Protein central to being male plays key role in wound healing

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A molecular receptor pivotal to the action of male hormones such as testosterone also plays a crucial role in the body's ability to heal, report scientists in the December issue of the *Journal of Clinical Investigation.*

In studies in mice, scientists at the University of Rochester Medical Center found that this receptor - the androgen receptor - delays wound healing. When scientists used an experimental compound to block the receptor, wounds healed much more quickly.

Scientists say that while the results in mice offer new insights into a potential new way to help the body heal faster, they stress that more research must be done before considering whether to explore the treatment in people whose wounds are slow to heal.

"This is a very interesting observation," said Edward Messing, M.D., a urologist and surgeon at the University of Rochester Medical Center who was not involved in the study. "For people at the marginal end of health - the elderly, or people who have impaired healing for other reasons, such as diabetes - maybe blocking the androgen receptor in certain cells could speed up wound healing and help prevent infections."

The work was led by Chawnshang Chang, Ph.D., director of the George Whipple Laboratory for Cancer Research and a widely recognized expert on the androgen receptor. The first author is former graduate student Jiann-Jyh Lai, Ph.D., who is now a researcher at the University of Massachusetts.

The work thrusts a sex hormone front and center into one of the most important and pervasive processes of the body. Inflammation is crucial for allowing the body to heal from wounds and to fight off invaders. But when our inflammatory response goes beyond what's necessary, or if it occurs in the wrong time or place, it hurts our health and can be deadly.

By identifying the androgen receptor as a key player in at least one form of inflammation, the work opens a new window for scientists investigating differences between the genders when it comes to autoimmune or inflammatory diseases.

"Many inflammatory diseases, such as atherosclerosis and asthma, manifest themselves differently in the genders, indicating that sexual hormones could be involved. We've found that the androgen receptor plays a role regulating the inflammatory response in wound healing. It will be very interesting to see if the receptor plays a similar role in other diseases," said Lai.

To block the receptor and speed healing, the team used ASC-J9, a synthetic chemical compound loosely based on a compound found in curry that can shut down the receptor selectively. ASC-J9 is being tested in Phase II trials as a treatment for severe acne by San Diego-based AndroScience Corp., a biotech company founded by Chang and colleagues. Both Chang and the University of Rochester own a stake in the company, which has licensed several of Chang's research findings.

Chang's current study delves in a detailed way into the molecular underpinnings of wound healing. When the body is injured, myriad cells rush to the scene, a bit like emergency responders hustling to a disaster. Some cells issue cries for help by sending out certain chemical messengers; other cells act as dispatchers to recruit more responders to the scene. It can seem like a great deal of chaos zeroed in on a small patch of skin. Usually, the body gets the job done, drawing upon dozens

of molecular actors to heal the wound efficiently and quickly; sometimes, though, the inflammation can be detrimental.

For the current study funded by the National Cancer Institute, Chang and colleagues studied several different types of cells involved in wound healing. The team created different types of mice, turning off the androgen receptor in certain cell types while leaving it functional in other cells. Then scientists applied ASC-J9 to block the activity of the androgen receptor and studied the effects.

The team found that the androgen receptor spurs white blood cells known as macrophages to produce a chemical messenger called TNF-alpha, which in turn stimulates the body's inflammatory response. The receptor also plays a role recruiting macrophages to the site of injury. When the team blocked the receptor, there were fewer macrophages and less TNF-alpha at the wound site, and the wound healed much more quickly.

"It is a surprise that the androgen receptor is involved in wound healing in so many ways," said Chang, who is a faculty member in the departments of Pathology and Urology and the James P. Wilmot Cancer Center. "People have suspected that the receptor plays a role in wound healing, but it's new that it plays a direct role guiding circulating macrophages to the area."

Shutting off the interaction between the androgen receptor and androgen hormones like testosterone is a goal in several areas of medicine. The action is taken by doctors most commonly to treat patients with advanced prostate cancer. For some patients, doctors prescribe "chemical castration" and shut down the body's supply of hormones like testosterone. This causes severe, systemic side effects that can include impotence, loss of libido, osteoporosis, and fatigue.

Scientists like Chang are exploring another way to prevent that same interaction, by shutting down the androgen receptor itself in select tissues but keeping the flow of hormones intact.

Messing, a surgeon who regularly treats men with prostate cancer, says that the ability to turn off the effects of androgens in just the tissues necessary is a challenge but holds great promise.

"Currently there is no way of preventing androgens in your body from reaching just one particular wound or one specific part of the body," said Messing. "To stop them anywhere, you need to turn off androgens throughout the body, which has severe and unpleasant side effects, particularly in men. Turning off the androgen receptor only where you want to, and nowhere else, could lead to new treatments for diseases like prostate cancer and for speeding wound healing."

Provided by University of Rochester Medical Center