Targeting pancreatic cancer drug resistance

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Pancreatic cancer is one of the most deadly and intractable forms of cancer, with a 5-year survival rate of only 6%. Novel therapies are urgently needed, as conventional and targeted approaches have not been successful and drug resistance is an increasing problem.

Previously it had been thought that poor penetration of the drugs into pancreas tumors was the main reason for treatment failure. But now a team of scientists led by Cold Spring Harbor Laboratory (CSHL) Professor David Tuveson M.D., Ph.D., shows there are other factors at work, too.

In a paper published online today in the *Proceedings of the National Academy of Sciences*, Dr. Tuveson's group shows that there are survival cues inside the pancreatic tumor mass. Molecules in the milieu around the cancer cells, such as Connective Tissue Growth Factor (CTGF), provide "pro-life" signals that overcome the killing power of chemotherapeutic drugs.

"In addition to drug delivery being a problem, there is also this nurturing aspect that prevents cancer cells responding to the drugs," says Tuveson.

But he and his colleagues may have found a way to prevent this. The antibody FG-3019, a molecule that is now in phase 1/2 clinical investigation as a treatment option for pancreatic cancer, binds to CTGF and prevents it from providing cells with survival cues. Those cues seem to be mediated, at least in part, through a molecule within the cell called XIAP (X-linked inhibitor of apoptosis). XIAP derives its name from its function—an ability to help keep the cell alive by preventing a process called apoptosis, a form of cellular suicide.

The Tuveson lab used a novel mouse model for pancreatic cancer to test FG-3019. Tumors in mice treated with FG-3019 in combination with the chemotherapeutic drug gemcitabine stopped growing. Inside the tumor there was an increase in the amount of cancer cells dying through apoptosis, which was associated with a decrease in levels of XIAP. Importantly, mice treated with both FG-3019 and gemcitabine also had an increased lifespan.

This suggests that overcoming resistance to medicines in cancer may be possible using combination therapy—co-administering molecules that help open up the tumor to drugs as well as other molecules that prevent cancer cell survival signals alongside the chemotherapeutics. Both CTGF and XIAP have been shown to be present in human pancreatic cancer tumors so combination therapy using antagonists of either molecule could be a feasible approach, says Tuveson.

There are other compounds that sensitize cancer cells to die, for example, antagonists of Bcl-2 and Bcl-xL, cellular proteins that prevent apoptosis. "These are pro-apoptosis medicines, so it's not impossible to imagine that one could target these types of pathways in cancer cells with drugs. We haven't done those studies yet but that would be the logical progression," says Tuveson, who is the Director of the Lustgarten Foundation Pancreatic Research Laboratory at CSHL and Director of Research for the Lustgarten Foundation.

More information: "CTGF antagonism with mAb FG-3019 enhances chemotherapy response without increasing drug delivery in murine ductal pancreas cancer" is published online in *Proceedings of the National Academy of Sciences* of the USA on July 8, 2013. The authors are: Albrecht Neesse, Kristopher K. Frese, Tashinga E. Bapiro, Tomoaki Nakagawa, Mark D. Sternlicht, Todd W. Seeley, Christian Pilarsky, Duncan I. Jodrell, Suzanne M. Spong, and David A. Tuveson. The paper can be obtained online at doi: 10.1073/pnas.1300415110

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