Study identifies key player in the body's immune response to chronic stress

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Osteopontin (OPN), a protein molecule involved in many different cellular processes, plays a significant role in immune deficiency and organ atrophy following chronic physiological stress, resulting in increased susceptibility to illness. These findings appear in the September 4th issue of the *Proceedings of the National Academy of Sciences*.

The study is supported by the National Space Biomedical Research Institute (NSBRI), the Busch Biomedical Research Grant, National Multiple Sclerosis Society, and Rutgers Technology Commercialization Fund. Authors on the paper include Dr. Yufang Shi, investigator on NSBRI's Radiation Effects Team and professor of molecular genetics, microbiology and immunology at the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, Dr. David T. Denhardt, one of the discoverers of OPN, professor of cell biology and neuroscience at Rutgers, the State University of New Jersey, and Kathryn X. Wang, graduate student in the Rutgers Graduate Program in Cell and Developmental Biology.

"Following periods of prolonged physical stress such as when astronauts live in microgravity, white blood cells that fight disease, called lymphocytes, die at an increased rate and immune system organs like the thymus and spleen lose mass and begin to atrophy," said Dr. Shi.

Immune system organs include the thymus, spleen, lymph nodes and bone marrow.

"By determining the role of lymphocyte death in a stressed immune system, we may be able to develop therapies to maintain a healthy immune system, which can help in space and in clinical settings to prevent and treat malignancy and infections," Shi said.

It is known that spaceflight and long periods of physiological stress cause changes in the immune system. "Until now, the role of OPN in the stress response of immune organs has never been examined," Shi said.

Evidence suggests that astronauts may suffer increased rates of infection after flight. Through an animal study, Shi and colleagues simulated spaceflight conditions to investigate its effects on the immune system. They found that infection-fighting white blood cells inappropriately die off in large numbers, leading to immune-organ atrophy and the decreased ability of the immune system to protect the body from illness.

The team studied two types of mice, one group with the normal OPN gene and another group lacking this gene. The mice experienced three days of hindlimb unloading, a widely used technique to simulate the physiologic changes that astronauts experience during spaceflight. With this technique, body fluids shift similarly to how they do in microgravity (toward the head instead of toward the extremities) and immune system changes occur.

Mice of both types made up the control groups, which did not undergo unloading.

After three days, the researchers compared the mice with normal OPN and the OPN-lacking mice. The normal OPN mice experienced weight loss, spleen and thymus atrophy, and a reduced number of white blood cells. In addition, increased levels of corticosterone, a steroid that contributes to the death of white blood cells, were found only in the normal OPN mice studied.

By contrast, the mice lacking the OPN gene showed statistically insignificant changes in weight and the levels of corticosterone, and were more similar to the control group.

"White blood cell death in the spleen and thymus was evident only in the mice with normal OPN," Shi

said. “Since white blood cells were dying rather than increasing, that indicates partly why immune system organs atrophy during prolonged physical stress.”

The team concluded that under chronic physical stress, OPN must be present for the increase in corticosterone, which leads to atrophy and white blood cell death.

Shi hopes that this finding will lead to preventative treatments in the future.

“Already we’re researching an antibody that can remove OPN from blood serum. Perhaps one day, we can turn this research into a therapy to counteract white blood cell death in immune system organs and keep humans healthier during times of prolonged physical stress,” Shi said.

Shi and colleagues want to better understand the mechanisms through which stress affects the immune system, so they can prevent illness in space and help those who suffer from illness following physiological stress here on Earth.

Source: National Space Biomedical Research Institute