論 文 要 旨

Prevention of non-infectious pulmonary complications after intra-bone marrow stem cell transplantation in mice

（マウスモデルにおいて骨髄内骨髄移植は移植後肺合併症の発症を予防する）

包括的研究

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Non-infectious pulmonary complications including idiopathic pneumonia syndrome (IPS) and bronchiolitis obliterans syndrome (BOS), which are clinical and diagnostic manifestations of lung chronic graft-versus-host disease (GVHD), cause significant mortality after allogeneic stem cell transplantation (SCT). Increasing evidence suggests that alloantigen reactions in lung tissue play a central role in the pathogenesis of IPS and BOS; however, the mechanism is not fully understood. Several clinical and experimental studies have reported that intra-bone marrow (IBM)-SCT provides high rates of engraftment and is associated with a low incidence of acute GVHD. In the present study, allogeneic SCT was conducted in mouse models of IPS and BOS, to compare intravenous (IV)-SCT with IBM-SCT. Allogeneic IBM-SCT improved the clinical and pathological outcomes of pulmonary complications compared to those of IV-SCT. The mechanisms underlying the reductions in pulmonary complications in IBM-SCT mice were explored. The infiltrating lung cells were mainly CD11b+ myeloid and CD3+ T cells, in the same proportions as in transplanted donor cells. In an *in vivo* bioluminescence imaging, a higher proportion of injected donor cells was detected in the lung during the early phase (1 h after IV-SCT) than after IBM-SCT (16.7 ± 1.1 vs. 3.1 ± 0.7 × 10^5 photons/s/animal, IV-SCT vs. IBM-SCT, $P = 1.90 \times 10^{-10}$). In the late phase (5 days) after SCT, there were also significantly more donor cells in the lung after IV-SCT than after IBM-SCT or allogeneic-SCT (508.5 ± 66.1 vs. 160.1 ± 61.9 × 10^6 photons/s/animal, IV-SCT vs. IBM-SCT, $P = 0.001$), suggesting that the allogeneic reaction induces sustained donor cell infiltration in the lung during the late phase. These results demonstrated that IBM-SCT is capable of reducing injected donor cells in the lung; IBM-SCT decreases donor cell infiltration. IBM-SCT therefore represents a promising transplantation strategy for reducing pulmonary complications, by suppressing the first step in the pathophysiology of chronic GVHD.