Compound offers prospects for preventing acute kidney failure

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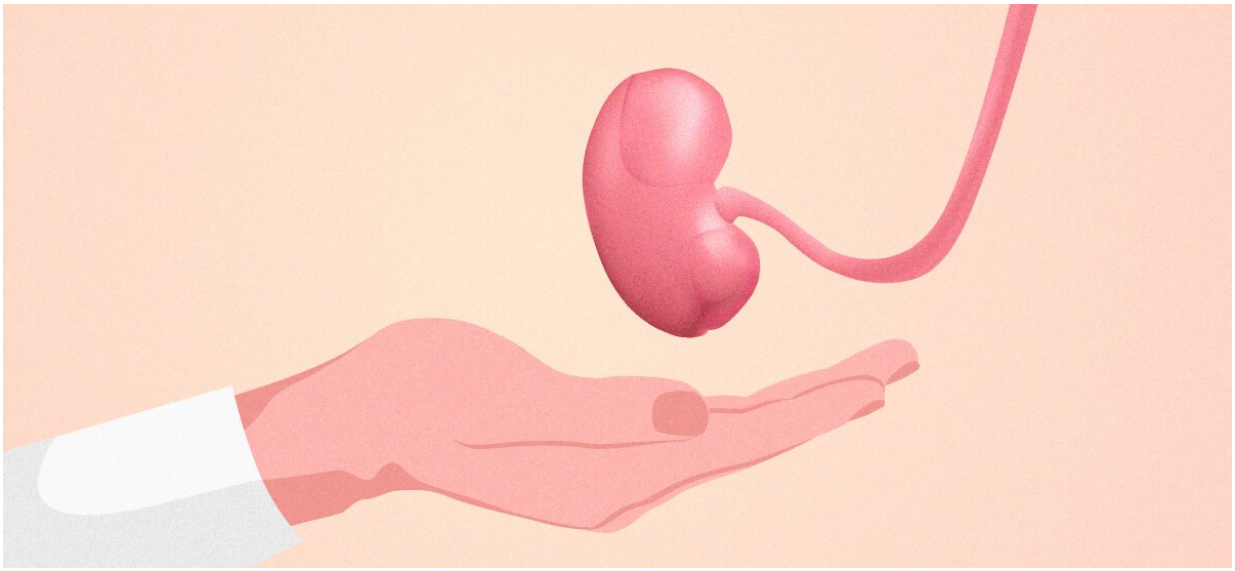

Illustration. Kidney care. Credit: Elena Khavina/MIPT

Russian researchers from the Moscow Institute of Physics and Technology, the Institute of Cell Biophysics, and elsewhere have shown an antioxidant compound known as peroxiredoxin to be effective in treating kidney injury in mice. The study in *Cell and Tissue Research* reports tripled survival rates in test animals treated with the chemical prior to sustaining an ischemia reperfusion injury. The team says peroxiredoxin also offers prospects for longer kidney transplant storage.

Ischemia reperfusion causes kidney failure

Living tissues rely on a constant inflow of blood for survival. Restrictions in blood supply, known as ischemia, lead to a shortage of oxygen and nutrients. This may make the tissue more acidic and impair cell membrane permeability. Ultimately, tissue damage can arise, with the kidney, heart, and nerve tissues being the most vulnerable.

When normal blood inflow resumes, this so-called reperfusion does not cause the damaged tissue to regenerate. Instead, the concentration of reactive oxygen species grows, bringing about oxidative stress and further harming the cells. A pathologically high ROS count may trigger the cells to self-destruct in what is known as apoptosis.

The causes of ischemia include blood vessel constriction, changes in blood pressure or heart rate, loss of blood, and trauma. The ischemia reperfusion syndrome remains a key factor in organ pathologies. When it affects the kidneys, acute renal failure may occur, resulting in death in half of the cases.

Antioxidants offer treatment options

Since oxidative stress is involved in the tissue damage under ischemia reperfusion, antioxidants are a particularly promising treatment option. These are compounds that reduce oxidative stress by lowering ROS concentration.

In their recent study, the Russian researchers used antioxidant enzymes from the peroxiredoxins family. In addition to being involved in cell signaling, they reduce the level of the ROSs called peroxides. Among the six known enzymes in this family, peroxiredoxin 6—aka PRDX6—has the greatest appeal. Shown in figure 1, it has the capacity to neutralize

the largest number of peroxides, both organic and inorganic.

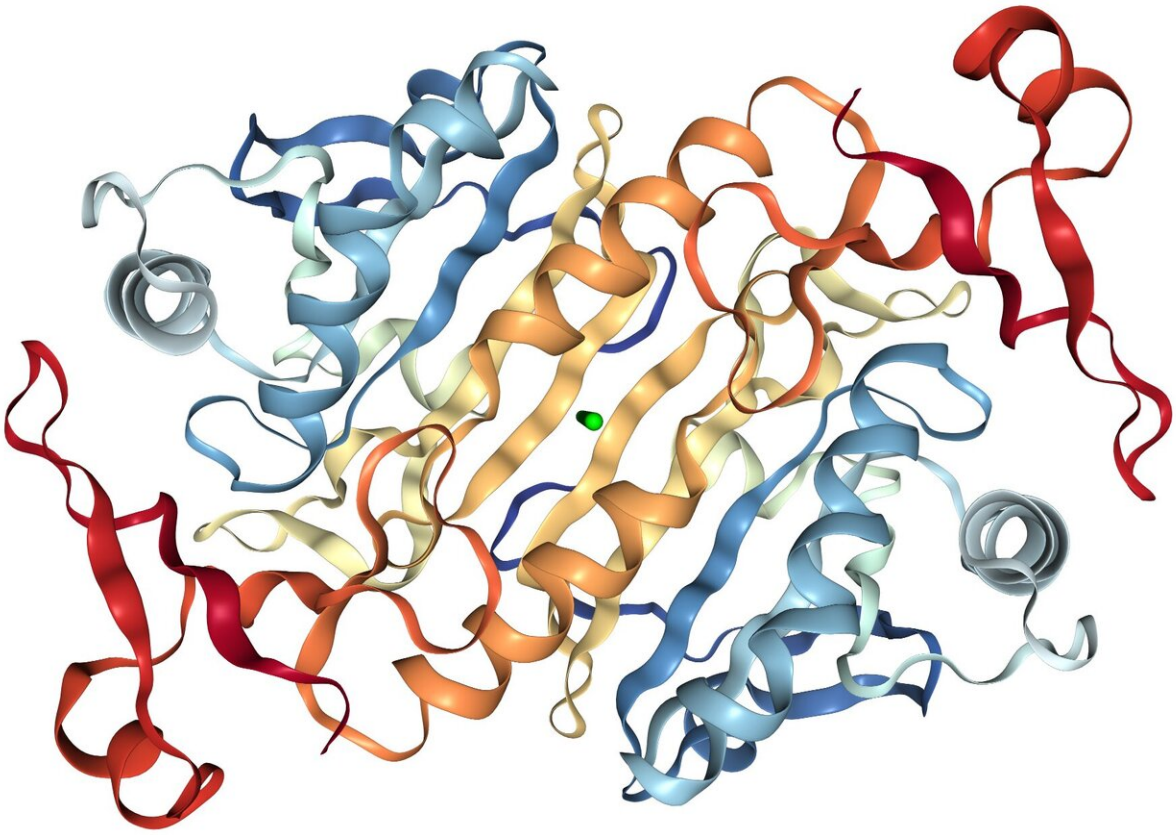

Figure 1. The crystal structure of the human peroxiredoxin 6 enzyme in sulfinic acid state. Image from RCSB PDB. Credit: "NGL Viewer: Web-Based Molecular Graphics for Large Complexes" (2018), A.S. Rose et al./Bioinformatics

Peroxiredoxin 6 boosts mouse survival

To prove the efficiency of the enzyme in kidney ischemia reperfusion treatment, the researchers modeled this injury in mice and compared the survival rates of the animals that received PRX6 treatment and those that

did not. In the latter group, one in five mice survived by day four, compared with three in five mice alive by that time in the group that received a PRX6 infusion 15 minutes prior to ischemia.

The induced ischemia reperfusion in untreated mice was accompanied by edema, blood-engorged vessels in the kidneys, renal tubule degeneration, as well as an increased concentration of kidney damage markers and the transcription factors responsible for inflammation development. By contrast, the kidneys of the test animals receiving PRX6 displayed much smaller changes of pathological and morphological nature.

To rule out the possibility that the benefits of PRX6 are not related to peroxide suppression, the team synthesized a mutant version of the enzyme. It has the same structure, yet it does not affect peroxide levels. Administering the mutant enzyme 15 minutes before ischemia had no positive effect on mice survival. It is thus the compound's ability to keep peroxides in check that gives rise to its therapeutic effect.

The study's senior author Mars Sharapov of MIPT and the Institute of Cell Biophysics commented on the team's findings: "We observed the intravenously infused PRX6 in the animals' bloodstream, under kidney ischemia reperfusion. That is, it did not enter the cells. Despite this, PRX6 effectively neutralized the peroxides that were released by the cells into the extracellular environment. This suppressed oxidative stress and apoptotic cell death, resulting in significantly less tissue damage."

More information: 10.1007/s0044 R. G. Goncharov et al. Protective role of exogenous recombinant peroxiredoxin 6 under ischemia-reperfusion injury of kidney, *Cell and Tissue Research* (2019). DOI: 10.1007/s00441-019-03073-z

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