

Are Cyst-Associated Macrophages in Polycystic Kidney Disease the Equivalent to TAMs in Cancer?

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Kidney injury leads to rapid infiltration of immune cells, presumably as a preemptive measure to protect the organism from the danger of invading microbes that may exploit the compromised epithelial barrier of injured tubules. Prominent among these infiltrating immune cells are the macrophages that arrive early on the scene after injury. Previous studies have shown that infiltrating macrophages are initially of the proinflammatory, classically activated M1-like type that can exacerbate tubular injury due to their release of reactive oxygen and nitrogen intermediates.¹ The likely purpose of this initial response is to recruit as many aggressive macrophages as quickly as possible—with guns blazing—to have a head start in the anticipated battle with hostile microbes. Evolution probably weighed the collateral damage caused by these macrophages as preferable over the almost certain death of the organism that would result from an out-of-control bacterial infection of an injured kidney. After the kidney is “convinced” that there is no acute danger of infection, the M1-like macrophages are converted to alternatively activated M2-like macrophages, which then play a very different role.¹ M2 macrophages are profibrotic and stimulate the proliferation of tubule cells for the apparent purpose of facilitating the repair of the sustained injury. The profibrotic response makes sense, because additional extracellular matrix and thickened basement membranes should further restrict access for pathogens and facilitate the re-epithelialization of tubules. After repair is completed, macrophages are no longer needed, and everything returns back to normal.

This scenario—certainly oversimplified in its description here—is what is supposed to occur in response to renal injury.

What might happen if something goes wrong and if macrophages are called to the kidney without injury, turn into M2-like macrophages, and never leave? This should lead to out-of-control fibrosis, vast deposition of extracellular matrix, thickened basement membranes, and relentless proliferation of tubule cells. With nowhere else to go, their proliferation would lead to dilated tubules and eventually, cysts that would keep on growing ever larger over time. Of course, this scenario sounds familiar, because it describes the hallmark features of polycystic kidney disease (PKD), which has been described as an aberrant state of futile kidney repair.²

A paper by Cassini *et al.*³ in this issue of the *Journal of the American Society of Nephrology* leads to a better understanding of how macrophages contribute to the pathogenesis of PKD. It was already known that M2-like macrophages are prevalent in PKD kidneys in patients and rodent models, where they are frequently located near cysts.^{4–7} Ablation of macrophages in PKD mice by treatment with liposomal clodronate led to inhibition of cystic progression,^{4,6} suggesting that macrophages seem to be at least a partial driver of renal cyst growth. However, it had remained poorly understood how and when macrophages are called to the kidneys in PKD and whether they play roles in inflammation and/or fibrosis as a consequence of the pathology or rather, as a driver or perhaps even initiator of pathology.

To delineate the order of events, Cassini *et al.*³ now used a genetic mouse approach, in which the timing of gene knockout can be controlled. Knockout of the *Pkd1* gene, the orthologous gene to the one affected in most patients with autosomal dominant PKD, led to relatively rapid upregulation of monocyte chemoattractant protein-1 (MCP1). MCP1, also known as CCL2, was already implicated in the recruitment of macrophages to kidneys in PKD.⁵ Cassini *et al.*³ found that MCP1 upregulation was quickly followed by renal infiltration of monocytes that differentiated into M1-like macrophages accumulating around nascent cysts, leading to cell flattening and injury, including oxidative DNA damage, but relatively little induction of proliferation. However, just a few weeks later, most macrophages were transformed into the M2-like phenotype and promoted fibrosis and tubule cell proliferation, leading to massive renal and cyst enlargement. Next, the authors investigated double-knockout mice, in which both the *Pkd1* and MCP1 genes were deleted simultaneously in the same tubule cells. Strikingly, those double-knockout mice showed very little macrophage infiltration and had strongly reduced cyst growth, preserved renal function, and extended lifespan.

There are four major lessons learned from this work. First, simply the loss of the *Pkd1* gene product polycystin-1 (PC1) leads to secretion of MCP1 by the affected tubule cells, apparently without any need for renal injury. Second, secretion of MCP1 by tubule cells seems to be necessary and sufficient to

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recruit circulating monocytes to the kidney and lead to their M1-like differentiation. Third, these infiltrating macrophages are not merely patrolling the area but are actively injuring tubule cells, presumably by secreting reactive oxygen and nitrogen intermediates. Fourth, M1-like macrophages do not seem to induce proliferation and cyst growth. Instead, the later M2-like macrophages are the drivers of fibrosis and cyst growth, and apparently, they persist forever.

These results raise a number of questions. The finding that Pkd1-KO in mature kidneys alone is already sufficient to induce cystogenesis in a short period of time is surprising, because previous work using inducible Pkd1-KO mice revealed that there was no cyst growth for many months after Pkd1 gene deletion. However, subsequent induction of kidney injury caused rapid cyst growth in these Pkd1-KO mice, which led to the concept of a “third hit” (injury) as a requirement for cystogenesis.⁸ Apparently, there are significant differences in the doxycycline-inducible Pkd1-KO mice used by Cassini *et al.*³ compared with the tamoxifen-inducible model used previously.

What is the mechanistic connection between the loss of PC1 and the induction of MCP1 secretion? This may be an indirect effect, perhaps involving some phenotypic change in the affected tubule cells that causes them to secrete MCP1 to signal the immune system that they are somehow injured. Macrophage migration inhibitory factor is a likely upstream regulator of MCP1 secretion in PKD.⁷

How are the kidneys able to change the M1-like macrophages into M2-like macrophages? Previous work has suggested that tubule/cyst cells emit unidentified soluble factors that lead to this transformation.⁶ The classic cytokines that lead to M2 polarization of macrophages are IL-4 and IL-13. We previously showed that PC1 regulates STAT6, which is activated in PKD cysts, leading to secretion of high levels of IL-13 and other factors implicated in cyst growth.⁹ These factors may be involved in the induction of the M2 phenotype, and they may perhaps play a role in keeping these M2-like macrophages attracted to cysts forever.

It seems likely that there is a signaling interplay creating a positive feedback loop between cyst-lining epithelial cells and macrophages, in which both cell types maintain each other in a perpetual state of activation and proliferation, respectively. This scenario seems very similar to the role of tumor-associated macrophages (TAMs) that are coaxed by tumor cells to adopt trophic tissue repair features. These TAMs are thought to facilitate fibrosis, angiogenesis, tumor growth, and eventually, metastatic spread (for example, in breast cancer).¹⁰

If cyst-associated macrophages are indeed the equivalent to TAMs in cancer, then PKD research may benefit from that knowledge in the cancer field, because TAMs are actively pursued as pharmacologic targets in cancer. Cassini *et al.*³ already took advantage of the availability of an antagonist to

CCR2, the receptor for MCP1 on monocytes, and showed that this drug ameliorates renal cyst growth. Other than drugs aimed at disruption of macrophage recruitment to tumors, other therapeutic approaches are the depletion of TAMs and their progenitors and the reprogramming of macrophages toward tumoricidal function.¹⁰ It may be worth testing some of these therapeutic strategies in PKD models.

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See related article, “Mcp1 Promotes Macrophage-Dependent Cyst Expansion in Autosomal Dominant Polycystic Kidney Disease,” on pages 2471–2481.