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M2 macrophages eliminate renal crystals by phagocytosis

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Objective: We recently reported the evidence that Mφs might eliminate crystals in hyperoxaluric mice. Mφs have 2 phenotypes: inflammatory (M1) and anti-inflammatory (M2). Because M2Mφs are involved in tissue repair, we focused on their potential suppression of renal crystal formation. Hence, we investigated the role of M2Mφs in renal crystal formation in colony-stimulating factor-1 (CSF-1)-deficient mice, which lack M2Mφs, and the ability of M2Mφs 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 M2Mφ-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, M2Mφs were cultured ex vivo by CSF-1 stimulation of bone marrow cells. Mature M2Mφs were incubated with fluorescently labeled calcium oxalate monohydrate (COM) crystals. We further characterized renal Mφs 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. M2Mφs 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 Mφs or renal tubular cells. M2Mφs expressed higher levels of crystal-binding proteins than the other cell types. Neutralization of CD44 reduced the capacity of M2Mφs to phagocytize COM. Finally, microarray analysis demonstrated that Mφs in $M2^-$ mice exhibited lower expression levels of stone-related genes than those in $M2^+$ mice.
Conclusion: M2Mφs eliminate renal crystals by phagocytosis.