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mTOR inhibitor rapamycin induce polymorphonuclear myeloid-derived suppressor cells mobilization and function in protecting against acute graft-versus-host disease after bone marrow transplantation

Yu Lin [a,b,1], Binsheng Wang [a,1], Wei Shan [a], Yamin Tan [a], Jingjing Feng [a], Lin Xu [a], Limengmeng Wang [a,b], Biqing Han [a], Mingming Zhang [a], Jian Yu [a], Xiaohong Yu [a], He Huang [a,b,*]

[a] Bone Marrow Transplantation Center, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China
[b] Institute of Hematology, Zhejiang University, Hangzhou, China

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ABSTRACT

The mammalian target of rapamycin (mTOR) inhibitor rapamycin (RAPA) has been shown to be an effective immunosuppressor in the management of acute graft-*versus*-host disease (aGVHD) after bone marrow transplantation. Myeloid-derived suppressor cells (MDSCs) also have a protective effect in aGVHD regulation. However, the relationship between RAPA and MDSCs in aGVHD models is unclear. Meanwhile, the effect of RAPA on different subgroups of MDSCs is also less well described. In this study, we demonstrate that *in vivo* administration of RAPA results in the expansion and functional enhancement of polymorphonuclear MDSCs (PMN-MDSCs) in a murine model of aGVHD. RAPA treatment can enhance the suppressive function of PMN-MDSCs *via* up-regulation of arginase1 (Arg1) and induced nitric oxide synthase (iNOS) at later time points. Moreover, RAPA can also induce a strong immunosuppressive function in PMN-MDSCs from murine bone marrow *in vitro*, but has a contrary effect on monocytic MDSCs (M-MDSCs). We found that RAPA-treated PMN-MDSCs can restrain the differentiation of Th1/Th2 cells and promote induction of regulatory T cells in *in vitro* studies.

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1. Introduction

Myeloid-derived suppressor cells (MDSCs) have been identified as a heterogeneous group of immature myeloid cells at various stages of differentiation, including myeloid progenitors and precursors of macrophages, granulocytes and dendritic cells (DCs). They are characterized by a remarkable ability to suppress the activity of T cells and NK cells [1]. Murine MDSCs are characterized by the expression of CD11b and Gr1 cell markers. Based on the expression of Ly6C and Ly6G molecules, MDSCs can be subdivided into two major subsets. $CD11b^+Ly6G^-Ly6C^{high}$ cells are identified as monocytic MDSCs (M-MDSCs), while cells with a $CD11b^+Ly6G^+Ly6C^{low/int}$ phenotype are defined as polymorphonuclear MDSCs (PMN-MDSCs) [2–3]. MDSCs have been found to obviously proliferate in several pathological conditions, such as cancer, various infectious diseases, sepsis, trauma, transplantation and some autoimmune diseases. They have also been shown to have a protective effect in acute graft-*versus*-host disease (aGVHD) regulation [4–8]. To strengthen the protective effect, there is an urgent need to search for effective and feasible methods to increase the quantity or enhance the immunosuppressive function of MDSCs. MDSCs are derived from myeloid precursors and are differentiated and elicited by several cytokines and molecules, such as granulocyte/macrophage colony-stimulating factor (GM-CSF), granulocyte CSF (G-CSF), interleukin-6 (IL-6), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), IL-1β, vascular endothelial growth factor (VEGF) and Toll-like receptor (TLR) ligands [9–12]. Besides the combination of cytokines, several studies suggest that the mammalian target of rapamycin (mTOR) plays a key role in MDSCs' expansion in some autoimmune diseases [13–14] and organ transplantation [15]. Nevertheless, the effects of mTOR on MDSCs after bone marrow transplantation are not yet fully understood.

mTOR is a conserved 289 kDa serine/threonine kinase and a key regulator of cell growth, proliferation and metabolism [16]. The mTOR protein contains at least two distinct signaling complexes: mTORC1 and mTORC2. Rapamycin (RAPA) is a specific mTORC1 inhibitor with potent immunosuppressive properties [17]. Currently, it is widely used in prevention of allograft rejection after solid organ transplantation [18–19] and has recently emerged as a possible alternative immunosuppressor in the management of aGVHD [20–21]. RAPA was first reported to be effective in inhibiting Th1 or Th1 cytotoxic (Tc1) cytokine production and $CD8^+$ and $TCR\gamma\delta^+$ T cell-mediated GVHD

* Corresponding author at: Bone Marrow Transplantation Center, The First Affiliated Hospital, School of Medicine, Zhejiang University, No. 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China.
E-mail address: huanghe@zju.edu.cn (H. Huang).
[1] These authors contributed equally to this work.

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[22]. In recent years, RAPA has been shown to be a central point in various innate and adaptive immune cell development and function [23]. However, the effect of RAPA on different subgroups of MDSCs has been less well described.

As there is high plasticity of MDSCs in response to different stimuli, MDSCs' regulation is distinctly variable even among patients suffering from the same disease. The aim of this study was to explore the role of the mTOR inhibitor RAPA in inducing MDSCs in a murine model of bone marrow transplantation. We found that RAPA treatment can alleviate aGVHD symptoms and mortality in this model. It can significantly enhance PMN-MDSCs' accumulation in the spleen and potentiate their immunosuppressive function. In addition, we found RAPA can induce a very strong suppressive function of mice bone marrow PMN-MDSCs but not M-MDSCs *in vitro*.

2. Materials and methods

2.1. Mice

Male BALB/c mice (H-2Kd) and C57BL/6 mice (B6, H-2Kb) (SLAC Laboratory Supplies, Shanghai, China) were used at 8–10 weeks of age. All mouse experiments were conducted under specific pathogen-

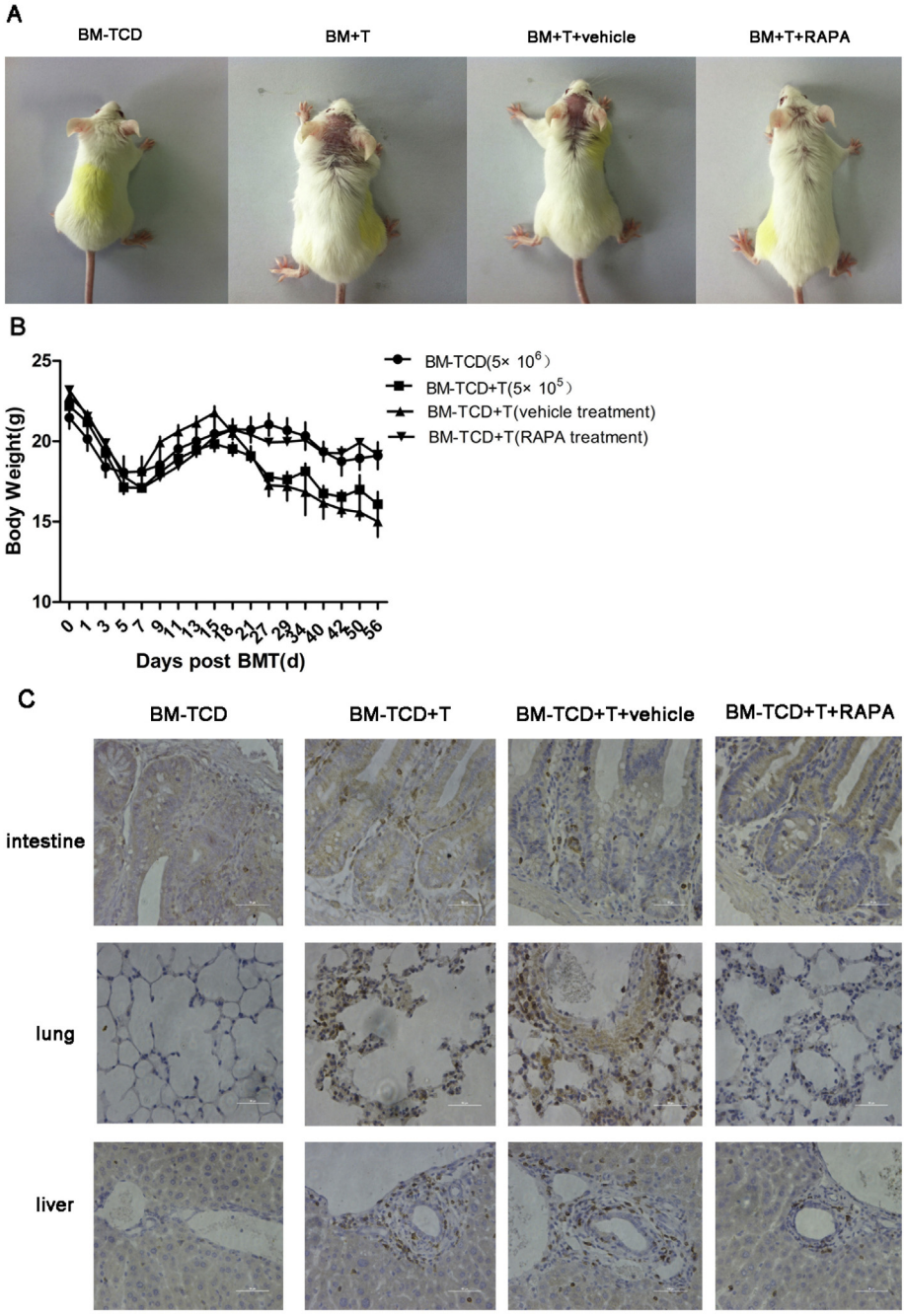

Fig. 1. RAPA treatment can significantly alleviate aGVHD after bone marrow transplantation. BALB/c were lethally irradiated and underwent transplantation with 5×10^6 BM- TCD with or without 5×10^5 T cells from B6 donors. Mice in treatment groups received vehicle or RAPA (1.5 mg/kg·d) intraperitoneal injection from day 0 to day 15 after bone marrow transplantation ($n = 8$ in each group). (A) Symptom of alopecia in BM-TCD, BM-TCD + T, vehicle treatment and RAPA treatment groups on day 20 after transplantation. (B) Weight change of mice in the different four groups. Mice receiving RAPA treatment experience less-pronounced weight loss compared with vehicle group. (C) Immunohistochemical staining of $CD3^+$ T cells in intestine, lung and liver on Days 20 after transplantation were observed and taken photographs under optical microscope (400×). One representative result of three independent experiments is shown.

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