Tuning the radio with CD47

By Lauren Martz, Staff Writer

One potential problem with radioprotectants for normal tissues is they can also shield tumor cells from the radiation therapy aiming to knock out the cancer. Researchers at the **National Cancer Institute** have found that blocking a pathway involving thrombospondin-1 and its cell-surface receptor, CD47, can not only protect healthy tissues from radiation damage but also improve the antitumor efficacy of radiotherapy.¹

Thrombospondin-1 (TSP-1; THBS1) acts through CD47 to curb the prosurvival effects of nitric oxide (NO). NO turns on cyclic guanosine monophosphate (cGMP) signaling, which prevents apoptosis in healthy cells. Therefore, blocking the TSP-1-CD47 pathway could preserve protective NO levels and increase survival of healthy cells subjected to radiation as part of cancer treatment.

Previous studies by the NCI group have shown that CD47 does not mediate cGMP signaling in cancer cells as it does in healthy cells. Those data thus suggested that inhibiting TSP-1-CD47 signaling might not have the same prosurvival effects on cancer cells.²

Indeed, studies in mouse endothelial cells have shown that knocking out either TSP-1 or CD47 increases both NO signaling and resistance to tissue damage following ionizing radiation.^{3,4} In addition, *tsp-1* or *Cd47* knockout mice were resistant to high-dose radiation injury.⁵

In a new paper published in *Science Translational Medicine*, the NCI group replicated the knockout results using an antisense CD47 morpholino oligonucleotide but saw better antitumor efficacy for antisense plus radiation versus that for radiation alone.

In mice with melanoma or squamous cell carcinoma, morpholino treatment followed by radiotherapy delayed tumor regrowth by 89% and 71%, respectively, compared with radiotherapy alone. Mice receiving the combination had less alopecia, tissue ulceration and fibrosis of healthy cells than mice given radiation plus either mismatched morpholino or vehicle control.

The treated mice also had better vascular perfusion and reduced death of healthy skeletal muscle and bone marrow cells, which are highly sensitive to radiation.

The vasoprotective effect was important, said Joel Greenberger, chairman of the Department of Radiation Oncology at **The University of Pittsburgh School of Medicine**. "Every organ has a common factor—they require blood supply. An intervention that protects the blood vessels is very exciting," he said.

In addition, Greenberger said "two other critical tissues when it

comes to radiation damage are the bone marrow and the GI tract. So, testing accepted models for these two systems will be required. They have done these studies in the mice; now they need to perform the tests in dog and nonhuman primate models."

Making sense

What is still unknown is the precise mechanism by which blocking CD47 leads to greater tumor sensitivity. The NCI team said one possibility is that blocking CD47 serves to protect immune cells that attack tumors.

"CD47 was first discovered as a tumor-associated antigen. It is expressed on all cells but is at a higher level on a variety of tumor types. Work from other groups shows that this elevated CD47 protects against both natural killer and macrophage killing of tumor cells," corresponding author David Roberts told *SciBX*. "We propose that lowering CD47 on the tumor cells enhances the synergies between antitumor immunity and radiotherapy."

Roberts is chief of the biochemical pathology section of the laboratory of pathology at NCI's Center for Cancer Research.

The next step for Roberts' group is to study the antisense molecule in more cancers and more animals.

"The antisense morpholino used in this study was designed to hybridize with the human CD47 sequence that is well conserved across species," Roberts noted. "Therefore, the drug we used in mice is identical to that which could be used in humans. This could be used without further changes in clinical trials."

Still, testing the strategy in additional indications will be required before moving forward. "We have only showed the approach to work in two tumor types, and one of these is known to be immunogenic. We need to test some of the more common cancers," said Roberts.

Greenberger agreed that "the results are dramatic and impressive, but now they have to reproduce them in other species, look at the side effects in other species and determine which critical step to target in the pathway to make this most effective."

Down the line, the team plans to explore different ways of blocking the pathway.

"In the longer term, additional antisense strategies including small interfering RNA and peptide-nucleic acid suppression of CD47 could be developed," Roberts added. "We are also interested in developing small molecule antagonists of CD47 for use in cancer radiotherapy."

Greenberger agreed and said it will also be important to determine how blocking CD47 fits with other classes of radioprotectants such as small molecule antioxidants or reactive oxygen species scavengers.

Roberts said the U.S. government has filed patent applications covering the antisense approach and its use in radiotherapy. He said the IP is available for licensing.

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