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Dynamic duo helps to heal irradiated mice

Protein and antibiotic treatment works even 24 hours after exposure.

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An antibiotic and a protein can work together to fight radiation-induced infections better than either can manage alone. Doctors already use antibiotics to treat radiation sickness. But the addition of a protein from the immune system — bactericidal/permeability-increasing protein (BPI), which acts against poisons called endotoxins — improves the survival rate of irradiated mice, according to a study published today in *Science Translational Medicine* [1].

The combination of BPI with the antibiotic fluoroquinolone helped mice that were treated up to a day after exposure to radiation. This is important, because most existing treatments for radiation sickness — including those stockpiled by the US government, such as potassium iodide and the protein granulocyte colony-stimulating factor — must be taken before or within hours of exposure, which is not always possible. In the event of a nuclear crisis that exposes hundreds or thousands of people to radiation, the ensuing chaos could delay treatment.

People who have been exposed to radiation need effective therapies that can be administered more than a few hours after exposure.

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"The most important thing about the BPI and fluoroquinolone combination is that it is effective at 24 hours after exposure," says Eva Guinan, a haematologist at Harvard Medical School in Boston, Massachusetts, who led the study.

A model for radiation sickness

Guinan and her colleagues first suspected the beneficial effects of BPI while they were monitoring levels of various molecules in the blood of people who had undergone bone marrow transplants and radiation treatment. Radiation exposure slows the replacement of cells in the intestinal wall, allowing bacteria to leak through and cause infections elsewhere in the body. The researchers noticed that natural levels of BPI dropped in the immune systems of patients who contracted such infections.

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"We wondered what would happen if we gave them BPI," says Guinan. But transplant patients are not good models for people who have been accidentally poisoned by radiation: in an emergency, radiation victims would lack the intensive hospital care given to transplant patients, and would experience different immune-system complications. And there are ethical barriers to radiation experiments in humans — instead, US federal guidelines call for radiation research on multiple animal species. The team

chose to test its hypothesis in mice.

The researchers exposed all the mice in the study to 7 grays of radiation. The dose killed all but 5% of untreated mice after 30 days. On its own, BPI had no measurable effect on a second batch of mice.They treated a third batch of irradiated mice with fluoroquinolone alone. About 40% of the animals survived for 30 days. A final batch was given both fluoroquinolone and BPI — and 75% survived the first month after radiation.

The mice treated with the combination also recovered more bone marrow cells, which produce immune system molecules, over the course of the month.

The result is "pointing in the right direction", says Brett Giroir, director of the Institute for Innovative Therapeutics at Texas A&M University in College Station, who has studied the use of BPI to treat meningococcal disease. Humans are far more sensitive to the endotoxins treated by BPI than are mice, he adds, so such treatments may be even more effective in humans.

Both BPI and ciprofloxacin, the human equivalent of fluoroquinolone, are common and well understood drugs, says Giroir, so "the other great thing about these molecules is you have the human safety data already". The compounds also have a long shelf-life, which makes them easy to stockpile in case of emergency.

The study suggests scientific questions, says John Chute, a haematologist at Duke University in Durham, North Carolina. "This observation raises a possibility that the BPI effect is dependent on the antibiotic," he says. In an emergency situation, radiation patients would get antibiotics in addition to any new molecule, but Chute asks, "Why is it this BPI treatment needs the antibiotic on board?"

Guinan says that she and her colleagues "don't really know" why BPI and antibiotics work best together. "It may be that BPI has a function beyond just bonding endotoxins. We find that incredibly provocative and we're investigating it," she says.

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References

1. Guinan, E. C. *et al*. *Sci. Trans. Med.* **3**, 110ra118 (2011).
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