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TARGETED IMMUNOMODULATION THERAPIES AS NEW OPTIONS TO CURE URINARY TRACT INFECTIONS

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Abstract
With their high prevalence and predisposition to recurrence, urinary tract infections are important contributors to antibiotic prescription worldwide. Studies involving alternative urinary tract infections treatments emerged as a priority in the last years, developing as a response to rapid global dissemination of multi-drug resistant uropathogens. One of these non-antibiotic strategies is based on the hypothesis that recurrent and severe forms of urinary tract infections have a genetic susceptibility pattern, involving the variability of the innate immune response to germs aggression. Yet insufficient studied, the immunology of urinary tract infections is still a subject for new bold researches. By focusing the precise defect that leads to predisposition towards severe or recurrent evolution of the disease and by targeting to correct them, these new therapies examples outlined in our review can bring a ray of hope in the treatment of UTI and the burden they represent.
Keywords: *urinary tract infection, innate immune response, immunomodulation, therapeutic targets.*

Rezumat
Infecțiile de tract urinar sunt printre cele mai frecvente patologii infecțioase și contribuie semnificativ la prescripția mondială de antibiotice. Ca reacție la problema globală majoră a antibio-rezistenței, terapiile alternative în infecțiile de tract urinar au cunoscut o dezvoltare importantă în ultimii ani. Una dintre direcțiile de cercetare se bazează pe identificarea mecanismelor imunologice ale reacției de apărare a gazdei după colonizarea tractului urinar cu germeni uropatogeni. Prin definirea cu precizie a defectului care predispune la reacții imune exagerate și prin identificarea moleculelor care pot fi adresate terapeutic țintit, studiile pe care le prezentăm în acest referat deschid noi perspective în tratamentul infecțiilor de tract urinar.
Cuvinte cheie: *infecția de tract urinar, răspuns imun, imunomodulare, ținte terapeutice.*



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Introduction

Antimicrobial resistance is a major problem of global health[1]. With high prevalence and predisposition to recurrence, urinary tract infections (UTI) are important contributors to antibiotic prescription worldwide[2,3]. That is because, despite the burden they represent on health care systems, treatment options for UTI are surprisingly limited.

Regimens alternative to antibiotics are either of weak effectiveness or controversial and insufficient studied. It is not hard to understand why trials involving alternative UTI treatments emerged as a priority in the last years, developing as a response to rapid global dissemination of multi-drug resistant uropathogens[4,5]. One of these non-antibiotic strategies is based on the hypothesis that recurrent and severe forms of UTI have a genetic susceptibility pattern, involving the variability of the innate immune response. Addressing the innate immune system in treating UTI in recurrence-susceptible individuals is not a new subject, but until now all the means tested were not efficient enough: non-steroidal anti-inflammatory drugs and corticosteroids can impair germ clearance, vaccines are still insufficient developed and limited to particular germ strains[6].

Therefore, novel therapeutic strategies, specifically targeting immunity, are expected to modulate the response to microbial aggression and reduce the susceptibility for persistent/recurrent/severe UTI.

UTI immunology and potential new therapeutic targets emerging from this concept

Yet insufficient studied, the immunology of UTI is still a subject for new bold researches. The reason for the wide variability in the predisposition to UTI, their severity and their recurrence is still a matter of debate. We know for sure that women are anatomically predisposed to UTI and epidemiology taught us that one of two feminine patients will experience recurrences of the infectious episodes, but the mechanism that facilitates the persistence or the reappearance of the infection in some hosts is not elucidated[7,8]. While the virulence of the uropathogen germs is only partially responsible, it seems that the central part in this process is acted by the immune system of the host - a dual player: it can be a either a protector or a promoter of the disease after urinary tract colonization[6,9,10].

In some individuals, the innate immunity provides a rapid defensive response to uropathogens, by recognizing them and blocking their access to host tissues, yet supporting the physiologic flora of the urinary tract[11,12]. After the colonization of the urinary tract, there is an acute response with the induction of local and systemic chemokines

and cytokines, exfoliation of the urothelium, and infiltration of innate immune cells such as neutrophils and monocytes; in this way the uropathogens are cleared from the healthy urinary tract[13,14]. In other individuals, a late recognition or an incommensurate response can produce an inflammatory over-reaction with undesired consequences: severe disease, progression to chronic inflammation, balder scars[15,16]. The difference between the two ways of action seems to involve several players that can be emphasized and targeted to restore the functional innate immune response and to stop this response to generate exaggerated forms. There are several molecules studied for their role in the process of correct recognition and clearance of the uropathogens.

The most recent results regarding the substances involved in the transition from a homeostatic innate immune response to a severe mucosal inflammation and sometimes to chronic bladder disease are focusing interleukin-1beta (IL-1β) and the matrix metalloproteinase (MMP7). Other researches founded that the pain sensor neurokinin 1 receptor (NK1R) and the cyclic adenosine monophosphate (cAMP) levels also play different roles in this process[17]. Roles of yet undetermined importance and unexposed addressability are attributed also to IL-6, IL-8-receptor (CXC chemokine receptor 1), tumor necrosis factor alfa (TNF-ά) and others[18,19].

IL-1β

It is secreted by macrophages and monocytes and produces infiltration of neutrophils in the bladder mucosa and epithelial damage. The recent studies of Ambite and colleagues in Lund University performed on mice and also on human subjects pointed out that hyper-activation of IL-1β contribute to a severe inflammatory response during the acute cystitis episodes[15,20]. The transformation of IL-1β in its active form was performed by large quantities of enzyme MMP7, found in individuals lacking two constituents called inflammasome and known to naturally repress the MMP7 and NK1R activity: ASC (Apoptosis-associated speck-like protein containing a CARD) and NLRP-3 (NACHT, LRR and PYD domains-containing protein 3)[21]. The process depends on susceptibility genes expression, but also it can be influenced by the germ strain[22]. Some uropathogens (group B2 Escherichia coli, Proteus mirabilis) express a large amount of virulence factors, like hemolysin and cytotoxic necrotizing factors (CNF), that can induce over-formation of IL-1β[23,24].

Based on these findings, Ambite and co. studied the effect of an IL-1 receptor antagonist (IL-1RA) - Anakinra - in the treatment of severe acute cystitis. It proved to attenuate the hyper-activation of IL-1β and, therefore, it can limit the over-reaction of the bladder epithelium to germs aggression in individuals predisposed to severe disease forms[15,25]. More recently, other researchers extended the use of short-term immuno-therapy with Anakinra to the severe forms of bladder pain syndrome (BPS), interrupting the vicious circle of inflammation and ameliorating the pain[26].

MMP7

Targeting the processes exposed before, and the influence of MMP7 in chemokines over-activation and excessive defense response, the broad-spectrum MMP inhibitor Batimastat can also limit the inflammation cascade. It can indirectly but successful inhibit the excessive IL-1β response, therefore contributing to reduce the severity of the host tissue reactions and accelerating the process of bacterial clearance[9,15,25].

NK1R

Going further on the mechanism of innate immune response, targeting NK1R has been



shown to reduce the pain, inflammation and also micturition deficiencies. Therefore, it ameliorates the overactive bladder syndrome, BPS and symptoms of interstitial cystitis. Studies involving the NK-1 antagonists - aprepitant and serlopitant - were performed since early 2000 and they continue in our days, with promising results[25,27-29].

cAMP and IL-6

Another recently discovery involves the role of cAMP in the clearance of some uropathogens. It is known that UPEC are able to resist antibiotic treatment by entering the cells and binding within fusiform vesicles of superficial epithelial cells of the bladder, creating an intracellular reservoir[30,31]. It was demonstrated that cAMP levels regulate the exocytosis of these vesicles depending on the bladder distension[32]. Therefore, it is possible that by increasing the content of cAMP in urothelial cells we can lead bacteria to exit the urothelial cells. Forskolin, a labdane diterpene, is the active component of the plant Coleus forskohlii and it has been studied for its effect as an artificial enhancer of cAMP[33]. In pilot experiments, Duke University researchers showed that they could diminish the persistence of UPEC infection by stimulating the exocytosis of bladder epithelial cells with Forskolin; also, the urine levels of IL-6 were significantly lower in treated subjects[6,34].

There are also other studies connecting the low IL-6 genetic or acquired deficiencies to increased susceptibility to recurrent/severe UTI due to alterations in cAMP production[35]. As an escape mechanism, UPEC were found to suppress IL-6 secretion of the urothelial cells and their virulence correlates inversely with this capacity[36]. It is also proved that tocilizumab, a humanized monoclonal antibody directed toward IL-6, favors genitourinary infections as a side effect[37]. Backwords, strategies are expected that trigger IL-6 and block its inhibition, in order to hasten UTI resolution.

IL-8R

The genetic predisposition of some individuals to UTI was explained by researchers in Lund University as being a defective expression of the IL-8 receptors CXCR1 and CXCR2 on the surface of the neutrophils[18,38,39]. More recent, there was a confirmation that CXCR2 receptor is poorly expressed in premenopausal women with recurrent UTI[19]. In normal conditions, as response to uropathogens invasion - especially UPEC - human urothelial cells secrete IL-8 and other CXC chemokines. After they bind with the specific transmembrane receptors, chemokines start acting like potent neutrophil chemotactic and activating peptides. Neutrophils reach the epithelial cells and go further, crossing into the lumen of the urinary tract, where they contact and phagocytose uropathogenic bacteria. In individuals with low IL-8R expression neutrophils accumulated in the tissue and do not pass the epithelial barrier

in the urine, therefore resulting an inefficient bacterial clearance, the persistence/ recurrence of UTI and evolution to renal scarring[19,40]. The findings necessitate further evaluations and also the discovery of a specific therapeutic tool in order to address and cure this inherited condition.

Conclusion

The extent of the immune response in UTI is an important determinant in the evolution of the infection, as new studies identified specific host cell receptors and active molecules responsible for the intensity of the defense reaction. Pointing out immunity dysfunctions that can cause exaggerated inflammation and severe disease or/and germ persistence in the urinary tract epithelium is the first step to control the disease.

Promising studies performed in some cases regarding the effect of specific therapeutic molecules offer a step forward. They can also lead a way to address infections caused by antibiotic-resistant strains. By focusing the precise defect that lead to predisposition towards severe or recurrent evolution of the disease and by targeting to correct them, these new therapies examples presented in our review can bring a ray of hope in the treatment of UTI and the burden they represent.

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