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M2 macrophages eliminate renal crystals by phagocytosis

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Objective: We recently reported the evidence that Mψs might eliminate crystals in hyperoxaluric mice. Mψs have 2 phenotypes: inflammatory (M1) and anti-inflammatory (M2). Because M2Mψs are involved in tissue repair, we focused on their potential suppression of renal crystal formation. Hence, we investigated the role of M2Mψs in renal crystal formation in colony-stimulating factor-1 (CSF-1)-deficient mice, which lack M2Mψs, and the ability of M2Mψs to phagocytize crystals ex vivo.

Materials-Methods: We divided 8-week-old male wild type and heterozygous (M2+ ) and homozygous (M2− ) CSF-1-deficient mice into untreated and M2Mψ-transfused groups (4 groups total). Glyoxylate (80 mg·kg−1) was administered daily by intra-abdominal injection, and renal crystal formation was examined on days 0 and 6. We performed immunohistochemistry and flow cytometry to detect expression of M1-related and M2-related genes. Expression of crystal-binding genes was examined by immunohistochemistry and polymerase chain reaction, respectively. Additionally, M2Mψs were cultured ex vivo by CSF-1 stimulation of bone marrow cells. Mature M2Mψs were incubated with fluorescently labeled calcium oxalate monohydrate (COM) crystals. We further characterized renal Mψs isolated from M2+ and M2− mice by gene expression profiles using DNA microarrays.

Results: The amount of renal COM crystal deposition was significantly greater in M2− than in M2+ mice. M2Mψs transfusion increased expression of M2-related genes and markedly decreased the number of renal crystals in both M2− and M2+ mice. Additionally, crystal phagocytosis assay demonstrated that the capacity for phagocytosis of COM crystals was higher in M2− than in M1-polarized bone marrow-derived Mψs or renal tubular cells. M2Mψs expressed higher levels of crystal-binding proteins than the other cell types. Neutralization of CD44 reduced the capacity of M2Mψs to phagocytize COM. Finally, microarray analysis demonstrated that Mψs in M2− mice exhibited lower expression levels of stone-related genes than those in M2+ mice.

Conclusion: M2Mψs eliminate renal crystals by phagocytosis.