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## NEWS AND COMMENTARY

## Interleukin-22 in urinary tract disease – new experimental directions

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Interleukin (IL)-22 is a cytokine produced by immune cells with bimodal functionality depending on the tissue it is expressed in and the context of its expression. IL-22 has antimicrobial properties and can limit bacterial infections but also drive pro-inflammatory responses that may have deleterious consequences for disease progression. Conversely, IL-22 can also promote epithelial cell repair, regeneration and restoration of mucosal barrier function. IL-22 may also alter the microbiota, which has broad implications for the maintenance of homeostasis at mucosal surfaces colonised by commensal microorganisms, such as the gastrointestinal or the urinary tract. A critical limitation in the exploration of IL-22 function, at sites such as in the urinary tract, is a lack of appropriate experimental tools. Studies using newly available, genetically modified reporter mice have led to the identification of the cellular source and location of IL-22, while Cre-lox expressing transgenic mice permit specific targeting of IL-22 in the urinary tract. With a greater understanding of the role of IL-22 in the urinary tract, repurposing of emerging novel human immunotherapies that either inhibit or activate IL-22 may create new opportunities for the treatment of urinary tract diseases.

**IL-22 AT MUCOSAL SURFACES**

IL-22 is an IL-10 family cytokine produced mainly by immune cells of the lymphoid lineage

including group 3 innate lymphoid cells (ILC3), mucosal-associated invariant T cells (MAIT), natural killer T cells (NKT), T helper 22 cells (Th22) and  $\gamma\delta$ T cells<sup>1</sup> (Figure 1a). However, macrophages or neutrophils can also produce IL-22 under certain circumstances, such as in a model of dextran sodium sulphate-induced colitis, in which IL-22-expressing neutrophils contribute to epithelial repair in the colon.<sup>2</sup>

IL-22 signals through the IL-22 receptor (IL-22R), which is composed of two heterodimeric subunits, IL-22R1 (encoded by *Il22ra1* in mice) and IL-10R2.<sup>1</sup> IL-22 has a high affinity for IL-22R1, and while it has no affinity for IL-10R2, the IL-22-IL-22R1 complex has a strong binding affinity for the IL-10R2 subunit (Figure 1a). IL-22R1 expression is restricted to renal tubular epithelial cells in mice.<sup>3</sup> Its expression in the bladder epithelium is unreported, but it is typically expressed in epithelial surfaces.

Indeed, IL-22 primarily targets non-haematopoietic epithelial cells at mucosal barrier sites (e.g. lung, skin, gastrointestinal tract), where it promotes proliferation of epithelial cells and tissue regeneration after injury.<sup>2</sup> IL-22 regulates host microbial defences through induction of antimicrobial peptides, such as the Reg family of proteins during *Citrobacter rodentium* infection.<sup>4</sup> Studies in the gastrointestinal tract demonstrate that IL-22, expressed by ILCs, helps to maintain containment of commensal bacterial strains, and in the absence of these cells, specific microbes can

breach the gastrointestinal barrier.<sup>5</sup> Given that IL-22 is produced at sites of inflammation, it may either mediate a physiologic response to repair local tissue damage or it may contribute to inflammatory lesions.<sup>1</sup> Therefore, caution is needed when interpreting the impact of IL-22 in disease models and there is a clear need for organ- and tissue-specific tools to accurately assess its function.

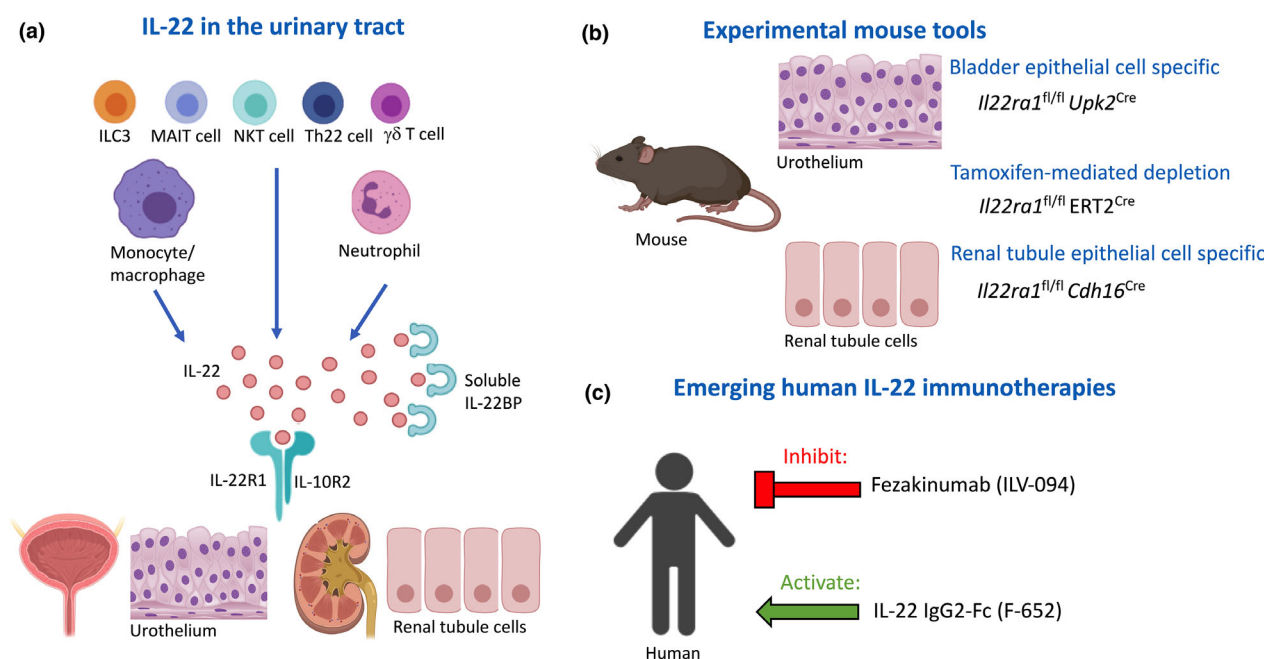
## IL-22 IN THE KIDNEY

The role of IL-22 in the kidney is reasonably well studied (reviewed in Weidenbusch *et al.*<sup>6</sup>). Infiltrating immune cells secrete IL-22, inducing progressive kidney remodelling following unilateral ureteral obstruction, which augments renal tubular epithelial integrity and epithelial barrier function.<sup>7</sup> IL-22 accelerates kidney regeneration and ameliorates renal ischaemia–reperfusion injury,<sup>3,8</sup> suggesting, overall, that IL-22 function in the kidney is most likely

tissue-protective and that restoring optimal IL-22 function may be beneficial in certain kidney diseases. Interestingly, however, endogenous IL-22 does not play a role in glomerulonephritis,<sup>9</sup> highlighting that IL-22 function in the kidney is disease-dependent.

## NEW EXPERIMENTAL DIRECTIONS FOR FUNCTIONAL CHARACTERISATION OF IL-22 IN THE URINARY TRACT

There are various experimental mouse tools that can facilitate a detailed mechanistic understanding of IL-22 function *in vivo*. IL-22 reporter mice (e.g. *Il22<sup>td-tomato</sup>* mice<sup>10</sup>) allow for quantification of endogenous IL-22<sup>+</sup> immune cells in the urinary tract and other tissues without *ex vivo* cell stimulation used in intracellular cytokine staining procedures.<sup>10</sup> This is a strategic advantage as it gives a readout of IL-22 expression in tissue and eliminates the caveats of artificial stimulation *ex vivo*. Reporter mice also bypass



**Figure 1.** IL-22 and IL-22 receptors in the urinary tract, new tools to assess their function *in vivo* and emerging immunotherapies. **(a)** IL-22 is produced by several immune cell subsets including group 3 innate lymphoid cells (ILC3), mucosal-associated invariant T cells (MAIT), natural killer T cells (NKT), T helper 22 cells (Th22),  $\gamma\delta$ T cells, macrophages and neutrophils. IL-22 signals through a membrane-bound heterodimer complex consisting of IL-22R1 and IL-10R2 expressed on urothelium and renal tubule epithelial cells in the bladder and kidney, respectively. The binding of IL-22 to this membrane-bound receptor complex activates downstream signalling pathways to induce antimicrobial, pro-inflammatory or tissue repair/regenerative responses. IL-22 activity is negatively regulated by the soluble high-affinity receptor IL-22BP. **(b)** Experimental mouse tools that specifically target IL-22 receptor in the bladder and kidney epithelium, respectively. Conditional depletion of IL-22 receptor at specific time points can be achieved by tamoxifen administration. These tools may enable future detailed mechanistic studies for multiple urinary tract disease models. **(c)** Emerging immunotherapies that target IL-22 in humans.

reliance upon antibody specificity for the intracellular cytokine, although nonspecific fluorescent leakage of reporter mice is still a concern. In addition to identifying the cells producing IL-22, localisation of cytokine-producing cells is possible using 3-dimensional imaging of optically transparent IL-22 reporter mouse tissue in high resolution with 2-photon fluorescent microscopy.<sup>11</sup> Finally, reporter mice can be used for real-time *in vivo* imaging and tracking of IL-22<sup>+</sup> cell migration into organs of the urinary tract.

IL-22-deficient and IL-22 receptor-deficient mice are key to providing information on the impact of a lack of IL-22 signalling systemically. However, because of the complex multifaceted and context-specific nature of IL-22 signalling, systemic deletion will likely provide confounding results. IL-22 is also critical for the maintenance and regulation of the gastrointestinal microbiota,<sup>4,5</sup> which is known to impact multiple diseases of the urinary tract both clinically and experimentally. To improve future experimental design and limit unintentional off-target effects of IL-22 systemically and on the microbiota, mice that specifically lack the IL-22 receptor in bladder or kidney epithelial cells should be created. This can be achieved by crossing IL-22 receptor-floxed (<sup>fl/fl</sup>) mice (*Il22ra1<sup>fl/fl</sup>*, The Jackson Laboratory, USA) with the mouse uroplakin 2 (Upk2) promoter driving Cre recombinase (<sup>Cre</sup>) expression (*Upk2<sup>Cre</sup>*, The Jackson Laboratory) in the bladder urothelium or by crossing the *Il22ra1<sup>fl/fl</sup>* mouse with Cre recombinase under the control of the mouse cadherin 16 (Cdh16) promoter (*Cdh16<sup>Cre</sup>*, The Jackson Laboratory) resulting in loss of IL-22 receptor expression in the renal tubules of adult mice (Figure 1b). *Il22ra1<sup>fl/fl</sup>* mice could also be crossed with tamoxifen-induced (ERT2)<sup>Cre</sup> mice to control when IL-22 is disrupted in a given urinary tract disease model, with the caveat that tamoxifen-mediated deletion is not restricted solely to the urinary tract.

## EMERGING IL-22 IMMUNOTHERAPIES – POTENTIAL FOR THE TREATMENT OF URINARY TRACT DISEASES

There are novel human immunotherapies in the clinical trial that either inhibit or enhance human IL-22 activity (Figure 1c). Clinical safety and pharmacokinetic studies are completed for both of these therapies, and both are in phase IIa trials

for human diseases.<sup>12,13</sup> Fezakinumab (ILV-094, Pfizer) is a human anti-IL-22 monoclonal antibody that blocks IL-22 and was developed for the treatment of moderate-to-severe atopic dermatitis.<sup>12</sup> IL-22 IgG2-Fc (F-652, Generon BioMed) is a human recombinant IL-22 developed to promote IL-22-mediated tissue repair and regeneration in the context of graft-vs-host disease and alcoholic hepatitis.<sup>13</sup> To facilitate the translation of emerging immunotherapies targeting IL-22 in human urinary tract diseases, the critical first step will be to provide proof-of-principal studies in experimental mouse models of urinary tract disease, using tools that restrict the manipulation of IL-22 specifically to the urinary tract. In this way, it will be apparent whether the addition or inhibition of IL-22 is beneficial to the host response to urinary tract diseases.

## CONCLUSION

Without a clearly defined role for IL-22 in the urinary tract using experimental approaches, it will be difficult to justify whether inhibition or enhancement of IL-22 function in humans with urinary tract disease will be of therapeutic benefit. Strategies to specifically target these emerging immunotherapies to the urinary tract will be required as targeting IL-22 systemically may have unwanted off-target effects on other systems; however, the bladder, for example, is uniquely suited for local delivery *via* catheterisation. Careful consideration of the impact of IL-22 therapies on the microbiota and its subsequent impact on urinary tract disease will also need to be carefully considered in future clinical trial design.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

**Molly A Ingersoll:** Conceptualization; Writing-original draft; Writing-review & editing. **Malcolm R Starkey:** Conceptualization; Writing-original draft; Writing-review & editing.

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