Mast Cells: Subordinates or Masterminds in Autoimmunity?

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Mast cells have long been known as effector cells in allergic disorders. By binding IgE, they rapidly release a plethora of preformed cytokines, chemokines, Bradykinins, and other highly active substances that mediate bronchospasm and urticaria. Over recent years, it has become clear that mast cells also regulate other immune cells such as dendritic cells, B cells, and T cell populations. Intriguingly, they appear to exert either pro- or anti-inflammatory effects depending on the surrounding milieu.

In this issue of JASN, Gan and coworkers describe a pivotal role of mast cells in the regulation of autoimmunity in a murine model of ANCA vasculitis with necrotizing GN. Their findings support increasing evidence for an immunoregulatory, rather than an effector role of mast cells in inflammatory kidney diseases. Thus far, it has been described in experimental nephrotoxic serum nephritis that mast cells have protective functions. It was previously unclear, however, how these effects were mediated. Gan et al. now provide compelling evidence that IL-10 production by mast cells is essential for their immunosuppressive effects in a model of experimental ANCA vasculitis. By secreting IL-10, mast cells increased the number of regulatory T cells (Tregs) in the draining renal lymph nodes. Tregs are potent anti-inflammatory cells that have been shown to counteract the proinflammatory T cell populations such as TH1 and TH17 cells. A disrupted balance between the pro- and anti-inflammatory cell populations is regarded as a trigger for the development of autoimmune diseases such as inflammatory bowel disease, lupus erythematosus, and others, as well as inflammatory kidney diseases such as Goodpasture’s disease. Importantly, Gan et al. note that the increase in absolute numbers of mast cells and Tregs limits the TH17 response in vivo within the draining lymph nodes.

In inflammatory kidney disease, immunoregulation is orchestrated within the lymph node. Here, mast cells, as well as Tregs, provide a zone of immunosuppression. After induction of ANCA vasculitis, Gan et al. found elevated numbers of both cell populations in the lymph node, in close proximity to each other. However, it is unclear whether mast cells and Tregs migrate, or rather proliferate, in the in vivo situation. The investigators hypothesize that mast cells migrate from the immunization site to the lymph nodes, but provided no direct experimental evidence to support this assumption. Alternatively, mast cells might change the phenotype of Tregs to inducible IL-10–expressing Tregs. In addition, mast cell-derived IL-10 decreases infiltration and expression of costimulatory molecules of dendritic cells, thereby limiting the activation and proliferation of effector T cells such as TH1 and TH17 cells. Thus, it cannot be completely ruled out that the described immunoregulatory effect of mast cells in the experimental model of ANCA vasculitis is attributable to dendritic cells.

In addition, IL-10 has also been shown to inhibit innate immune cells such as neutrophilic granulocytes and macrophages in a model of chronic low-dose ultraviolet B irradiation. Both cell populations are known to play key roles in ANCA vasculitis. However, in a model of nephrotoxic serum
of nephrotoxic serum nephritis, with one research group reporting proinflammatory effects of mast cells in nephrotoxic serum nephritis and immunoregulatory effects of mast cells in ANCA vasculitis. One critical determinant of outcome might be the localization of mast cells. In the healthy kidney, mast cells are scarce and located only in the capsule. Their numbers do not increase within the renal tissue in acute models such as nephrotoxic serum nephritis or ANCA vasculitis. In this model of inflammatory kidney disease, mast cells were found to limit disease activity. However, in chronic disease models they infiltrate the target organ such as the kidney or joints and may prolong inflammation and trigger the development of fibrosis. More information regarding these different facets of mast cell biology will be crucial for the development of therapeutic strategies to influence the function of mast cells and their interaction with Tregs in inflammatory kidney diseases such as ANCA vasculitis and Goodpasture’s disease.

Further studies also need to be conducted to gain a more detailed understanding of mast cell biology in autoimmunity. First, it will be crucial to evaluate whether other mast cell components such as histamine and TGF-β might play a role in their immunosuppressive function. Second, the interaction of mast cells with dendritic cells in kidney and autoimmune diseases needs to be further evaluated. Third, the scarce data on the role of mast cells in the chronic phase of autoimmunity need to be supplemented. Fourth, the next steps toward developing therapeutic options that target mast cells need to be taken. The use of mast cell-stabilizing agents would offer one possibility and is yet to be tested in murine kidney and autoimmune disease models. Nevertheless, it needs to be decided whether mast cells are really the best target, because of their opposing roles as effector and immunoregulatory cells. Regulatory T cells, which have only immunosuppressive actions, might provide a better target in autoimmune and kidney diseases and therapeutic strategies that influence these cells are closer to being ready for clinical practice.

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DISCLOSURES

None.

REFERENCES
