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**Immunotherapy - a new approach to treating bacterial infections**

Urinary tract infection (UTI) is one of the most common infections affecting humans. UTIs can take different form depending on the affected organ and the virulence of the pathogen: acute pyelonephritis (infection of the kidney), acute cystitis (infection of the bladder) or asymptomatic bacteriuria (ABU). Uropathogenic *Escherichia. coli* (UPEC) is the most common pathogen during symptomatic UTI. It is estimated that 40–50% of women and 5% of men worldwide develop UTI at least once in their lifetime, and UTIs account for more than 1 million hospitalizations and $1.6 billion in medical expenses each year in the USA alone. If not properly treated, UTIs also cause premature delivery and perinatal mortality, chronic renal disease and renal failure and dramatically reduce the quality of life.

The pathogenesis of UTIs starts when UPEC come into contact with uroepithelial cells, the outer mucosal cells of the urinary tract, through attachment at the cell surface. Uroepithelial cells respond by activating the innate, and later the adaptive immune responses through the secretion of cytokines that activate immune cells (dendritic and mast cells) and chemokines that recruit inflammatory cells (polymorphonuclear neutrophils, PMNs; monocytes; lymphocytes) from the bloodstream. As a result, PMNs cross the epithelial barrier into the urine, and bacteria are
phagocytized and eliminated. However, bacteria can use the secretion of several survival factors as a mean to inhibit the innate host response. In asymptomatic UTI, ABU, bacteria establish a commensal-like state with no or weak innate immune activation that is mutually beneficial for the host and the bacteria.

Innate immunity is finely modulated for protection against bacterial infections, but at the same time it is also responsible for acute symptoms and tissue damage. It is still unclear whether inflammation and pathology are the price to pay to fight infection or if there are specific molecular factors that can distinguish between “good” or “bad” inflammation. To optimally treat infection it is necessary to develop specific immunotherapies capable of reviving and boost the immune protective state while attenuating the destructive response.

Due to the increased microbial resistance to antibiotics, UTIs are getting more difficult to treat. Determining the molecular basis of infection and susceptibility to UTIs is thus crucial in order to develop novel immunotherapies.

Our studies have recently described the genetic basis behind both acute cystitis and acute pyelonephritis. Acute cystitis was shown to be a hyper-inflammatory disorder driven by a dysregulated activation of IL-1β, a classic pro-inflammatory cytokine processed and activated by the inflammasome. Susceptible mice were effectively treated by using an IL-1 receptor antagonist, demonstrating a promising alternative to antibiotics for the treatment of acute cystitis.

In pyelonephritis, we found that the innate immune response to bacterial infection relies on a tight balance between the transcription factors IRF-3 and IRF-7. In mice, deletion of Irf3 led to overexpression of Irf7 and to an IRF-7–driven hyper-inflammatory phenotype, which was entirely prevented if Irf7 was inhibited. By Irf7 siRNA treatment, Irf3−/− mice were protected against infection and renal tissue damage. These findings identify IRF-7 as a therapeutic target for protection against bacterial infection.

We have also shown that bacterial infection activates specific neuropeptides and their receptors that are essential molecular determinants of mucosal inflammation. Finally, we have identified different transcriptional factors specifically regulated during cystitis or pyelonephritis infection, and the bacterial factors that regulate these host transcriptional regulators.

A deeper knowledge of the molecular basis of UTIs and of the host-pathogen interaction is needed to design novel molecular immuno-therapies against these common bacterial disorders.