identifying reproductively intact cells in tissues to fully document the maturation of AECII to senescence.

This manuscript represents the first gene expression analysis demonstrating changes in AECII senescence after irradiation and adds a whole new set of markers that can and should be used in evaluating interventions for the mitigation of radiation-induced pulmonary injury.

References

Novel Facts About FAK: New Connections to Drug Resistance?
Christina M. Annunziata and Elise C. Kohn

Resistance to taxane chemotherapy presents a major hurdle in the treatment of recurrent ovarian cancer. The majority of epithelial ovarian cancers are sensitive to paclitaxel or docetaxel with initial treatment, but resistance ultimately develops in the majority of women. Development of a successful method to maintain susceptibility to taxane and platinum chemotherapy is an unmet clinical need. The article by Kang and colleagues in the current issue of the Journal describes a novel mechanism of taxane resistance, through FAK-dependent upregulation of MYB-1, a transcription factor that in turn upregulates CD44 (1). Intriguing findings in their work include the importance of nuclear-activated p397Tyr-FAK for this resistance process, and the demonstration that nuclear colocalization of activated FAK and p102Ser-YB1 dichotomized overall survival of patients with ovarian cancer.

How might this relate to taxane resistance in ovarian cancer? The mechanism of anticancer activity of taxanes relies on their ability to bind and stabilize polymerized tubulin. Stabilization of tubulin filaments prevents spindle disassembly during mitosis, leading to catastrophic cell death. Lack of tubulin depolymerization also prevents transport of proteins within nondividing cells, a likely cause for neuropathy associated with taxane therapy. Additionally, the decrease in free tubulin leads to mitochondrial hyperpolarization and release of cytochrome c, triggering proapoptotic cascades (2,3). Class III β-tubulin overexpression in clear cell carcinoma of the ovary was shown to discriminate poor prognosis; in the same study, p-glycoprotein did not correlate with clinical outcome (9). However, β-tubulin changes have not been borne out as common mechanisms of taxane resistance in ovarian cancer; nor has MDR-1 been demonstrated as a major mechanism of chemotherapy resistance in ovarian cancer (10). When analyzed together, however, colocalization of urokinase plasminogen activator, CD44, and MDR1 together did prognosticate a poor outcome for ovarian cancer (11).

FAK is a cytoplasmic tyrosine kinase that mediates cell adhesion, migration, and survival by coupling integrins with cytoskeletal signaling cascades (12). In addition to autophosphorylation (p397Tyr), it is phosphorylated and activated by Src and Src family kinases, downstream of receptor tyrosine kinases, including c-MET/HGFR, EGFR, VEGFR, and other receptor tyrosine kinases active in ovarian cancer and the ovarian cancer microenvironment. Activation of FAK can trigger prosurvival and antiapoptotic/antiangiogenic cascades via its activation of the ERK (13) and the phosphatidylinositol-3’ kinase (PI3K)/AKT pathways. One of the earliest prosurvival functions of FAK was shown to be abrogation of anoikis, programmed cell death occurring in the absence of cell attachment (14), a concept key to ovarian cancer, which relies on malignant effusions as a primary mechanism of early dissemination. Relevant to the current topic, increased MET activity, which leads to FAK phosphorylation, can induce taxane resistance in ovarian cancer (15). FAK activation stimulates the ERK/MEK pathway. Similarly, transient activation of ERK downstream of paclitaxel mediates resistance, and inhibition of ERK in ovarian cancer cells abrogates resistance (7,8).

Notes
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The current findings suggest that the interaction of FAK and YB-1 could interplay in several of these mechanisms. Kang et al. pinpoint FAK upstream of YB-1 in this in vitro drug resistance mechanism, and propose FAK inhibition as a means to sensitize ovarian cancer to paclitaxel. Consistent with the results in the current article, others have shown that YB-1-mediated upregulation of CD44 in breast cancer cells increased mammmosphere formation and caused paclitaxel resistance (16). CD44 signaling upregulates Nanog, a transcription factor for the MDR1 gene; increased MDR1 protein then led to taxane resistance in a cell line model of ovarian cancer (17). Indeed, expression of tumor stem cell markers Nanog and CD44 on primary ovarian cancer cells has been linked to poor outcome after primary treatment of women with ovarian cancer (18).

It appears that combining FAK inhibitor with paclitaxel intends to overcome resistance to paclitaxel by downregulating CD44, perhaps reversing the “cancer stem cell” phenotype. CD44-mediated resistance may be due to upregulation of the MDR gene, increasing drug efflux from the stem-like cancer cells. Abrogation of MDR1 drug efflux activity has been attempted several times in cancer therapy, most commonly by use of agents competitive for the efflux pump. The epitholine class of drugs was designed to bypass MDR1, but otherwise act similarly to taxanes in stabilizing tubulin (19). It is unclear, then, whether the FAK/paclitaxel combination will have additional activity over epitholines such as ixabepilone, currently approved as monotherapy or in combination with capcitabine for the treatment of taxane-resistant breast cancer. Although some activity of ixabepilone has been shown in ovarian cancer (20), its use has not been embraced.

There are several FAK inhibitors currently under investigation in clinical trials. PF-00562271 is an orally active FAK inhibitor, reported to have minimal toxicity with headache and nausea most common and dose limiting; 15 of 91 (16%) evaluable phase 1 patients remained on drug for six or more three-week cycles (21). Defactinib/VS-6063, the agent used in the preclinical elements of Kang et al.’s study, is undergoing investigation presently in combination with weekly paclitaxel (NCT01778803). The dose-escalation phase of this clinical trial has recently completed, but has not been formally reported.

Where does this new finding lead us? It reinforces the longstanding enthusiasm for FAK as a therapeutic molecular target in ovarian and other cancers. FAK’s key roles in invasion, angiogenesis, and anoikis underscore it as a central target. The findings in the report by Kang et al., linking nuclear FAK regulation to drug susceptibility, suggest a more broadly reaching potential of FAK inhibitors to modulate malignant cell behavior. However, the lack of peer-reviewed phase 1 data for VS-6063 dampens its immediate applicability to ovarian cancer. Advancement of this concept should be accompanied by validation of nuclear expression of activated FAK and YB-1 as integral biomarkers, selective and/or predictive for VS-6063 patient benefit.

References

Notes
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