary peritoneal cancer samples (Davidson et al 2006). In suboptimally debulked advanced epithelial ovarian cancers obtained from women enrolled in GOG111, the expression level of cyclin E correlated with a 6 month shorter median survival and worse overall survival (Farley et al 2003). Analysis of the subset of patients with serous carcinomas (72% of total study) showed an 11 month difference in median survival and suggested that the role of cyclin E was limited to the serous histology as nonserous tumors showed no statistically significant difference in survival based on cyclin E expression. The association between cyclin E amplification and poor outcome has also been identified in recent German and Japanese studies, although the correlation was not statistically significant in the latter (Mayr et al 2006, Nakayama et al 2010). Two independent labs have also suggested that amplification of the cyclin E gene was associated with primary treatment resistance and targeting cyclin E expression with siRNA reduced cell viability and increased apoptosis (Etemadmoghadam et al 2009, Etemadmoghadam et al 2010, Nakayama et al 2010). These studies suggest that cyclin E amplification/expression may serve as both a prognostic and predictive factor in ovarian cancer as well as a therapeutic target in the treatment of ovarian cancer.

Several studies have evaluated the expression levels of many other cell cycle regulatory proteins, however few appear to show gene amplification. Although overexpression of cyclin D has been reported, levels of expression did not correlate with clinical outcome and the mechanism of overexpression was not through amplification of the gene (Courjal et al 1996, Dhar et al 1999, Hung et al 1996, Masciullo et al 1997). High copy number amplification of cdk2 was found in only 4-6% of cases (Cancer Genome Atlas Research Network, 2011, Marone et al 1998). Genomic loss of the region containing the retinoblastoma (Rb) gene and loss of heterozygosity of Rb has been described, however loss of expression occurred in few cases leading the investigators to conclude that Rb did not play a significant role in high-grade ovarian carcinomas (Dodson et al 1994, Kim et al 1994, Li et al 1991). Recently, two families of mitotic kinases have been implicated in ovarian cancer: the Polo-like kinases and Aurora kinases. Overexpression of both has been associated with a shortened survival time in patients with ovarian cancer and these targets have been the focus of recent clinical trials, however only the Aurora A gene was found to be amplified (in 15-27% of ovarian carcinomas) (Chen et al 2009, Mendiola et al 2009, Tanner et al 2000, Weichert et al 2004). Level of amplification of the Aurora A gene has been inconsistent with regards to tumor characteristics (histology or grade), level of expression, or patient outcome, with reports of greater association with early stage and low grade ovarian cancers as well as an association with poor prognosis (Fu et al 2006).

Many cell cycle associated kinase inhibitors are in early phase development (reviewed in (De Falco and De Luca 2010)), but few have been tested in ovarian cancer (Table 6). Interestingly, a mitotic regulatory inhibitor that affects the polo-like kinases (among others), had clinical benefit for a chemorefractory ovarian cancer patient for 24 months (Jimeno et al 2008). Preliminary results with MLN8237, an Aurora A kinase inhibitor, in a phase I trial showed one long term response (>1.5 yrs) in a patient with platinum refractory ovarian cancer (Dees et al 2010). A phase II study of ENMD-2076, an oral small molecule kinase inhibitor with activity against aurora kinases among other

kinases, showed modest activity in platinum-resistant ovarian cancer(Matulonis et al 2011). Inhibition of aurora kinase has been reported to sensitize cells to treatment with paclitaxel(Hata et al 2005, Scharer et al 2008) and the combination of paclitaxel and MLN8237 is being evaluated in a phase II randomized clinical trial. Results from these clinical trials are eagerly awaited.

7. Chromatin remodeling and transcription

Epigenetic modifications, such as DNA methylation and histone modifications, interact to remodel chromatin and result in the dysregulation of genes and pathways leading to uncontrolled cell growth. These mechanisms are primarily under the regulation of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) and therapeutic agents inhibiting these epigenetic modifiers are currently in clinical use for the treatment of certain hematologic malignancies and are being evaluated in clinical trials for ovarian cancer (reviewed in Matei and Nephew(Matei and Nephew 2010)). Other chromatin remodeling proteins are emerging as potentially important in the pathogenesis of ovarian cancer and may be useful therapeutic targets. Amplification of the chromosome 11q13.5 locus is frequently detected in human cancers, including ovarian carcinomas. This region was amplified in 13-16% of high grade ovarian carcinomas but not in any of the normal ovarian tissues, benign ovarian tumors, or low grade ovarian carcinomas analyzed(Nakayama et al 2007, Shih Ie et al 2005). The only gene within the amplicon that showed consistent overexpression was the gene encoding HBXAP/Rsf-1, a subunit of the RSF chromatin assembly complex. Patients whose tumors harbored amplification of Rsf-1 had a shorter overall survival compared with those without amplification(Nakayama et al 2007, Sheu et al 2010, Shih Ie et al 2005). Rsf-1 amplification (and ensuing overexpression) was identified as an independent prognostic factor based on multivariate analysis and this may be secondary to its ability to confer resistance to treatment with paclitaxel(Choi et al 2009). Elevated levels of Rsf-1 was shown to induce chromosomal instability, and in non-transformed cells, induced growth arrest and activated DNA damage response pathways. However in the presence of an inactivated p53, long-term overexpression of Rsf-1 stimulated cellular proliferation. While Rsf-1 is only amplified in a subset of high-grade ovarian serous carcinomas, inactivation or disruption of the RSF complex may be a useful therapeutic approach for tumors that depend on this protein for a proliferative advantage.

Other genes, such as MYC, NACC1 (which encodes Nac1), EMSY, MECOM, and PAK1 involved in chromatin remodeling and transcription, have also been shown to be amplified in ovarian carcinomas(Dimova et al 2009, Schraml et al 2003b, Shih Ie et al 2011). The expression of some, such as Nac1, has been associated with poor progression-free survival and paclitaxel resistance(Davidson et al 2007, Jinawath et al 2009, Nakayama et al 2006a). For others, such as MYC and EMSY, the significance of the amplification in high grade serous carcinoma is unclear and they may not be the oncogenic driver within the amplicon(Shih Ie et al 2005). Others are likely only relevant for a subtype, as in ARID-1A in clear cell carcinomas. A number of amplified genes identified by the TCGA and others have potential drugs currently in preclinical development or early phase clinical trials. However further work is necessary to determine whether any of these are prognostic markers or predictive of response to therapy.

8. Conclusion

Despite the identification of several amplified pathways, the results of the clinical trials of therapeutic agents targeting these pathways in ovarian cancer have been disappointing. There are several potential reasons for the poor response rates. The majority of studies of new targeted agents enroll patients with advanced disease often after several lines of standard cytotoxic therapy have failed. Even when used in combination with cytotoxic chemotherapy, these agents may not be able to overcome the mechanisms of resistance that the tumor has developed. Of interest would be evaluating these drugs in low-volume or early (marker only) recurrent disease or in combination with initial chemotherapy. Another strategy would be to test these typically cytostatic agents as maintenance therapy in patients who are in a complete clinical remission.

Resistance to targeted agents is mediated through a variety of mechanisms including mutation of the target, constitutive activation of downstream effectors, or activation of compensatory pathways. Defining the mechanisms of constitutive or acquired resistance requires thorough investigation in cellular and animal models. Emphasis should be placed on characterizing resistance mechanisms and developing better predictive markers to identify subsets of patients who are more likely to respond to therapy.

Targeting codependent pathways, rather than the amplified genes directly, may be another approach to cancer treatment. Cancer cells typically co-opt metabolic and stress response pathways becoming functionally reliant on them for continued proliferation while normal cells are not dependent on their function. Raj et al. recently used this strategy to preferentially eliminate cancer cells by targeting the oxidative stress response pathway (Raj et al 2011). This approach is similar to the synthetic lethality seen with PARP inhibitors in tumors with BRCA mutations.

In summary, while at present there is not a clear role for targeting the amplified pathways in ovarian cancer outside of a clinical trial, elucidating strategies of tumor resistance and compensatory mechanisms may allow for the development of novel therapeutic agents or the rational combination of existing agents to improve the prognosis of patients with ovarian cancer.

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10. References

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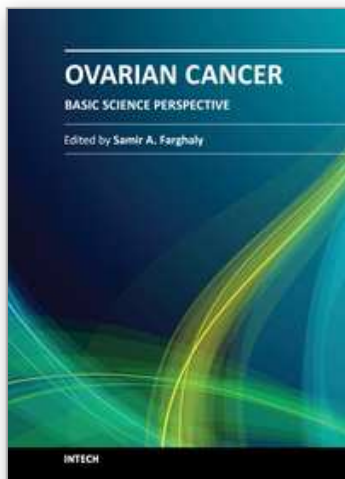
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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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