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Macrophages—Stealth Cells Below the Radar

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Macrophages are innate immune cells with roles in tissue homeostasis, injury, repair, and scarring. Recent findings have described macrophage biology in much more detail than previously known and have established a high degree of heterogeneity and plasticity of these cells.

Macrophages in the kidneys originate from 2 sources. In the normal steady state, prenatally seeded, yolk sac-derived, and self-maintained tissue-resident macrophages make up the majority. On tissue injury, bone marrow-derived monocytes from the blood are rapidly attracted to the kidneys, differentiate into macrophages, and make up a large proportion of the effector cells at the site of injury.[1,2]

Cellular plasticity, the ability of cells to change their phenotype and cellular functions in response to environmental clues, is a key feature of monocytes and macrophages. The concept of macrophage polarization (Figure 1a) emerged in the 1990s and initially defined 2 subsets. Proinflammatory macrophages, also called classically activated macrophages and labeled M1, are part of the initial defense and promote a Th1-like adaptive response. In contrast, regulatory macrophages, also referred to as alternatively activated macrophages and labeled M2, downregulate the proinflammatory immune response, promote a Th2-like adaptive immune response, and promote tissue remodeling, repair, and wound healing. It was soon realized that a scenario relying on an M1/M2 balance was too simplistic. Instead, a spectrum of macrophage polarization between the extremes of M1 and M2, which changes over time, would better explain the diverse macrophages functions observed *in vivo*.[3] Recently, the introduction of single-cell transcriptomics has added a new layer of complexity.[4] Results from single-cell RNA sequencing suggest that several clusters of macrophages with diverse functional phenotypes exist at the same time and that the composition of the populations changes dynamically over time.[5] In the kidneys, the spatial composition of these clusters is currently unknown, and it is not clear if and how macrophages belonging to a certain cluster at a given time point change their gene expression profiles and cluster affiliations over time.

Many diseases, including infections, autoimmunity, metabolic diseases, and circulatory disturbances can initiate tissue injury in one or more compartments of the kidneys. Although in some diseases (e.g., bacterial haemolytic uremic syndrome, anti-GBM-antibody glomerulonephritis) injury usually happens as a one-time hit, most kidney diseases have either a continuous (e.g., IgA nephropathy, hypertensive nephropathy) or a relapsing course (e.g., antineutrophil cytoplasmic antibody-associated glomerulonephritis, lupus nephritis). This is important because the kidney microenvironment will change accordingly. Regardless of the insult, tissue injury will initially trigger active inflammation and the ensuing repair will result in resolution and/or scarring (Figure 1b). Macrophages play important roles both in the active phase, when they participate in the removal of proinflammatory stimuli, and in the resolution phase, when they actively suppress inflammation and support tissue remodeling and restoration of the normal tissue architecture.[6] Scarring, characterized by glomerulosclerosis, interstitial fibrosis with tubular atrophy, and arteriosclerosis, is a frequent and deleterious consequence regardless of the etiology of the initial insult. Obviously, macrophages are involved, not only by contributing anti-inflammatory and profibrotic cytokines; however, there is good evidence that some of them change their phenotypes to become myofibroblasts and directly contribute to extracellular matrix deposition, a process termed macrophage-to-myofibroblast transition.[2]

Given their central role in the orchestration of tissue repair and remodeling, macrophages are an attractive target for therapeutic interventions.[2,7,8] The difficult question is: which macrophage

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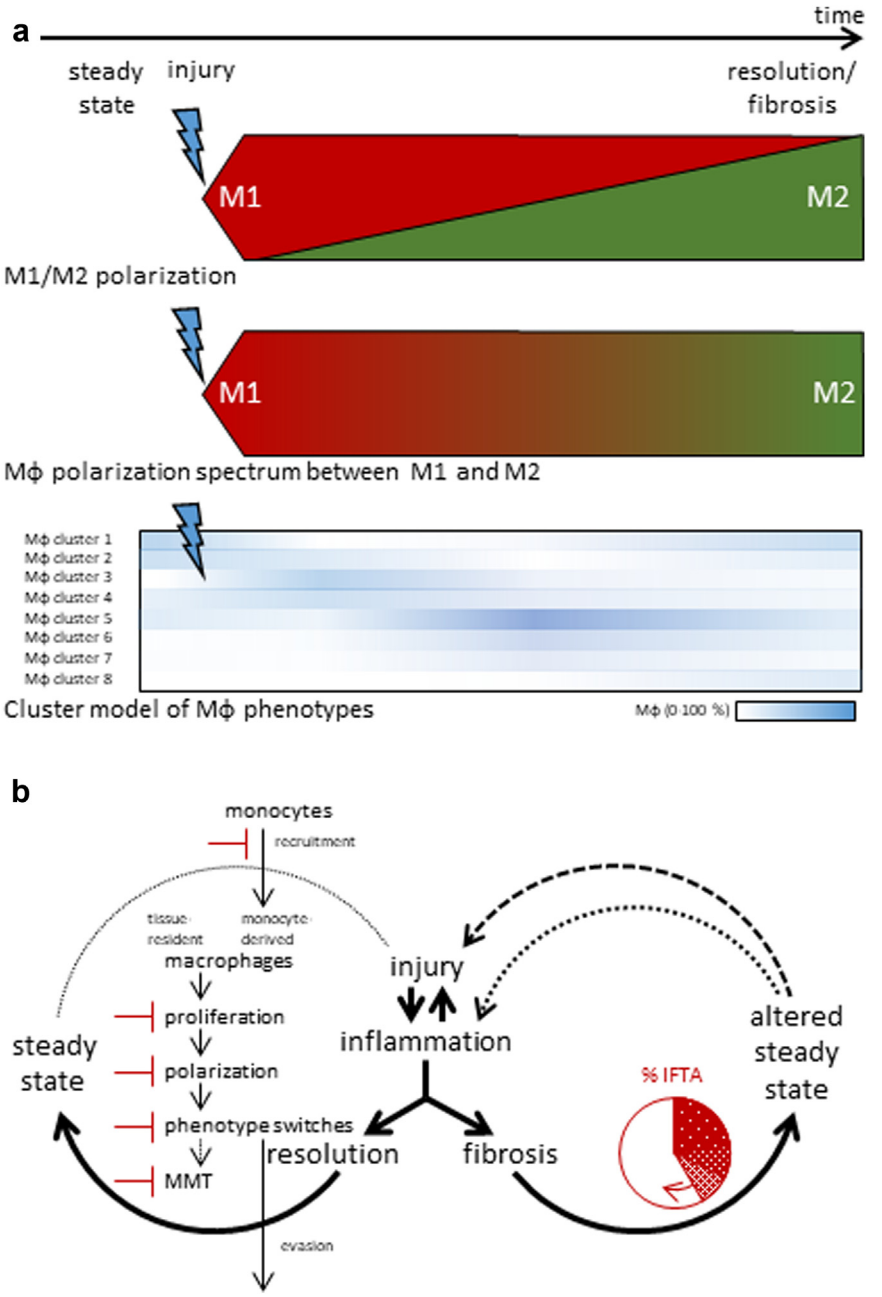

Figure 1. (a) Concepts of macrophage polarization. (b) Concept of tissue injury, inflammation, and repair in the kidneys and the role of macrophages. Red lines indicate potential therapeutic targets. IFTA, interstitial fibrosis with tubular atrophy; MMT, macrophage-to-myofibroblast transition.

clusters should be treated at a given time in the disease course?

Kidney biopsies provide a static snapshot of the processes described above with the purpose of giving an accurate diagnosis to help with the choice of treatment and provide some prognostic information. In contrast to granulocytes, lymphocytes, and plasma cells, even expert pathologists cannot reliably detect and quantify macrophages in routine stains. Immunohistochemistry of formalin-fixed and paraffin-embedded tissue is a robust and reliable technology used in pathology laboratories on a daily basis and is helpful to detect macrophages. However, compared with the extensive armamentarium at hand to phenotypically characterize B cell neoplasms, for example, the tools to label macrophages are limited to few antibodies and these antibodies likely do not reflect the functional plasticity of these cells.

In this issue of *Kidney International Reports*, Pfenning and Schmitz *et al.*[9] show that a sophisticated phenotypical analysis of macrophage is currently not necessary to gain biopsy-derived prognostic information across a large variety of kidney diseases. They use pixel-based quantification of biopsies stained with CD68 (a well-established pan-macrophage marker) and CD163 (a marker found in the context of M2 polarization). Macrophage density correlates with the estimated glomerular filtration rate at the time of biopsy, and more importantly, high macrophage densities associate with a poor prognosis at follow-up. In their analysis, macrophage density, although significantly correlated, performed much better than the amount of interstitial fibrosis with tubular atrophy.

Unfortunately, the actual densities and differences are so small that a visual scoring without morphometric quantification is impossible. Therefore, a digital pathology set-up will be necessary to implement its measurement in routine practice. If independent and prospective validation studies support the results presented by the authors, this will provide prognostic information independent of the basic renal disease.

It is interesting to note that both CD68 and CD163 provided very similar results. This indicates that the branching toward resolution or fibrosis is central to prognosis. Hopefully, experimental and translational studies will give us more insights soon. A phenotypic marker indicating one or the other

will then probably outperform the macrophage markers investigated.

DISCLOSURE

The author declares no competing interest.

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