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Targeting high affinity LFA-1 to prevent GVHD and preserve GVL

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Allogeneic bone marrow transplantation (alloBMT) is an effective therapy for hematological malignancies. But the limiting factor is graft-versus-host disease (GVHD), and the same T cell-mediated alloimmune responses are strongly associated with the beneficial graft-versus leukemia (GVL) effect. Therefore, alloBMT has been exploited as a platform to deliver immunotherapy for leukemia and other malignant diseases. LFA-1 regulates T cell activation via immunological synapse and is constitutively expressed in the low affinity state. LFA-1 changes to the high affinity state upon activation which is an important mechanism for regulation. We found that high affinity LFA-1 regulates T cell activation and proliferation. The activation of LFA-1 directly enhances TCR signal pathway, thus decreasing T cell activation threshold by promoting IL-2 production and proliferation. Although blocking high affinity LFA-1 can inhibit the proliferation of human cytotoxic T lymphocytes (CTL) upon TCR and antigen-specific stimulation, their antigen-specific cytotoxic function against target cells remains intact. T cell proliferation requires mature synapse formation after prolonged stimulation and high affinity LFA-1 generates an additional signal to enhance T cell activation. In contrast, the CD8+ CTL secretory synapse for targeted delivery and cytolytic response is transient and does not require the high affinity LFA-1. Previous studies report that effector T cells are responsible for GVL while the proliferation and differentiation of naïve T cells contribute to GVHD. The high affinity LFA-1 promotes naïve T cell activation and mediates GVHD. Meanwhile low affinity LFA-1 is sufficient for the secretory synapse formation and cytolitic function to mediate GVL. The differential immunomodulatory effects of LFA-1 on the T cell proliferation versus cytoxicity provide a mechanistic explanation for GVHD and GVL, and targeting high affinity LFA-1 can prevent GVHD while preserve GVL.

Biography

Qing Ma has completed her Ph.D. from Thomas Jefferson University and postdoctoral studies from Harvard medical School. She is an associate professor in the department of stem cell transplantation and cellular therapy at University of Texas M.D. Anderson Cancer Center.