Macrophages in Renal Development, Injury, and Repair

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Summary: Macrophages have long been regarded as classic mediators of innate immunity because of their production of proinflammatory cytokines and their ability to induce apoptotic cell death. As a result of such activities and the detrimental long-term effect of kidney inflammation, macrophages principally have been regarded as mediators of glomerular damage, tubular cell death, and the downstream fibrotic events leading to chronic kidney disease. Although this has been the accepted consequence of macrophage infiltration in kidney disease, macrophages also play a critical role in normal organ development, cell turnover, and recovery from injury in many organs, including the kidney. There is also a growing awareness that there is considerable heterogeneity of phenotype and function within the macrophage population and that a greater understanding of these different states of activation may result in the development of therapies specifically designed to capitalize on this variation in phenotype and cellular responses. In this review, we discuss the current understanding of induction and consequences of classic versus alternative macrophage activation and highlight what additional therapeutic options this may provide for the management of both acute and chronic kidney disease as well as renal cancer.

Semin Nephrol 30:255-267

Keywords: *Macrophage, kidney development, innate immunity, classic activation, alternative activation, chemokines, CSF-1*

In all vertebrates, macrophages are the first leukocytes to appear in the embryo. During postnatal and adult life they differentiate from hematopoietic precursor cells, a process that occurs exclusively in the bone marrow.[1] In contrast, during early mammalian development primitive fetal macrophages appear to differentiate from a different cell origin independent of the blood monocyte.[2-4] Macrophages in the embryo serve as specialized phagocytic cells.[5] They are formed in the yolk sac and then migrate through the mesenchyme to invade the tissues of the embryo proper. With formation of the primitive vasculature, fetal macrophages migrate from the yolk sac into the liver. Fetal macrophages also proliferate and differentiate locally within tissues before forming tissue-specific macrophages.[6,7] Macrophages are essential during embryogenesis and play an important role in programmed cell death and tissue remodeling during organogenesis.[5,8] The production of both liver and bone marrow–derived macrophages is controlled by the growth factor colony stimulating factor (CSF)-1, also termed *macrophage colony stimulating factor*. CSF-1 binds to the CSF-1 receptor (CSF-1R) and genetic deletion of either of these genes in mice results in marked depletion of tissue macrophages.[9,10] The CSF-1–deficient *op/op* mouse (CSF-1^{op}/CSF-1^{op}) has revealed the importance of macrophages in the development of many organs, especially the bone, brain, and endocrine systems. In the brain, neuroepithelial cell

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This study was supported by an Australian Stem Cell Centre and Monash University Joint Scholarship Scheme (T.W.); Dr Little is a Principal Research Fellow of the National Health and Medical Research Council; the research of the authors was supported by the Australian Stem Cell Centre.

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0270-9295/ - see front matter

 doi:10.1016/j.semnephrol.2010.03.011

growth requires macrophages.[11] Macrophages also are required for the normal development of the pancreas and mammary gland.[12,13] Indeed, embryonic macrophage populations exist within almost all developing organs and adopt highly specific locations, phenotypes, and functions. In developed organs, the Kupffer cells of the liver, Langerhans cells of the skin, osteoclasts in the bone, and microglia in the brain all represent highly specialized resident macrophage populations.[3]

Once permanent or definitive hematopoiesis is established with increased gestation, the proliferative capacity of the macrophage declines and a distinct set of phagocytes, the monocyte–macrophages, are formed.[4,14,15] In the adult, macrophages are involved in inflammation and immune surveillance. However, the heterogeneity and cellular plasticity of macrophage populations with their ability to change phenotype in response to local stimuli allows these cells to be highly specialized and display a wide and apparently opposing range of functions. Indeed, there is strong evidence that subpopulations of macrophages directly contribute to wound healing and tissue repair, supporting the concept that some macrophage phenotypes can promote organ regeneration after injury. However, this ability to change phenotype and function makes categorizing macrophage populations relatively difficult.

CLASSIC VERSUS ALTERNATIVE ACTIVATION STATES

Evidence supports the notion of two key macrophage polarization states described as M1 "classically activated" proinflammatory macrophages, and M2 "alternatively activated" immune regulatory macrophages[16,17] (Fig. 1). In general, these two phenotypic states are somewhat comparable with the opposing Th1 and Th2 cells. A key factor driving M1 polarization and activation is interferon-γ (IFN-γ), derived from $CD4^+$ Th1 cells, $CD8^+$ cytotoxic T cells, and natural killer cells, either working alone or in conjunction with lipopolysaccharides (LPS), tumor necrosis factor-α (TNF-α), and other microbial products.[18] Culture of human $CD14^+$ monocytes in the presence of granulocyte macrophage CSF also induces M1 polarization. M1 macrophages produce proinflammatory cytokines, in particular interleukin (IL)-12 and IL-23, are phagocytic, present antigen via major histocompatibility complex (MHC) class II molecules,[19] and generate toxic nitrogen and oxygen intermediates.[20] This equips M1 macrophages to eliminate intracellular pathogens and even some tumors effectively.[21,22] The IL-12 produced by M1 macrophages drives further Th1 polarization and stimulates additional IFN-γ production from T cells and natural killer cells, thereby perpetuating the inflammatory response. In kidney disease a predominantly M1 macrophage infiltrate results in tissue damage and cell loss followed by the accumulation of extracellular matrix (ECM) proteins. The downstream effect of the proinflammatory cascade is the development of renal interstitial fibrosis and impaired organ function. Thus, macrophage phenotype and the corresponding polarization state ultimately determines the outcome of acute inflammation and the progression to irreversible chronic scarring.[23]

Given a favorable microenvironment, M2 macrophages counteract progressive damaging inflammation and contribute to ECM remodeling and tissue repair. However, the exact definition of M2 alternatively activated macrophages is still under debate. Martinez et al[24] have classified M2 macrophages into three subsets, namely M2a, M2b, and M2c macrophages, which differ in their mode of activation, cytokine profile, and function.

M2a macrophage polarization after exposure to IL-4 and IL-13 or glucocorticoids results in increased expression of pattern recognition receptors including the mannose receptor (CD206) and scavenger receptor (CD163) together with up-regulation of MHC class II molecules and production of the chemokines CCL17, CCL22, and CCL24.[16,25] M2a macrophages show an enhanced capability for endocytosis, pinocytosis, and antigen presentation. There is also increased production of the prototype ECM protein fibronectin, transforming growth factor (TGF)-β–induced matrix associated protein MP78/70 (βig-H3),[26,27] and insulin-like growth factor, which has been shown to stimulate re-epithelialization in dermal wound healing.[28,29]