Cellular Immunology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Research paper

Bladder resident macrophages: Mucosal sentinels

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ARTICLE INFO

Keywords:
Bladder
Urinary tract infection
Bladder cancer
Tissue-resident macrophage, monocytes
Uropathogenic *E. coli*
BCG immunotherapy
Schistosoma haematobium

ABSTRACT

Macrophages are instrumental in the response to infectious and noninfectious diseases, however, their role in the bladder is poorly understood. Indeed, the bladder is a mucosal tissue frequently overlooked in research, despite the prevalence of illnesses such as urinary tract infection and bladder cancer. Notably, bladder tissue macrophages are among the most populous resident immune cells in this organ and recent studies support that resident macrophages and infiltrating monocytes play nonredundant roles in response to infection, immunotherapy, and inflammation. Advancing our understanding of macrophage behavior in the bladder is complicated by the difficulty in obtaining tissue-resident cells. Surmounting this challenge, however, for a greater understanding of macrophage ontology, impact on innate and adaptive immunity, and regulation of homeostasis, will ultimately contribute to better therapies for common afflictions of the bladder.

1. The bladder

The bladder is an expandable hollow organ located in the pelvic area. It is part of the urinary tract system, which includes the kidneys, ureters, and urethra. Its main function is to store urine produced in the kidneys prior to voiding [1]. Despite its apparent simplicity, the bladder has a complex morphology with multiple cell types, including the most impenetrable epithelium of the body [2]. This feature is vital to protect host tissues from toxins accumulated in the urine and to prevent invasion of microorganisms [3]. Structurally, a strong muscular wall, the lamina propria, and a layer of adipose tissue surround and support the epithelial layer in the bladder, the urothelium [4]. The urothelium is composed of three to six layers of cells. The basal layer is most proximal to the lamina propria, followed by intermediate cells, which make up one or more layers of cells. Very large binucleated cells, called umbrella or facet cells, make up the superficial layer.

The urinary tract is particularly vulnerable to infection as the urethral opening is in close proximity to the terminus of the gastrointestinal tract. As such, the bladder has multiple mechanisms of host protection [5]. The immune cell compartment is well characterized in naïve mouse bladders [6]. It is primarily composed of phagocytic antigen presenting cells, such as dendritic cells and macrophages [6]. Additional resident immune cells include $CD4^+$ and $\gamma\delta^+$ T cells, NK cells, monocytes, eosinophils, and mast cells [6]. Innate lymphoid cells are also likely resident in the bladder, however additional studies are needed to address this possibility. Much less is known about the bladder-resident immune cell compartment in humans, although MHC II^+ cells are evident by histology [7]. Additional innate bladder defense mechanisms include (i) micturition, which may act to impede bacterial ascension or colonization, but appears to facilitate adhesion for certain uropathogens; (ii) a mucin layer that impedes bacterial adherence to the urothelium; and (iii) soluble factors, such as complement and antimicrobial peptides, immunoglobulin A, Tamm-Horsfall protein, and iron sequestering lactoferrin and lipocalin [5,8–11].

Finally, similar to other anatomical sites, the bladder harbors a unique microflora, which is distinct from the gut and vagina microbiomes, and is not sterile, as previously thought [12–17]. The urinary microbiome appears to differ between men and woman. Women may have a more diverse urinary microbiome than men, however, the very small number of individuals sampled in this study precludes making broad generalizations about microbial diversity [16]. Urinary diseases, such as infection and catheterization can disrupt the healthy microbiome in men and women, leading to transient or long-term changes in its composition [16,17]. While more studies are needed, the urinary microbiota may prevent colonization of the bladder by uropathogens through competition for resources or niches or may more generally support urinary tract health. Supporting this hypothesis, alterations in the microflora have been linked to non-infectious urological diseases, such as interstitial cystitis [18–20].

2. Diseases of the bladder

Urinary tract infection (UTI) is one of the most common infections in humans and is the most common hospital-acquired infection

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https://doi.org/10.1016/j.cellimm.2018.01.018
Received 25 October 2017; Received in revised form 18 January 2018; Accepted 31 January 2018
0008-8749/ © 2018 Published by Elsevier Inc.

[21–23]. Uropathogenic *Escherichia coli* (UPEC) is the causative agent in more than 80% of UTI [24]. Other uropathogens include, but are not limited to *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Staphylococcus saprophyticus,* and *Proteus mirabilis* [25–27]. UTI exhibits a sex-bias, in which women are more susceptible to infection than men. Indeed, approximately 50% of all women will experience a UTI, and approximately one-fourth to one half of these woman will have a recurrent infection within 6–12 months [28]. Susceptibility to UTI may be determined by genetic factors, functional abnormalities of the urinary tract, use of catheters, or composition of the urinary microbiota [29,30], although these factors cannot entirely explain the prevalence of infection. Genetic predisposition appears to be a major factor in UTI morbidity, as individuals with a family history of UTI are at increased risk of developing acute cystitis [23,29,31,32].

Bladder cancer is the ninth most common malignancy in the world and is much more common in men than in women [33–35]. Nonetheless, women are more likely to have locally advanced tumors and worse outcomes compared to male patients [34]. Exposure to carcinogens, including those in cigarette smoke, is a major risk factor for developing bladder cancer [36]. Additional risk factors include exposure to arsenic and occupational exposure to chemicals, such as aromatic amines and 2-chloroaniline [37]. Bladder cancer can be subdivided into nonmuscle and muscle invasive disease, with distinct treatments and outcomes associated with each [33]. In addition, a distinct form of squamous cell carcinoma develops in the bladder following chronic bladder infection by *Schistosoma haematobium* [38]. *Schistosoma haematobium* is endemic in Egypt and other parts of Sub-Saharan Africa, making squamous cell carcinoma the predominant form of bladder cancer in this part of the world [39–41].

Lastly, the bladder can be affected by a relatively poorly understood disease called interstitial cystitis (IC). IC or painful bladder syndrome (PBS) is a sterile chronic inflammatory condition primarily occurring in women. IC/PBS symptoms include the frequency and urgency to urinate, and discomfort and pain in the bladder and pelvic region [42]. IC/PBS is poorly defined and clinical symptoms are shared with other diseases, such as irritable bowel syndrome and fibromyalgia, which makes diagnosis and treatment challenging [43]. The etiology of the disease is also unknown. However, one possibility is that symptoms arise following an inappropriate inflammatory response to an infection [44,45]. As the bladder tends to be overlooked and research in bladder diseases is severely underfunded [46], there is still a large gap in our knowledge of specific mucosal immune responses following inflammation, infection, and cancer. This translates to limited therapeutic options for these bladder diseases.

3. The role of macrophages during urinary tract infection

Bacterial ascension into the urinary tract may lead to infection. Once invading bacteria reach the bladder mucosa, they can induce a strong inflammatory response arising from nonimmune and immune cells [8]. The presence of phagocytes and antigen presenting cells in the bladder suggests these cells play an important role in immune surveillance locally. Macrophages comprise nearly 40% of all $CD45^+$ cells in the bladder immune cell compartment of mice [6]. Consequently, they contribute to the host immune response to UTI in several ways.

3.1. Recognizing uropathogens

The host inflammatory response to infection is initiated upon innate bacterial sensing by pattern recognition receptors (PRR). Notably, many PRR, such as Toll-like receptors (TLR)2, TLR4, TLR5, TLR11 are expressed in the bladder [8]. Although these receptors are typically associated with macrophages, dendritic cells, or epithelial cells, their expression patterns in the bladder have not been mapped to specific cell types. Among the various PRR, TLR are the best characterized in the context of UTI. Components of UPEC, such as type I pili, activate TLR4, for example [47]. TLR4 signaling from both the hematopoietic and stromal compartments is critical to mount an effective immune response against UPEC [48]. Moreover, variation in the promoter of the *TLR4* gene is associated with human UTI susceptibility [49], suggesting that TLR4 plays a protective role in UTI. In addition to TLR4, CD14, an LPS receptor, can be detected during UPEC infection, and its loss leads to a modest increase in bacterial burden and an aberrant transcriptional signature in the bladder in experimental UTI [50]. Finally, mice lacking TLR5, which recognizes bacterial flagellin, have increased bacterial burden and inflammation 5 days post-infection compared to wildtype controls [51].

3.2. Inducing inflammation

Inflammation is critical to induce recruitment of immune cells that subsequently kill uropathogens, and macrophages are likely an important source of pro-inflammatory cytokines during UTI [52]. In addition to PRR activation, production of pro-inflammatory cytokines follows bacterial recognition through intracellular receptors such as inflammasomes [53,54]. For example, inflammasome activation leads to the release of proinflammatory mediators, such as IL-1β, and UPEC strains induce the NLRP3 inflammasome in mouse models of UTI [54]. Furthermore, inflammasome activation is enhanced in ATG16L1 hypomorphic mouse bone marrow derived macrophages infected with UPEC, leading to increased IL-1β secretion [55]. Accordingly, infected ATG16L1 hypomorphic mice have improved bacterial clearance compared to wildtype animals [55]. A specific phylogenetic group of UPEC expresses a virulence factor, Toll/IL-1 receptor–containing (TIR-containing) protein C (TcpC), that, in mouse bone marrow derived macrophages, interacts with the NLRP3 inflammasome to reduce caspase-1 activation and IL-1β release compared to UPEC deficient in this protein [54]. *In vivo*, mice infected with TcpC deficient-UPEC have reduced levels of IL-1β in the urine compared to mice infected with wildtype bacteria [54]. A number of different UPEC strains associated with symptomatic UTI induce inflammasome activation, IL-1β release, and cell death to different degrees in human monocyte-derived macrophages and mouse bone marrow derived macrophages [56]. Inflammasome responses in mouse macrophages are largely dependent on the UPEC virulent factor α-hemolysin, while cell death and IL-1β secretion in human macrophages occur independently from this toxin [56]. This divergence in response between human and mouse macrophages suggests that UPEC may be differently recognized, resulting in the activation of distinct pathways, depending on the host cell species. Alternatively, these differences may reflect studies performed *in vitro* in macrophages matured by different means.

Despite the cellular machinery fighting infection, bacteria may subvert the immune system to persist in the host. One study suggests that UPEC subverts macrophage killing and survives inside bone marrow derived macrophages up to 24 h [57]. However, as the number of bacteria recovered 24 h post-infection in this study was much lower than the initial bacterial input, it is difficult to conclude that UPEC can survive inside macrophages, particularly with a single time point measurement [57]. Alternatively, it may be that bacteria do not necessarily survive, but are not entirely killed at 24 h post-infection. Additional time points, uptake and degradation studies, and *in vivo* experiments are needed to determine whether UPEC can truly persist inside macrophages. It is noteworthy that only one study has investigated UPEC infection using macrophages isolated from the bladder [58]. In this study, macrophages isolated from mouse bladders upregulate iron sequestering molecules, thereby likely limiting iron availability for UPEC and inhibiting growth in the bladder [58]. By contrast, the vast majority of *in vitro* studies investigating macrophage-UPEC interactions rely upon monocyte-derived or peritoneal macrophages. These macrophages are widely used to perform *in vitro* studies given the ease in obtaining high number of cells. However, they do not truly resemble tissue resident macrophages, which, in most tissues have an

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