



Commentary

Realizing the Potential for Recipient Immune Cells in Adoptive Immune Therapy



Sanjive Qazi

Biology Department, Gustavus Adolphus College, Saint Peter, MN 56082, United States

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Despite the extensive use of animal models to better understand disease progress, efficacy and toxicity of therapeutic interventions a vast majority of promising treatments fail in human trials (Holzapfel et al., 2015). One approach has been to humanize mouse model systems to recapitulate disease processes by conditioning mice to permit engraftment of human cells utilizing immune-deficient mice such as NSG strains (NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ) in pre-clinical studies. One major advantage of this is to allow detailed molecular profiling of diseased cells and targeting aberrant processes for individual patients by growing patient derived cells xenografted into immune-deficient mice (Malaney et al., 2014). However, major shortcoming of humanized xenograft mouse models include: the absence of a tumor microenvironment to study cytokine/chemokine interactions that are critical for cancer progression and metastasis; and toxicity arising from induction of cytokine storms cannot be tested.

To expand the use of xenograft models in preclinical studies by reconstituting human hematopoietic and lymphoid immune systems, Xia et al. (2016) report findings from a proof of principle study whereby humanized mice were transplanted with human fetal thymic tissue (FTHY) in and followed the progression of leukemia using stem cells derived from CD34+ fetal liver cells (FLCs) transduced with leukemia associated fusion gene MLL-AF9. These humanized mice developed B-cell Acute Lymphoblastic Leukemia (B-ALL) that could be transferred to a secondary recipient with an autologous immune system to assess the anti-leukemic efficacy of recipient leukocyte infusion (RLI), which is an anti-tumor response from the “host” immune system as opposed to the more commonly used technique of donor leukocyte infusion (DLI) that exhibits anti-tumor activity from allogenic T-cells. DLI has proven very useful treatment option resulting in remission following hematopoietic stem cell transplantation (HSCT), but also induces toxic graft versus host disease (GVHD). A multicenter report from UK reports that up to 71% of cases (68 cases examined) developed GVHD and half

of them were classified as Grades III–IV (Scarlsbrick et al., 2015) and this grade of morbidity requires further third-line interventions such as administration of mTOR inhibitors, anti-TNF antibodies, IL-2 receptor antibodies and mesenchymal stem cell transplantation (Dignan et al., 2012). RLI has the potential to markedly reduce the occurrence of graft versus host disease that is observed with DLI (Saito et al., 2006). Since one of the ultimate goals of allogenic-HSCT for treating hematological malignancies is to separate graft versus leukemia and graft versus host disease mechanisms induced by donor T-cells, RLI provides a means to achieve this goal.

Xia et al. (2016) compellingly demonstrated that NSG mice develop a human immune system and leukemia, and further show that RLI mediated anti-leukemia activity in the presence of lymphopenia conditions presenting the translational research community with a tractable model system to study leukocyte infusions for immune therapies. Conditioning for HSCT can result in long lasting lymphopenia (Daikeler et al., 2012) thereby limiting the use of DLI, but permitting the use of RLI as a potential treatment strategy. In this investigation, NSG were conditioned with 2Gy total body irradiation and transplanted with CD34+ FLCs and thymic tissue fragments. These humanized mice developed B-ALL and flow cytometric analysis confirmed reconstitution of human peripheral blood mononuclear, T-subtype, B-subtype and myeloid immune cells in this model system. Transplantation of ‘recipient’ FTHY and CD34+ FLCs into NSG mice provided a source for RLI treatment utilized to investigate anti-leukemic potential of the recipient immune system against autologous (‘recipient’) and allogenic (‘donor’) mixed chimera mice. Mixed chimera mice were made from ‘donor’ CD34+ FLCs (obtained from a different fetal liver than the one for the RLI source), recipient CD34+ FLCs and recipient thymic tissue. RLI treatment of these MCs did not exhibit a strong host versus graft reaction. However, one of the significant findings of this study suggested a strong host versus graft reaction could be elicited upon removal of the recipient thymic tissue or depletion of T cells in the MC to mimic lymphopenia, boosting the myeloid count by increasing the production of human cytokines via hydrodynamic injection of cytokine containing plasmids and depleting regulatory T-cells using anti-human CD25 microbeads. In this response the proportion of donor CD45+ T-cells was markedly reduced and the recipient population of CD3+ cells was increased after 4 weeks of RLI treatment. RLI treatment resulted in the loss of donor CD45 and CD19 cells that was more pronounced in lymphopenic MCs. This ability to manipulate the cytokine stimulation and to selectively populate the engraftment of immune cells entertains the possibility of designing

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adoptive immune therapies employing the emerging roles of NK cells and Treg cells in reducing GVHD and enhancing anti-leukemic effects (MacDonald et al., 2016; Pierini et al., 2016).

Clinical significance of this finding was demonstrated by the knock-down of GFP labelled leukemia cells following 7 weeks of treatments and expansion of the activated/memory phenotype CD45RA[−]/CD45RO⁺ T-cells. The humanized mouse model system reported by Xia et al. (2016) has the potential to further investigate the dynamics and timing of the emergence of different T-cell populations involved in effect or function, proliferative capacity, memory formation and immune reconstitution central to delivering effective adoptive immune therapies. For example basic ontological questions concerning linear differentiation model, decreasing potential model or progression models can be directly examined for RLI therapy (Busch et al., 2016) providing clues to which populations of T-cells can be harnessed to enhance anti-leukemic effects while reducing GVHD.

Moving forward into the clinical setting, it still needs to be elucidated how RLI therapy can be sourced and administered to patients. The molecular features and mechanisms of RLI action once characterized could be used to generate the cellular sources for adoptive immune therapies utilizing recipient cells.

Disclosure

The author declared no conflicts of interest.

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