Macrophage-Colony Stimulating Factor (M-CSF) Is a Novel Preventive Agent Against Renal Stone Disease by Inducing Anti-Inflammatory Macrophages

Introduction and Objective: Macrophages are related to metabolic syndrome, and considered as promotional factor. There are some reports macrophages play not only an inflammatory role but also anti-inflammatory role. We have reported that macrophages were related to stone formation in a microarray study and an interesting phenomenon involving the spontaneous elimination of renal crystals. We speculated there was some correlation between this phenomenon and macrophages. We investigated renal macrophage functions in order to clarify their anti-inflammatory effect for stone formation using macrophage-colony stimulating factor (M-CSF)-deficient mice.
Materials and Methods: We divided eight-week-old male M-CSF-deficient mice into 3 groups: wild type (+/+), homozygous (op/op), and homozygous injected with M-CSF (op+CSF). They were administered 80mg/kg glyoxylate by daily intra-abdominal injection, and the kidneys were extracted to examine crystal formation, at days3, 6, 9, 12, 15. We performed CD68 and CD163 staining to evaluate the expression of renal macrophages. CD68 was used for detection of inflammatory macrophages whereas CD163 for anti-inflammatory ones. Both crystal and macrophage formations were evaluated with scanning electron microscopy (SEM) and transmitted electron microscopy (TEM). Expression of inflammation-related genes was examined by immunohistochemistry (IHC) and quantitative reverse transcriptase polymerase chain reaction (qPCR).
Results: The number of renal crystals in op/op was markedly higher composed to +/+. Crystal formations were detected in the cortical-medulla region in +/+ whereas crystals were detected in the papilla in op/op. SEM showed crystals were rough and larger size in op/op than +/+. IHC and qPCR showed high expression of osteopontin and CD44 but low expression of CD163 in op/op. After injection of M-CSF, the amount of stones in op+CSF was markedly decreased than op/op and it depended on the M-CSF concentration. Each gene expression in op+CSF returned to same level as in +/+. Furthermore, TEM revealed crystals were phagocytosed by anti-inflammatory macrophages in the cortical-medulla region, except for op/op.
Conclusions: Our study suggests that anti-inflammatory macrophages play a major role in defense against crystal formation by elimination in the renal interstitial space. We indicate that M-CSF could become a novel medicine for prevention of stone disease by inducing anti-inflammatory macrophages.