

 GLOMERULAR DISEASE

Breaches in the Bowman's capsule and CD8⁺ T cell infiltration in crescentic GN

The role of cellular immunity in various forms of glomerulonephritis (GN), including crescentic GN, is increasingly recognized. Several studies have demonstrated involvement of T helper cells and myeloid cells in GN, but the contribution of cytotoxic CD8⁺ T cells is unclear. Previous work by Heymann and colleagues demonstrated *in vitro* killing of podocytes by podocyte-specific antigen-directed CD8⁺ T cells but could not demonstrate direct interaction of these T cells with podocytes *in vivo*. The development of new tools has now enabled researchers to show that cytotoxic CD8⁺ T cells can attack podocytes *in vivo*, but only under circumstances where breaches in the Bowman's capsule enable T cells to access the glomerulus. "Our major finding is that podocytes are not normally accessible to cytotoxic CD8⁺ T cells, but after induction of nephrotoxic serum nephritis, breaches in the Bowman's capsule allow podocyte-targeted T cells to directly attack and destroy podocytes, resulting in rapidly progressive and destructive GN," explains Detlef Schlondorff.

To assess whether CD8⁺ T cells were able to access podocytes, Schlondorff and colleagues took advantage of two genetic mouse models. In one of these models, CD8⁺ T cells had been engineered to express a T cell receptor that recognizes enhanced green fluorescent protein (EGFP). The researchers injected T cells from these mice — termed just EGFP death inducing (Jedi) mice — or from control mice into transgenic mice that specifically expressed EGFP in podocytes (pod-EGFP mice). "Combining the Jedi CD8⁺ T cells with transgenic pod-EGFP mice allowed us to examine the interaction of Jedi T cells with EGFP-expressing podocytes under control conditions and under conditions of experimental nephrotoxic serum nephritis," says Schlondorff.

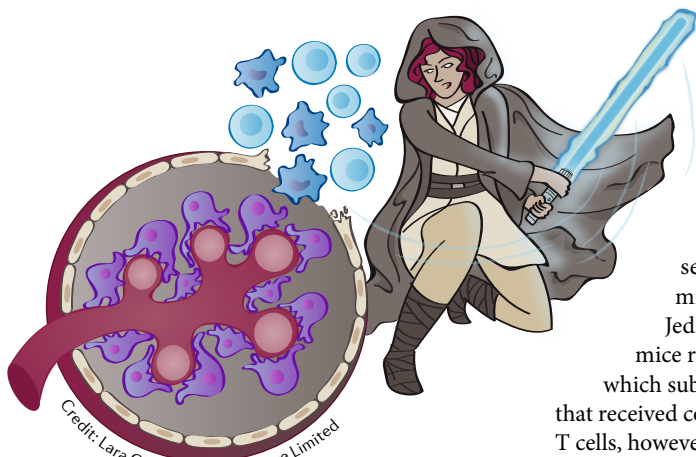
Injection of control CD8⁺ T cells or Jedi CD8⁺ T cells into pod-EGFP mice did not induce kidney damage or proteinuria. Co-injection of EGFP-expressing recombinant lentivirus resulted in the transduction of some splenocytes with EGFP, which were subsequently eliminated by Jedi CD8⁺ T cells, demonstrating that the Jedi T cells were activated and suggesting that the

inability of Jedi CD8⁺ T cells to eliminate EGFP-expressing podocytes might be due to the presence of a protective niche. To test this hypothesis, the researchers induced a mild form of nephrotoxic serum nephritis in pod-EGFP mice before the injection of Jedi or control T cells. These mice rapidly developed proteinuria, which subsequently declined in mice that received control T cells. Injection of Jedi T cells, however, exacerbated glomerular dysfunction. Histological analysis showed that kidneys of pod-EGFP mice injected with either nephrotoxic serum only or with nephrotoxic serum plus control T cells had mild to moderate crescentic GN; by contrast, kidneys of mice injected with nephrotoxic serum plus Jedi T cells had severe lesions with more crescents, defects in the Bowman's capsule, podocyte apoptosis, as well as periglomerular and interstitial infiltrates. Glomeruli with crescents — particularly those with ruptures or loss of the Bowman's capsule — exhibited the greatest loss of podocytes, with direct interactions between Jedi T cells and EGFP⁺ podocytes evidenced by 3D fluorescent deconvolution microscopy. Of note, infiltration of Jedi CD8⁺ T cells was only observed in glomeruli with crescents and breaches in the Bowman's capsule; in glomeruli with an intact Bowman's capsule, Jedi CD8⁺ T cells accumulated externally and did not interact with podocytes. "We demonstrated similar findings in biopsy samples from patients with rapidly progressive GN, where glomerular CD8⁺ T cell infiltration also correlated with breaches in Bowman's capsule," comments Schlondorff.

The researchers say their work strengthens the role of CD8⁺ T cells in the progression of rapidly progressive GN and supports the use of therapeutic interventions against CD8⁺ T cells in crescentic GN. "Our demonstration of a novel role for the Bowman's capsule in providing a barrier against CD8⁺ T cell infiltration should direct future research towards identifying the mechanisms involved in the destruction of the Bowman's capsule in crescentic GN," Schlondorff adds.

Susan J. Allison

ORIGINAL ARTICLE Chen, A. et al. Bowman's capsule provides a protective niche for podocytes from cytotoxic CD8⁺ T cells. *J. Clin. Invest.* <https://doi.org/10.1172/JCI97879> (2018)



Credit: Lara Crow/Springer Nature Limited

inability of Jedi CD8⁺ T cells to eliminate EGFP-expressing podocytes might be due to the presence of a protective niche. To test this hypothesis, the researchers induced a mild form of nephrotoxic serum nephritis in pod-EGFP mice before the injection of Jedi or control T cells. These mice rapidly developed proteinuria, which subsequently declined in mice that received control T cells. Injection of Jedi T cells, however, exacerbated glomerular dysfunction. Histological analysis showed