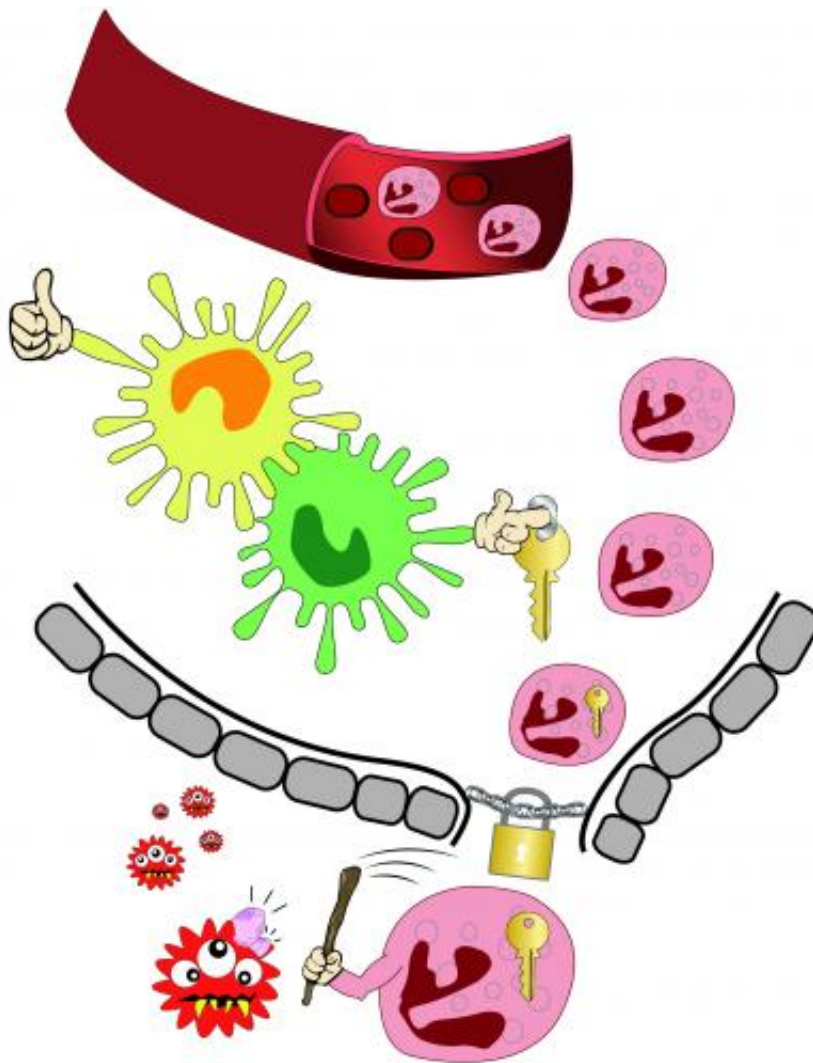


Immune cells need a second opinion: Decoding important mechanism which plays role in urinary tract infections

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In a urinary tract infection, the migration of neutrophils (red cell) from the blood (red vessel, above) to the infection is only possible following a consultation

between helper (yellow) and sentinel macrophages (green). Via the positive signal of the helper macrophages (thumbs up), the sentinel macrophage produces the protein CXCL2 (key) which allows the neutrophils to migrate through the basal membrane of the uroepithelium (chain with lock). Credit: P. Schreiner and M. Gerhards/UKB

Bacterial urinary tract infections are a painful nuisance. A team of researchers led by scientists from the University of Bonn Medical Center has now decoded the way in which immune cells communicate with each other in defense against infections via the messenger tumor necrosis factor (TNF). The results are now being published in the renowned journal *Cell*.

Urinary tract infections are amongst the most frequent infections and are triggered by intestinal bacteria which invade the urogenital tract through smear infections via the urethra. These infections are persistent because the bacteria are often not completely killed off. Nowadays the painful disease can be treated with antibiotics, however the infection can cause chronic kidney damage and possibly even promote the development of bladder cancer. "For this reason, a better understanding of the body's own mechanisms of defense against [urinary tract infections](#) is of great interest," says Prof. Dr. Christian Kurts from the Institute for Experimental Immunology of the University of Bonn Medical Center.

A group of researchers working with Prof. Kurts and his staff member Dr. Daniel Engel, in cooperation with an international team of scientists from Hamburg, Würzburg, Aachen, Leuven, Yale and Heidelberg, have now described a new immunoregulatory mechanism which controls the defense in [urinary tract](#) infections. "Particularly powerful weapons of the immune system are the so-called [neutrophils](#)," says Dr. Engel. They are particularly effective at combating pathogens – especially bacteria.

Minimize collateral damage in the tissue as much as possible

The neutrophils circulate in the blood and immediately penetrate into infected tissue in order to fight invasive bacteria there. They either eat up the intruders or kill them off by releasing toxins. "These powerful defense mechanisms must be controlled well so that they cause as little collateral damage in the tissue as possible," reports Prof. Kurts. The neutrophils are regulated by other [immune cells](#), known as macrophages. It has been known for a long time that macrophages produce various messengers which influence other immune cells. How they regulate the neutrophils has been unclear to date, however.

The team of researchers has now figured out that this regulation takes place through two types of macrophages. "An important result is that these two types of macrophages perform different functions," says Prof. Kurts. One type of macrophage is present in all tissues and exerts a sentinel function. As soon as pathogens penetrate, they are detected by these sentinel macrophages which then trigger an alarm. This takes place through the release of certain messenger molecules, the chemokines, which lure the neutrophils into infected tissue – in the bladder, in this case.

Safety mechanism for potent defense cells

In addition, the sentinel macrophages lure the other type, which the scientists refer to as helper macrophages. These cells likewise discern that there is an infection and communicate this to the sentinel macrophages. The latter then begin to release other chemokines, which allows the neutrophils to reach the bacteria in the infected part of the bladder. "The sentinel macrophages obtain a second opinion as to whether the infection they discerned is so dangerous that the neutrophils

should be activated," explains Dr. Engel. This is a safety mechanism whereby the potent defense cells only penetrate into the infected part of the bladder if there is actual danger.

The communication between the two types of macrophages takes place via the messenger [tumor necrosis factor](#) (TNF). "This molecule plays a central role in various immune-mediated diseases," says Prof. Kurts. Using drugs that block TNF, rheumatoid arthritis or chronic inflammatory bowel disease, for example, can be treated very effectively. However, bacterial infections, including urinary tract infections, were often observed to be a side effect. The findings now available explain the cause: If this messenger is blocked, the macrophages can no longer communicate with each other, and for this reason, the neutrophils are no longer sent to the site of the infection.

Basis for the development of new treatment strategies

This mechanism was decoded within the framework of doctoral theses by Marzena Schiwon and Christina Weisheit from the University of Bonn Medical center. "It is fundamental for our understanding of the antibacterial immune response," says Prof. Kurts. The signaling pathway may also play an important role in infections of other organs. This discovery may represent the basis for the development of new treatment strategies against bacterial infections in general.

More information: Crosstalk between sentinel and helper macrophages permits neutrophil migration into infected uroepithelium, *Cell*, [DOI: 10.1016/j.cell.2014.01.006](https://doi.org/10.1016/j.cell.2014.01.006)

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