Phosphatidylinositol 3-Kinase Inhibitors Are a Triple Threat to Ovarian Cancer

Commentary on Hu et al., p. 8208

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In this issue of Clinical Cancer Research, Hu et al. assess the role of phosphatidylinositol 3-kinase (PI3K) inhibition in vascular permeability, angiogenesis, and vascular remodeling in both tumor vessels and the peritoneal lining an athymic mouse model of intraperitoneal human ovarian carcinoma (1).

Ovarian cancer is a vicious disease. Often, ovarian cancer presents unexpectedly at an advanced stage with tumor cells widely infesting the peritoneal cavity. Current treatment for such patients is rarely adequate. Genetic analysis of tumor specimens led to the discovery that PIK3CA, a gene involved in numerous receptor signaling pathways, was a major oncogenic force in the development of ~40% of sporadic ovarian cancers (1). In ovarian cancer, multiple tumor cell lines exist that have increased PIK3CA copy number and gene expression. Such cell lines are useful models of the disease that can be studied in vitro and in mouse peritoneal xenografts (1).

The importance of PIK3CA to malignancy is not limited to ovarian cancer. PIK3CA was first recognized as an oncogene because of its ability to bind polyoma middle T antigen, a DNA tumor virus oncogene (2). Later, PIK3CA was found to be a retrolviral oncogene that transformed normal chicken embryo fibroblasts into tumors (3). Increased PIK3CA copy numbers are found not only in carcinomas of the ovary but also in carcinomas of the cervix, stomach, and thyroid (4–9). More recently, it has emerged that PIK3CA is one of the most frequently mutated human oncogenes in cancer (10, 11). Although missense mutations are prevalent in carcinomas of the colon and breast, they are rare in ovarian cancer (12). PIK3CA, therefore, seems to be a major oncogene in human epithelial malignancies, which is altered in ovarian cancer mainly through amplification.

PIK3CA encodes the catalytic p110 subunit of PI3Kα (p110α), which produces phosphatidylinositol-3,4,5-triphosphate (PI-3,4,5-P3). PI-3,4,5-P3 is a second messenger that stimulates a variety of proteins in the cell that activate proliferation, migration, translation, energy consumption, and angiogenesis and repress apoptosis (13). In normal cells, p110α responds to a variety of stimuli to produce a pulse of PI-3,4,5-P3 and then returns to its dormant state within minutes of activation. However, ovarian tumor cell lines with amplification of PIK3CA have increased levels of p110α enzyme and enzyme activity (2). In general, tumor cells use the enhanced PI-3,4,5-P to proliferate, migrate, and avoid cell death signals and importantly secrete vascular endothelial growth factor (VEGF), a key mediator of angiogenesis and capillary permeability (14, 15).

Recently, it has been shown that RNA interference knockdown of PIK3CA message has potent antitumor effects in ovarian lines with PIK3CA amplification (16). In addition, deletion of mutant alleles in colon cancer cells enhanced apoptosis substantially (17). A similar line of evidence has accumulated in tumor cells lacking the PTEN tumor suppressor, which have elevated PI-3,4,5-P, because PTEN is the phosphatase that inactivates PI-3,4,5-P. Here, reintroduction of PTEN inhibited p110α signaling and induced cell death (14, 18). This body of evidence strongly supports the hypothesis that p110α is critical to the viability of ovarian carcinomas with genetic alterations of the PIK3CA pathway. On these grounds, p110α would seem to be an excellent target for therapy in tumors that have a genetic activation of the gene.

There are two readily available inhibitors of p110α, wortmannin and LY294002. Both of these drugs are effective in cells: however, both drugs inhibit other members of the PI3K family at the same concentration (19, 20). In fact, LY294002 is known to inhibit the mammalian target of rapamycin (mTOR), an enzyme that is activated by p110α, and therefore may represent a synergistic off-target effect. Despite their lack of specificity, both of these inhibitors unequivocally shut down p110α and its downstream cascade of signals.

When ovarian tumor cells with PIK3CA amplification are exposed to LY294002 in tissue culture, cell death is induced (2). Cells lacking such genetic changes are only modestly affected by the drug. It is clear from in vitro data that cell lines lacking genetic alterations to PIK3CA are far less susceptible to the effects of a p110α inhibitor than cells that have such alterations (2, 17). Given these positive findings in vitro, the next major question is whether these inhibitors could also work in an animal model. Can sufficient drug levels be achieved? Can a therapeutic window be identified in a whole animal, given the multitude of physiologic signals that the PI3K family of enzymes regulates?

To study the potential therapeutic benefit of p110α inhibitors in vivo, Hu et al. at the University of California, San Francisco generated an intraperitoneal ovarian cancer mouse model using human cell lines in immunodeficient mice (3). With this model, they were the first to show that LY294002 inhibits tumor growth in vivo. Tumor inhibition occurred through the induction of apoptosis; when LY294002 was administered in combination with paclitaxel, almost no

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Received 8/8/05; accepted 8/8/05.

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www.aacnjournals.org 7965 Clin Cancer Res 2005;11(22) November 15, 2005

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found that PTEN or LY294002 could inhibit xenograft angiogenesis. In addition, it is well established that p110α has an important role in tumor secretion of VEGF and endothelial response to VEGF at the VEGF receptor (24, 25). Therefore, an inhibitor of p110α could block VEGF at two points: at its source of production in the tumor cell and at its target on the receptor in the endothelial cell. As predicted, Hu et al. showed that i.p. injections of LY294002 inhibited the accumulation of VEGF in blood and ascites secreted by the tumor, which is associated with reduced vascular permeability and angiogenesis.

Because p110α is a key inhibitor of tumor apoptosis, because p110α is a key activator of VEGF secretion, and because p110α is a key mediator of blood vessel development, LY294002 and other p110α inhibitors are a triple threat to ovarian cancer and other solid tumors (Fig. 1). It is time for this class of drugs to be tested in the clinic despite the reasonable fears of toxicity to the many organs that use the PI3K class of enzymes. Hu et al. have shown that skin toxicity can be managed in mice by altering the dosing. This study will provide a framework for measuring the effects of PI3K inhibition on other organ function and viability at a therapeutic dose. Work needs to be done to better define the minimum dose that will achieve a therapeutic effect without causing life-threatening toxicity in animal models and ultimately people. This will provide a framework for assessing novel p110α inhibitors as they emerge.

References

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