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学 位 論 文 名	Inhibition of donor-derived T cells trafficking into target organs by FTY720 during acute graft-*versus*-host disease in small bowel transplantation （小腸移植の急性 GVHD における FTY720 によるドナーT 細胞抑制機序）
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論 文 内 容 の 要 旨

〔 目 的 〕

Small bowel transplantation (SBTx) has become the treatment of choice for patients experiencing life-threatening complications of intestinal failure. As another type of immune response in SBTx, graft-versus-host disease (GVHD) often occurs after SBTx. GVHD is mediated by donor derived T cells recognizing host MHC alloantigens, and represents an important immunological event influencing life in experimental and clinical situation. We evaluated the possibility that a new sphingosine 1-phosphate receptor agonist, FTY720, could diminish GVHD in a rat SBTx model through traffic alteration of donor-derived T cells in target organs.

〔 方法 〕

Heterotopic SBTx was performed using a parent (WF)-into-F_1 (WF×ACI) rat combination. The protocol comprised 4 groups : Group A, syngeneic group (n＝6) ; Group B, untreated GVHD control group (n＝8) ; Group C, F_1 recipient rats treated with FTY720 by a low dose of 0.1 mg/kg (n＝6) ; Group D, F_1 recipient rats treated with FTY720 by a high dose of 0.5 mg/kg (n＝10). FTY720 administered to the recipient for 14 days after operation. Recipient survival, body weight and histopathology were measured. Flow cytometry was used for the analysis of donor-derived T-cell subpopulation from target organs and graft. Cytokine production from the cultured supernatants of target tissue lymphocytes were also compared with untreated controls by ELISA.

〔結　果〕

Untreated control recipients died of GVHD within a mean survival time of 16±1.69 days. FTY720-treated recipients displayed a significantly higher survival rate up to 34.1 days ($P<0.05$) when a lower dose of FTY720 (0.1 mg/kg) was administered for 2 weeks. Furthermore, recipients also had an obviously higher survival rate of

>100 days at a higher dose of FTY720 (0.5 mg/kg ; P＜0.01). FTY 720 (0.5 mg/kg)-treated group demonstrated significant inhibition of histopathological changes in the small bowel, liver and skin, resulting in an almost intact architecture. In the target organs of host, increased numbers and percentages of donor-derived TCR$\alpha\beta^+$ T cells, $CD4^+$ T cells and $CD8^+$ T cells in the liver, MLN and LP, in addition to $CD4^+$ T cells in PP, during GVHD were significantly reduced by FTY720 treatment. In the graft, however, percentages of donor-derived TCR$\alpha\beta^+$ T cells and $CD4^+$ T cells were increased to 62% and 48% in the MLN, and to 38% and 37% in the LPL by FTY720 treatment, respectively. After administration of FTY720, production of IFN-γ in all the sites of target organs was significantly diminished as compared with untreated rats. However, no significant differences in IL-4 production were observed between FTY720-treated and untreated recipients

〔 総 括 〕

1．FTY720 inhibited lethality and histopathological changes in target organs when administered at 0.5 mg/kg, possibly due to sequestration of donor-derived T cells in the intestinal graft.
2．FTY720 caused a significant reduction in donor T-cell numbers in target organs by promoting these cells to home into donor, but not recipient, secondary lymphoid tissues.
3．FTY720 significantly decreased production of IFN-γ in target organs.

We concluded that FTY720 effectively reduced recirculation of activated donor-derived T cells and redistributed into target organs of GVHD in SBTx. These properties may offer the potential to treat ongoing GVHD in small bowel transplantation.

論文審査の結果の要旨

本研究では、Wistar Furth（WF）から F1（WFxACI）への近交系ラット異所性小腸移植 GVHD モデル用いて、急性期 GVHD に対する新規免疫調節剤 FTY720（FTY）の効果につき検討した。FTY720 の２週間経口投与にて、有意な生存率の延長を認めた。病理組織学的検討では、GVHD の標的臓器である肝臓、腸管、皮膚において、炎症細胞浸潤の著明な抑制効果が認められた。FTY はドナーT 細胞のグラフトの二次リンパ組織へのホーミングを促進し、かつそこに留めて流出させない（sequestration）ことにより、標的臓器への移行を阻止し、その結果 GVHD の発症を抑制したと考えられた。本研究成果は、小腸移植の急性 GVHD における FTY720 によるドナーT 細胞抑制機序の重要な知見を示したものであり、学位の授与に値するものと認める。