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Pancreatic Cancer—Could It Be that Simple? A Different Context of Vulnerability

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In a recent issue of *Science*, Olive and colleagues document that inhibition of Hedgehog (Hh) signaling in a genetically engineered mouse model of pancreatic cancer can enhance the intratumor concentration of certain anticancer drugs. Could this finding provide us with a new method to attack pancreatic cancer?

Pancreatic cancer remains a major challenge for all of us. It is the fourth leading cause of death from cancer in the US, with an estimated 37,680 people diagnosed with the disease and 34,280 people dying from the disease each year (Jemal et al., 2008). Worldwide, more than 213,000 are diagnosed with pancreatic cancer each year (Koorstra et al., 2008). It has the worst 1 and 5 year survival of any cancer. In addition to a poor survival rate, patients with pancreatic cancer have a great deal of suffering, with a particularly high incidence of pain—mostly caused by a predilection for the tumor to invade the perineural space of nerves in the celiac plexus (Zhu et al., 1999). In addition, substantial weight loss and multiple gastrointestinal symptoms sap the energy of patients with the disease. If the above description of the disease is not bad enough, there has recently been worse news (Jones et al., 2008). In a comprehensive genetic analysis of 24 patients' pancreatic cancers, the authors noted an average of 63 genetic alterations in each tumor, the majority of which were point mutations. However, these alterations did define a set of 12 recurrent pathways as possible ways to attack the disease; the findings remind us just how challenging pancreatic cancer is to treat.

It is a mystery as to why so many currently available anticancer agents with demonstrated antitumor activity in in vitro and in vivo tumor models do not work in patients with pancreatic cancer. Is it just because of the inherent resistance or heterogeneity of pancreatic cancer? Other tumors, such as colon and lung, have inherent resistance and heterogeneity, yet anticancer agents frequently cause tumor shrinkage and improve survival for patients with those diseases. Why is this?

It has been recognized for some period of time that pancreatic cancers often demonstrate hypoperfusion (Park et al., 2009) (Figure 1). Microscopically, almost a sine qua non of pancreatic cancer is the dense fibroinflammatory reaction that invariably accompanies the disease (Mahadevan and Von Hoff, 2007). This appearance is also noted with other types of cancer, such as breast cancer. Could it be so simple that hypoperfusion explains why any therapeutic agent simply cannot get to the tumor cells because the circulation to pancreatic cancer is so poor? Pancreatic cancer is one of the tumor types to be consistently hypoxic, possibly because of hypoperfusion, and it is notoriously resistant to antiangiogenic agents (Van Cutsem et al., 2009). If hypoperfusion is the reason (or at least one of the reasons) for the resistance of pancreatic cancers to our therapies, Olive and colleagues (2009) have now given us a new window on how the stroma (the fibroinflammatory component of the tumor) may be altered, possibly improving our ability to deliver anticancer therapies to the tumor cells.

In a series of well-strategized and careful pieces of work, Tuveson and colleagues have generated genetically engineered mouse models that closely mimic the human disease condition (Hingorani et al., 2003, 2005; Hruban et al., 2006). Of particular interest is that KPC mice, which conditionally express endogenous mutant Kras and p53 alleles in pancreatic cells, have, as a very early histologic feature of tumorigenesis, the appearance of a characteristic stroma with infiltration of regulatory T cells, fibroblasts, and a fibroinflammatory component.

In an important follow-up study, Olive and colleagues (2009) now demonstrate that an Hh-signaling pathway antagonist could be used to deplete tumor-associated stromal tissues and improve the delivery of one of the few modestly active anti-pancreatic-cancer agents, gemcitabine, into the pancreatic cancer. They first show that tumors in KPC mice had

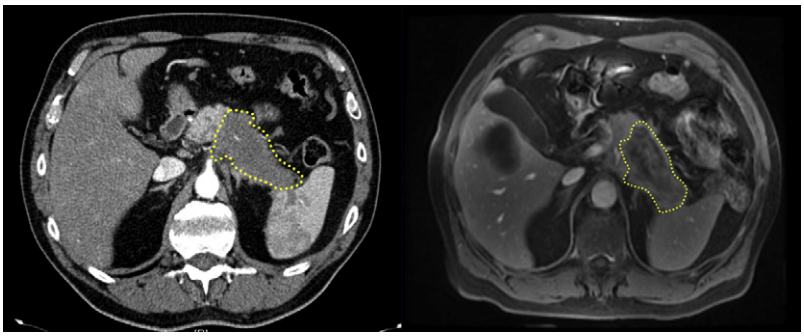

Figure 1. CT and MRI Demonstrate Hypoperfusion of Pancreatic Cancer
Hypoperfusion of pancreatic cancer on computer tomography (left) and on magnetic resonance image (right) as evidenced by less contrast material in the tumor (note circled areas).

dysfunctional vasculatures compared with transplanted tumors. They also demonstrate that blood vessel density was markedly decreased and that only a few vessels were embedded in a prominent stromal matrix in the pancreatic cancers in the KPC mice. Finally, they note, using an autofluorescent chemotherapeutic agent doxorubicin, that there was a "marked" decrease in drug delivery to pancreatic tumors in KPC mice. The agent that they selected to attempt to modify the stroma was an inspired choice, given the fact that paracrine Hh signaling for tumor cells to normal cells has been documented to "promote stromal desmoplasia" (Yauch et al., 2008; Bailey et al., 2008).

The Hh-signaling pathway has generated a tremendous amount of interest in the cancer research community, with the very substantial clinical activity of some inhibitors of the pathway (smoothened antagonists), such as GDC0449. This substantial clinical activity has so far been limited to tumor types that have intrinsic activated Hh pathway due to mutations in the *patched 1* or *smoothened* genes, such as advanced basal cell carcinoma.

Olive and team demonstrate convincingly that, by treating mice with the Hh-signaling inhibitor IPI-926 (also a smoothened antagonist), there is improved anticancer drug delivery to pancreatic cancer in KPC mice. They also show that the Hh-signaling pathway antagonist can intercept the activation of Gli family transcription factors and thus inhibit the generation of the stromal desmoplasia. Importantly, they demonstrate that oral IPI-926 resulted in accumulation of anticancer agents in the tumor tissue along with a decrease in expression of Gli1, a depletion in the desmoplastic stroma, a decrease in α-smooth muscle actin-positive stromal fibroblasts, and a decrease in collagen I content after 8–12 days of treatment. The depletion of desmoplastic stroma was accompanied by an increase in mean vessel density and improved delivery of both doxorubicin and gemcitabine (60% increase) to the pancreatic cancer cells.

The use of an inhibitor of the Hh-signaling pathway to alter the stroma, increase intratumoral vascular density, and improve the delivery of a therapeutic agent certainly gives clinicians, currently somewhat bereft of ideas, a different way to tackle this incredibly difficult disease. This work is promptly being followed up with a clinical trial. The clinical availability of Hh-signaling pathway antagonists enables us to try. Some investigators might feel that the increased drug transport by IPI-926 treatment is modest at best with only a modest increase in antitumor activity, and the effect unfortunately is short lived. However, at the very least, this study has once again awakened us to the importance of the vascularity and stromal issues of adenocarcinoma of the pancreas.

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