Mechanism for repairing bladder infection damage identified

March 10 2011, By Krista Conger

(PhysOrg.com) -- The bladder is a supple, muscular organ with a well-defined task: Store urine and release it at an appropriate time. Unlike its workhorse neighbor, the intestine, it doesn't need a lot of fussy cell division to get the job done. But when the bladder becomes infected, it launches a massive, scorched-earth attack, sloughing off the innermost layer of cells to keep invading bacteria from latching on to and burrowing into its inner lining.

Now scientists at the Stanford University School of Medicine have identified the key molecular pathways that form a control circuit involved in kick-starting cell division in the bladder to repair the damage. They've also pinpointed what appear to be bladder stem cells critical to the repair. The research could lead to new ways to treat bladder infections and other, more deadly problems.

"We suspect that this pathway of regeneration might be important in cancer development and metastasis in the bladder and other organs, like the prostate," said developmental cell biologist Philip Beachy, PhD

Beachy is the senior author of the research, published online March 9 in *Nature*. He is the Ernest and Amelia Gallo Professor at the medical school and a member of the Stanford Cancer Center and the Stanford Institute for Stem Cell Biology and Regenerative Medicine. He is also a Howard Hughes Medical Institute investigator. Kunyoo Shin, PhD, a postdoctoral scholar in Beachy's laboratory, carried out most of the experimental work and is first author of the paper.

About 10 percent of women each year experience bacterial infections of the bladder that can range in severity from irritating to painfully debilitating. The body's natural defense of shedding at least a portion of the inner lining in which the bacteria hide out works pretty well, but it's not perfect; over one-quarter of women will experience a recurrence within one year, sometimes even when antibiotics are used to treat the infection.

The bladder's inner lining is made up of a tightly connected layer of umbrella cells that protect the underlying cells from toxins and waste in the urine. Under them are intermediate and basal epithelial cells (together these umbrella, intermediate and basal cells make up the urothelium), and then a non-epithelial layer of cells called the stroma. The stroma is separated from the urothelium by a thin structure called the basement membrane. Beachy and his colleagues were interested in learning how the body regenerates the tissue so quickly and how it maintains the strict organization of various layers of tissue.

"The bladder is a great system in which to look at this because it's composed of a fairly simple, ordered tissue," said Beachy. "Most of the time, the cells in this tissue undergo little or no cell division, but injury with chemicals or bacterial infection causes rapid proliferation."

In fact, Beachy and his colleagues found in this study that it normally takes about 10 months to replace about half of the cells in the inner lining in the bladders of female laboratory mice. In contrast, in the presence of harmful bacteria, the cells of the bladder begin dividing dramatically and most turn over within 24 hours.

Beachy had another reason to be interested in bladder regeneration after injury. His lab has spent many years studying a molecular cascade called the hedgehog signaling pathway that is important for pattern formation in embryonic fruit flies and other animals. This pathway is involved in

specifying why we have two eyes and nostrils instead of one, why the thumb is different from the little finger, and why different types of neurons form in specific locations within the brain and spinal cord. The hedgehog pathway is also important for maintenance of patterns and structures in adult animals, but less is known about exactly how it functions in these postembryonic settings.

Beachy and his colleagues suspected that the hedgehog pathway might be involved in regenerating the tissue of the bladder.

To conduct the experiments, the researchers used a type of bacteria that causes bladder infections in humans. They introduced the bacteria into the bladders of female mice and watched to see how the cells responded. They found that, after infection, the basal cells in the urothelium and the stromal cells on the other side of the basement membrane "talk" to one another using a protein involved in the hedgehog signaling pathway, called sonic hedgehog, and at least one other signaling pathway, called Wnt.

The process occurred in what's known as a positive feedback loop: Sonic hedgehog stimulated the stromal cells to produce Wnt, and the Wnt stimulated the epithelial cells and the stromal cells to begin proliferating and make more sonic hedgehog. This loop serves to amplify the signal and encourages the cells of the urothelium to begin dividing quickly.

When Beachy and his colleagues looked more closely at what was happening, they found something interesting. "We genetically marked a subset of basal cells that express sonic hedgehog in the bladders of mice and then followed these cells and their progeny during injury," said Shin. "We learned that the sonic-hedgehog-expressing basal cells can regenerate the entire urothelium, including the umbrella cells, and that they seem to be self-renewing. We think these are bladder stem cells.

“We also isolated individual cells and watched what they did in culture,” added Shin. Specifically, after just a few weeks in culture, the basal cells began to form three-dimensional spheres made up of layers of cells that resemble those found in the bladder. The discovery opens up new avenues for learning more about how tissue is regenerated and how cancer forms and spreads.

“Understanding the physiology and the regulation of these regenerative processes might give us a better handle on how to treat bladder cancers and urinary tract infections,” said Beachy.

Furthermore, the discovery that the stromal cells and the basal cells of the epithelium are communicating to control cell division might explain how metastasis occurs.

“Perhaps circulating cancer cells communicate with stromal cells elsewhere in the body using similar signals,” said Beachy. “This could explain how they are able to settle down and start new colonies in other parts of the body.” Like the bladder, the prostate has a similar pattern of resting and rapid growth as it responds to hormones such as testosterone, and cancers in both structures tend to metastasize to other organs in similar patterns, Beachy noted.

The researchers are continuing their studies into bladder regeneration. They are particularly interested in understanding whether manipulation of the activity of the hedgehog, Wnt and other signaling pathways that make up this proliferation-control circuit might be useful in treating bladder infection or bladder cancer growth and metastasis.

Provided by Stanford University Medical Center

Citation: Mechanism for repairing bladder infection damage identified (2011, March 10)