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Alterations in Cell Cycle and MAP-kinase Pathway Contribute to the Transition from SMFs-associated Acute Renal Tubular Injury to Fibrosis: Field Direction Matters

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Objectives : Various mechanisms, including inflammation, oxidative stress, DNA damage, senescence, and apoptosis, are involved in the transition from acute kidney injury to chronic kidney disease (CKD). We previously showed the aggravation of acute renal tubular injury under static magnetic fields (SMFs). In this study, we tried to find the linking pathway between the acute injury and fibrosis by SMFs.
Methods : Human tubular epithelial cells (hTECs) were cultured on SMF platforms (119 mT; upward N→S: outward direction vs. downward N→S: inward direction). Adenine of 1, 2, and 4 mmol was treated for 72 hours on hTECs. We injected mice (C57BL/6, male, 8-week-old) orally with 2 mg of adenine daily for 14 days. Immunofluorescence assay, flowcytometry, and western blot were performed to evaluate the transition mechanism. P38 inhibitor (iP38) of 0.1 and 1 μmol was treated to verify the role of mitogen-activated protein (MAP)-kinase pathway.
Results : HIF-1α was increased, while E-cadherin was decreased, especially under inward direction of SMFs. Inward direction of SMFs more increased the expression of collagen-1, fibronectin, and pp38 than outward direction. SMFs decreased the proportion of G1 phase (control: 55.7% vs. outward and inward direction of SMFs: 35.2% and 30.7%, respectively). Ki-67-positive cells under SMFs were less than control (control: 54.6% vs. outward and inward direction of SMFs: 34.5% and 29.2%, respectively). Fibronectin, anti-smooth muscle antibody, and periostin under inward direction of SMFs were dose-dependently decreased after the iP38 treatment ($p < 0.05$). iP38 treatment decreased the fibronectin in adenine-treated hTECs under inward direction of SMFs ($p < 0.05$). Deposition of NGAL, F4/80, IL-17, p53, and p38 was significantly increased in adenine-induced CKD mice.
Conclusions : This study reveals that acute renal tubular injury under SMFs proceeds to fibrosis through maladaptive repair, including G1/S phase arrest and MAP-kinase pathway. And the field direction of SMFs affect the severity of injury and resultant fibrosis.

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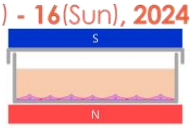

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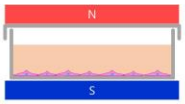

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