Objective: Patients who undergo peritoneal dialysis (PD) often develop peritoneal fibrosis. Bone marrow-derived macrophage-myofibroblast transition (MMT) may be a novel source of myofibroblasts during peritoneal fibrosis. Smad3 is required for MMT process.

Methods: Parietal peritoneal biopsy samples were collected from long-term PD patients (n = 10) and MMT cells were identified by CD68α-SMA+ cells using two-color immunohistochemistry. LysM-Cre/Rosa26tdTomato mice were constructed for macrophage fate mapping study in experimental PD model induced by hyperglycemic dialysis solutions. Mechanisms of MMT were studied in vivo using Smad3 wildtype (WT) and knockout (KO) mice.

Results: Immunohistochemical study showed that a minor population of α-SMA+ cells coexpressed CD68 in peritoneal biopsy tissues (5.08%). Immunofluorescence and flow cytometry results demonstrated that > 90% CD68+ macrophages in peritoneal tissues were labeled with the tdTomato fate marker in both control and model group. In addition, almost all tdTomato+ cells (> 99%) expressed CD45 in model group, indicating that these cells were recruited from bone marrow rather than resident macrophages. Three-color confocal imaging showed that CD68+tdTomatoα-SMA+ cells amounted to 9.39% of α-SMA+ myofibroblasts in model group and these cells also expressed Collagen I. Compared to Smad3 WT littermates, the percentage of CD68+α-SMA+ cells was markedly reduced in Smad3 KO model group (p < 0.001).

Conclusion: Bone marrow-derived macrophages may constitute a novel source of myofibroblasts during peritoneal fibrosis. Smad3 is required for the MMT process.