GLOMERULAR DISEASE

Tolerogenic cell therapy for glomerulonephritis

The available therapies for anti-myeloperoxidase (MPO) glomerulonephritis (GN) are broadly immunosuppressive and associated with serious adverse effects, particularly infections. A potentially safer approach is to specifically target anti-MPO immunity to restore tolerance to this autoantigen without compromising the immune response to pathogens. Now, Dragana Odobasic and colleagues report that tolerogenic dendritic cells (DCs) induced MPO-specific immunosuppression and attenuated anti-MPO GN in a mouse model.

"We chose to investigate tolerogenic DCs because they have a unique capacity to induce antigen-specific immunosuppression by presenting antigens to T cells, and because phase I trials have proven their feasibility and safety as a potential therapeutic approach in patients with various autoimmune diseases," explains Odobasic. To generate tolerogenic DCs that specifically inhibit anti-MPO autoimmunity, the researchers cultured DCs with a NF-κB inhibitor to induce an anti-inflammatory phenotype and then exposed them to MPO. "These MPO-loaded tolerogenic DCs can present MPO and thus turn off disease-driving MPO-specific T cells," says Odobasic.

Injection of the MPO-loaded DCs induced inhibitory IL-10-producing regulatory T cells in MPO-immunized mice and suppressed established anti-MPO autoimmunity, glomerular injury and proteinuria in mice with anti-MPO GN. The DCs did not inhibit immunity against an irrelevant antigen, confirming that their immunosuppressive effects were MPO-specific.

"These studies will pave the way for progress of MPO-presenting tolerogenic DCs into clinical trials," concludes Odobasic. "By turning off anti-MPO autoimmunity, this therapy comes as close as possible to a cure for anti-MPO GN and has the potential to provide immense benefit to patients by enabling them to avoid complications resulting from the non-antigen-specific effects of current therapies."

Ellen F. Carney

ORIGINAL ARTICLE Odobasic, D. et al. Tolerogenic dendritic cells attenuate experimental autoimmune antimyeloperoxidase glomerulonephritis. *J. Am. Soc. Nephrol.* https://doi.org/10.1681/ASN.2019030236 (2019)

IMMUNOLOGY

IL-6-dependent regulatory T cells in GN

Pathogenic T helper 17 (T_H17) cells have been implicated in immune-mediated glomerular disease, whereas T regulatory (T_{reg}) cells are known to have an anti-inflammatory and protective role. Now, Oliver M. Steinmetz and colleagues report on how IL-6 modulates T cell differentiation in a crescentic glomerulonephritis (GN) model.

"Targeting the IL-6–IL-6 receptor (IL-6R) axis has been successfully used to treat inflammatory diseases, but blocking IL-6 signalling aggravated experimental crescentic GN," explains Steinmetz. To investigate this discrepancy, the researchers created CD4-specific *Il6ra*$^{-/-}$ mice. In their model of nephrotoxic nephritis (NTN) induced with nephrotoxic sheep serum, loss of IL-6Rα on $CD4^+$ cells reduced T_H17 cell differentiation and secretion of T_H17 cytokines compared with wild-type controls.

To ensure that only $CD4^+$ T cells were *Il6ra*$^{-/-}$ in their system, the researchers adoptively transferred T cells into *Rag1*$^{-/-}$ (T cell-deficient) mice before inducing NTN. Compared with mice that received wild-type $CD4^+$ T cells, recipients of *Il6ra*$^{-/-}$ $CD4^+$ T cells had lower frequencies of splenic and renal T_H17 cells, and a significantly reduced kidney neutrophil infiltrate, but renal outcomes did not improve. Inhibiting the T_H17 cell response by blocking IL-6R signalling on all $CD4^+$ T cells was thus not effective in protecting the kidney from damage. Moreover, when only T_{reg} cells were deficient for IL-6Rα among the transferred $CD4^+$ T cells, renal outcomes were significantly worse compared with animals that received wild-type T_{reg} cells, despite a similar T_H17 cell response. These findings suggest a protective role for IL-6-dependent T_{reg} cells, which are enriched for $ROR\gamma t^+FOXP3^+CCR6^+$ T_{reg} cells.

"Our data revise the paradigm of IL-6 as a 'pro-inflammatory master switch' — we show that classic IL-6 signalling induces both pathogenic T_H17 cells and protective $ROR\gamma t^+FOXP3^+$ T_{reg} cells, which have an enhanced suppressive capacity," concludes Steinmetz.

Monica Wang

ORIGINAL ARTICLE Hagenstein, J. et al. A novel role for IL-6 receptor classic signaling: induction of $ROR\gamma t^+Foxp3^+T_{regs}$ with enhanced suppressive capacity. *J. Am. Soc. Nephrol.* **30**, 1439–1453 (2019)

RENAL CELL CARCINOMA

PAX8: a candidate oncogene in RCC

Transcription factors (TFs) have previously been identified as drivers of cell proliferation in cancer cell lines, but the contribution of specific TFs to tumorigenesis and their mechanism of gene regulation remain unclear. In new research, Giorgio Galli and colleagues identify *PAX8* as a candidate oncogene in renal cell carcinoma (RCC) cells and show that the TF this gene encodes activates expression of metabolic genes, including the ferroxidase ceruloplasmin (CP), by binding distal enhancer elements and recruiting histone acetylation activity. "We demonstrate that PAX8 regulates not only cell cycle genes but also metabolic pathways important for RCC," says Galli.

To identify core TFs that engage with regulatory elements in target genes, Galli and colleagues used a computational approach to map super-enhancers (identified by chromatin immunoprecipitation for H3K27ac) and chromatin accessibility regions (using ATAC sequencing), together with large-scale genetic screens. "Use of these technologies provided an unbiased and comprehensive view of TF dependencies in kidney cancers and led to the identification of PAX8 as a candidate oncogenic factor," explains Galli.

Further analyses demonstrated that PAX8 regulates the expression of a number of genes linked to cell cycle control and metabolic processes. To further assess the molecular functions of PAX8, the researchers focused on CP, which was the most dysregulated target of PAX8. They found that PAX8 binds to distal enhancer elements, which likely recruits an acetyltransferase-containing complex for gene activation. In cell lines, CP expression correlated with sensitivity to PAX8 silencing. Moreover, analysis of data from The Cancer Genome Atlas revealed an inverse association between expression of CP and survival among RCC cases. "Our findings suggest that understanding the protein complexes engaged by PAX8 in cancerous tissues might reveal the mechanisms that drive tumorigenesis and offer hints as to how PAX8 activity could be modulated for therapeutic purposes," notes Galli.

Susan J. Allison

ORIGINAL ARTICLE Bleu, M. et al. PAX8 activates metabolic genes via enhancer elements in renal cell carcinoma. *Nat. Commun.* **10**, 3739 (2019)