Researchers discover link between organ transplantation and increased cancer risk

July 16 2008

Researchers have determined a novel mechanism through which organ transplantation often leads to cancer, and their findings suggest that targeted therapies may reduce or prevent that risk.

In the July 15, 2008, issue of *Cancer Research*, researchers at Harvard Medical School found in animal and laboratory experiments that the anti-rejection, immunosuppressive drug cyclosporine ramps up expression of vascular endothelial growth factor (VEGF), which signals the growth of new blood vessels that can feed tumors.

They also found that simultaneously administering an anti-VEGF therapy with cyclosporine in mice repressed this tumor growth. Several inhibitors of VEGF are already in use in human cancer therapy.

The findings could offer some good news for the 15 to 20 percent of transplant patients who develop cancer within a decade of receiving new organs, according to the study's senior investigator, Soumitro Pal, Ph.D., an assistant professor at Harvard Medical School's Transplantation Research Center at Children's Hospital in Boston.

"It may be that anti-VEGF agents given judiciously after transplantation can reduce future cancer occurrence," he said.

VEGF expression is markedly increased in patients post-transplantation, and this can aid in the development of a blood supply to a transplanted organ, helping it survive and thrive. "But once the organ has stabilized, it

may be possible to lower the level of VEGF expression to prevent tumor growth," he said. "We would need to figure out how to balance benefit and risk to keep cancer at bay."

Tumors that develop after transplantation may have three potential sources: they may have pre-existed or could have been a recurrence of previous cancer – and in both of these cases, a patient's pre-transplant immune system might have kept these cancers in check – or cancer-causing viruses could have come from the donor organ. Physicians have long observed that immunosuppressive agents, such as the class of calcineurin inhibitors that includes cyclosporine, appear to promote cancer development, often in organs that are not transplanted, but the cause of this was unclear. The Harvard team tested the ability of cyclosporine to promote growth of pre-existing tumors in mice implanted with human renal (kidney) cancer cells. Mice treated with the agent formed tumors faster than untreated mice, but anti-VEGF therapy substantially reduced that excessive growth.

Digging deeper into the biological pathway of VEGF activation, the scientists found that cyclosporine activates two of the three forms of the common protein catalyst, protein kinase C, which leads to increased expression of VEGF.

"We think PKC-mediated VEGF transcriptional activation is a key component in the progression of cyclosporine-induced post-transplantation cancer," Pal said. "It is likely not the whole story, but this gives us a clue that we might be able to use existing or novel therapies to reduce cancer risk in transplanted patients."

Source: American Association for Cancer Research