Cells' energy factories linked to damaging inflammation

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Scientists have discovered that molecules called reactive oxygen species (ROS) produced by the energy factories, or mitochondria, in cells, may play a role in a rare inherited disorder in which uncontrolled inflammation damages the body's tissues. Their research in human and mouse cells suggests that blocking these molecules could reduce inflammation in TNF receptor-associated periodic syndrome (TRAPS) and possibly other inflammatory diseases.

The work, published online on January 31 in the *Journal of Experimental Medicine*, was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, a component of the National Institutes of Health.

TRAPS is one of a recently identified family of conditions referred to as autoinflammatory disorders, which are marked by unexplained inflammation. As discovered by Dr. Daniel Kastner's research group in 1999, TRAPS is caused by mutations in the gene coding for TNF receptor 1 (TNFR1), which binds tumor necrosis factor (TNF). TNF is a key inflammatory molecule in the body's response to infection, as well as in a number of common rheumatic diseases, including rheumatoid arthritis and ankylosing spondylitis. In people with TRAPS, TNF-mediated inflammation causes recurrent fevers, abdominal pain and skin rash. If not controlled, inflammation can lead to amyloidosis, a buildup of inflammatory proteins that can result in organ damage.

While blocking TNF with agents called TNF-inhibitors relieves

symptoms for some patients, others continue to have symptoms, says Richard Siegel, M.D., Ph.D., NIAMS autoimmunity branch chief and acting clinical director. Some go on to develop amyloidosis despite treatment.

The inadequacy of anti-TNF treatment in these patients led Dr. Siegel and his colleagues to look at ROS. ROS are chemically reactive molecules containing oxygen that have been implicated in a variety of conditions, including cancer and atherosclerosis. For some time, ROS have been known to play a role in protection against infection. It has also been shown that they can contribute to signaling pathways that lead to inflammation.

Using cells from patients with TRAPS and mice genetically altered to have mutations identical to those in TRAPS, the researchers found that the mutant cells produced elevated levels of ROS, and that blocking ROS significantly decreased the abnormally elevated inflammation in the cells.

In addition, working in collaboration with the laboratory of Dr. Michael Sack in the NIH's National Heart, Lung, and Blood Institute, Dr. Siegel and his team identified mitochondria as the source of ROS leading to inflammatory responses. Mitochondria provide energy for cells through a series of biochemical reactions that result in the generation of adenosine triphosphate (ATP), a key energy source; ROS are routinely generated as a byproduct of these reactions. In the cells of patients with TRAPS, however, the researchers found that mitochondria generate elevated levels of ROS. Blocking mitochondrial ROS in those cells reversed the inflammation.

Another crucial finding was that mitochondrial ROS play a role in inflammatory responses in normal cells, suggesting that this phenomenon also underlies normal inflammatory responses to some extent.

"Overall, I think the important idea is that there is a healthy balance of ROS in the cells," says Ariel Bulua, an M.D./Ph.D. student in the NIAMS Autoimmunity Branch and the study's lead author. "While there are some beneficial roles of ROS, when they are over produced, they can cause damage."

The researchers say blocking excessive ROS with antioxidants may be a way to reduce the inflammation in patients with TRAPS that is not controlled by TNF inhibitors alone. However, the efficacy of antioxidants in TRAPS will have to be studied in controlled clinical trials. "Although drugs that work in cells and mice do not always translate into humans, these studies provide a new avenue for future investigation," says Dr. Siegel.

Perhaps more importantly, he says this approach may lead to improved therapies for a wide range of inflammatory diseases – not just TRAPS. "This is like a test case on a very defined set of patients," he says. "If you get a big effect clinically, I think you could try other groups of patients."

More information: Balua, A.C., et al. 2011. *J. Exp. Med.* doi:10.1084/jem.20102049
For more information about autoinflammatory diseases, visit www.niams.nih.gov/Health_Info/ … ammatory/default.asp

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