Title: **Macrophage in injured area induces the migration of grafted neural stem cells through MCP-1/CCR2 and ERK pathway**

Author / Authors: Zhijian Cheng, Xijing He

[a] Department of Orthopedics, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Abstract:

After spinal cord injury, grafted neural stem cells (NSCs) can migrate toward injured area, where there are a large number of bone marrow derived macrophage. However, little is known about the effect of M1 macrophage from bone marrow on NSCs migration and the mechanism responsible for migratory responses of grafted NSCs in vitro and in vivo. Migration of NSCs were conducted by using the transwell chamber and SCI model. Conditioned medium from M1 macrophages (M1-CM) can attract NSCs migration in vitro. The number of migrated C-C chemokine receptor 2 (CCR2) -/- NSCs induced by M1-CM were significantly decreased compared with wild type (WT) NSCs (P<0.05). Furthermore, compared with M0 macrophages, the production of MCP-1 by M1 macrophages was significantly increased and M1-CM treated with anti-MCP-1 antibody to neutralize MCP-1 can lead to a significant reduction of NSCs migration (P<0.05). In addition, Western blot showed that ERK1/2 was dramatically activated following the stimuli of M1-CM and then ERK inhibitor can also inhibit M1-CM-mediated MSCs migration. Finally, CCR2 was needed for grafted NSCs migration toward injured area. Bone marrow derived M1 macrophage persisted within the epicenter of injured area and the expression of MCP-1 mRNA was significantly increased 7days after SCI (P<0.05). These results demonstrated the effect of M1 macrophages on NSCs migration and the important role of MCP-1/CCR2 and ERK signal pathway on M1-CM-induced NSCs migration.