Correspondence and offprint requests to: Stefan P. Berger; E-mail: s.p.berger@lumc.nl

Stefan P. Berger1,2 and Mohamed R. Daha1

1Department of Nephrology, Leiden University Medical Center, PO Box 9600, 2300 RC, Leiden, the Netherlands and 2 Department of Internal Medicine, Haga Teaching Hospital, PO Box 40551, 2504 LN, the Hague, the Netherlands

Abstract

Chavele et al. studied the role of the mannose receptor (MR) in crescentic nephritis [1]. The accelerated nephrotic model of glomerulonephritis was induced on both wild-type (WT) and MR-deficient mice. The mice lacking the MR showed a markedly altered phenotype. They were largely protected against the development of glomerulonephritis with less affected glomeruli, less proteinuria and much better renal function when compared to the WT mice. Whilst more infiltrating macrophages were present in the WT animals, there was no difference in the deposition of sheep and mouse immunoglobulins. To elucidate the mechanism of MR-mediated damage, the authors additionally performed a series of in vitro experiments. They show that the Fab portion of sheep immunoglobulins binds to MR binding domains. Interestingly, the MR seems to interact with FcR-mediated cellular reactions. When MR-deficient macrophages and mesangial cells were treated with immune complexes, the macrophages showed a significantly poorer oxygen burst when compared with WT cells. In line with this possible interaction between Fc receptors and MR, co-localization of Fcα-receptors and MR was demonstrated on macrophages. Additionally, the authors observed that MR-deficient mesangial cells in culture proliferated more abundantly and showed a markedly increased rate of spontaneous apoptosis compared with WT cells. These findings led the authors to test whether this increased apoptosis could play a role in the suppression of glomerular inflammation. Indeed, TNF-α production by LPS-stimulated macrophages was markedly reduced in the presence or apoptotic cells. The anti-inflammatory effect of apoptotic mesangial cells was increased when MR-deficient macrophages were used instead of WT cells (Figure 1).

Short review of the field

Recently, there has been increasing attention for the role of danger signalling in inflammatory renal disease [2]. This line of research has particularly focused on the role of Toll-like receptors (TLR) and their interaction with the so-called danger-associated molecular patterns (DAMP). These endogenous molecules are released during tissue damage and bound to pattern recognition molecules including the TLRs. Examples of processes associated with the release of danger molecules are apoptosis, necrosis, ischaemia or inflammatory tissue injury. Examples of molecules proposed to function as DAMPs are biglycan, HMGB-1, ds-DNA and heat shock proteins. Once released, e.g. in the setting of viral infections, DAMPs may promote the inflammatory response and could contribute to the perpetuation of tissue damage and the emergence of autoimmunity.

However, not all pattern recognition molecules are necessarily associated with activation of the immune system. The mannose receptor (MR) is a pattern recognition molecule belonging to the C-type lectin family [3]. It binds mannose, fucose and N-acetylglucosamine residues in a calcium-dependent fashion and is expressed by macrophages and certain dendritic and endothelial cell subsets, but has also been found on murine mesangial cells [4]. Various pathogens including bacteria, fungi and parasites bind to MR. This is followed by endocytosis and delivery of antigen to the MHCII compartment. Unexpectedly, MR-deficient mice do not show increased susceptibility to infections with *Candida albicans* [5] or *Pneumocystis jiroveci* [6].

Next to the interaction with pathogens, MR also plays a role in clearing endogenous ligands released in the inflammatory response including lysosomal hydrolases [7], tissue plasminogen activator and myeloperoxidase [8]. By contributing to the clearance of these potentially harmful molecules, the MR is thought to play a role in tissue protection during inflammation. The MR is typically expressed on alternatively activated macrophages. These IL-4- and IL-13-induced macrophages have been associated with an anti-inflammatory profile with a role in silent clearance of apoptotic cells, immune regulation and induction of tolerance [9].
Although the MR lacks an intracellular signalling domain, its ligation leads to an intracellular signalling response with resulting gene expression [10,11]. In order to trigger intracellular signalling, the MR depends on the interaction with other receptors. In line with this concept, the presence of Toll-like receptor 2 (TLR2) is essential for MR-mediated IL-8 secretion [12]. Next to the induction of IL-8 in response to P. jiroveci, MR-mediated signalling may also induce regulatory responses. When dendritic cells were treated with a specific antibody against the MR, their chemokine profile changed from a Th-1- to a Th-2-recruiting profile [11]. Interestingly, the chemokine response to MR ligation differed according to the ligands used in these experiments. This may be explained by differential interaction of the ligands with additional receptors necessary for MR-mediated intracellular signalling.

**What does this mean for the practising nephrologist?**

For the time being, these findings will not affect clinical practice. In view of the general notion that the MR has an immune regulatory function and participates in the non-inflammatory clearance of apoptotic cells and harmful molecules, the finding that the lack of the MR results in marked amelioration of the inflammation in this model is quite surprising. Though the authors do not clearly state their original hypothesis, they may very well have expected worsening of the disease in the MR-deficient mice. The discrepancy with the earlier concept may be explained by the function of additional receptors in MR-mediated intracellular signalling, as alluded to above. Possibly the relation with Fc receptor-mediated signalling is pivotal in the pro-inflammatory effect of the MR in this specific model of glomerulonephritis which has been shown to depend on Fc receptor-mediated damage [13]. The observed additional anti-inflammatory effect of the absence of the MR in the interaction between macrophages with apoptotic mesangial cells remains somewhat puzzling.

However, this work does point to some interesting potential directions. The finding that apoptotic mesangial cells have an immune regulatory effect on macrophages highlights the role of the kidney in protection against inflammatory insults. From a therapeutic perspective, intervention into these protective mechanisms may result in highly specific treatment of inflammatory renal diseases. Understanding that the kidney is not merely a helpless vic-

---

**Fig. 1. Proposed role for mannose receptor in crescentic glomerulonephritis.** (A) IgG may bind to the Fc receptor with the Fc domain and to the mannose receptor with the Fab portion leading to an increased oxygen burst (left). If the mannose receptor is absent, the oxygen burst is decreased (right). (B) Absence of the mannose receptor leads to an increased proliferation and apoptosis of mesangial cells. These apoptotic cells induce a non-inflammatory macrophage phenotype with IL-10 and TGF-β production (right). If the mannose receptor is present, mesangial cells proliferate less and are less apoptotic, and a pro-inflammatory macrophage phenotype with TNF-α production prevails.
tim in glomerulonephritis may offer interesting therapeutic alternatives to unspecific immunosuppression if we find methods to support the kidney in its self-defence.

**Take-home message**

Understanding the role of pattern recognition in renal damage and the associated renal response may in the long term lead to interesting approaches in the treatment of inflammatory renal disease.

**Conflict of interest statement.** None declared.

**References**


Received for publication: 2.7.10; Accepted in revised form: 2.7.10