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Rejuvenation of the Thymic Microenvironment by ESC-derived Thymic Epithelial Progenitors

Laijun Lai

*Department of Immunology and University of Connecticut Stem Cell Institute,
School of Medicine, University of Connecticut Health Center, Farmington, CT 06111,
USA*

1. Introduction

T-cells play a critical role in the adaptive immune system, providing protection against neoplasia and bacterial, viral, fungal and parasitic infections. Unfortunately, T-cell deficiencies can occur in a number of physiological and pathological situations. The thymus is the primary organ for T cell generation, and while it continues to export T-cells throughout life, the thymus undergoes age-dependent involution, resulting in decreased numbers and functional capacity of T-cells in the elderly (Dorshkind et al., 2009; Zediak and Bhandoola., 2005; Lynch., 2009; Taub and Longo., 2005). Various genetic and infectious diseases, such as AIDS, are associated with T-cell deficiencies. In addition, intensive chemotherapy or radiotherapy for cancer patients and preparative regimens for foreign tissue or organ transplants often result in severe and protracted T cell deficiencies. Furthermore, the recovery of T cells after hematopoietic stem cell transplantation is often slow and incomplete compared with that of myeloid, NK, or B-cells (Williams et al., 2007; Wils et al., 2005). T-cell deficiencies contribute to increased morbidity and mortality from opportunistic infections, the occurrence and relapse of cancers, and the failure of vaccinations and other immunotherapies (van den Brink et al., 2004).

There are two major pathways for T-cell reconstitution: thymus-dependent regeneration and thymus-independent homeostatic expansion (Williams et al., 2007; Mackall et al., 1996; Mackall and Gress., 1997). The former recapitulates thymic ontogeny and generates T-cells from bone marrow (BM)-derived T-cell progenitors that undergo positive and negative selection in the thymus. Therefore, T cells generated from this pathway usually have a diverse TCR repertoire, are capable of responding to a variety of foreign antigens, and tolerate self-antigens. In contrast, the thymus-independent pathway usually occurs by expansion of residual mature T cells in the periphery, thus producing T-cells with a limited TCR repertoire and the possible loss of self tolerance. Therefore, the thymus-dependent pathway is generally a preferred pathway for T-cell regeneration.

T-cell development in the thymus is dependent on the thymic microenvironment, in which epithelial cells are the major components (Anderson et al., 2006; Chidgey et al., 2007). Thymic epithelial cells (TECs) can be divided into cortical (cTEC) and medullary (mTEC) subpopulations. The former are thought to mediate positive selection and the latter are thought to control the negative selection process in which potentially autoreactive T-cells

are deleted. The importance of TECs has been underscored by the fact that defects in these cells results in T-cell deficiencies. For example, gene mutation or deletion of the forkhead transcription factor *Foxn1* in human or mouse affects thymic epithelial differentiation, resulting in loss of intrathymic T-cell development and severe immunodeficiency (Anderson et al., 2006; Chidgey et al., 2007). Furthermore, reductions in the number of TECs results in a reduced number of thymocytes (Jenkinson et al., 2008; Jenkinson et al., 2007; Revest et al., 2001).

Many studies have demonstrated that during aging, TECs undergo both a qualitative and quantitative loss believed to be one of the major factors responsible for age-dependent thymic involution (Dorshkind et al., 2009; Zediak and Bhandoola., 2005; Lynch., 2009; Taub and Longo., 2005). Transfer of young BM into aged recipients is not capable of restoring the thymic architecture to that of a young thymus, as these aged recipients still exhibit diminished thymocyte numbers as well as significantly reduced numbers of naïve T cells in the periphery. This suggests that there are some irreversible alterations in the aged thymic microenvironment (Zediak and Bhandoola., 2005). In addition, TECs are vulnerable to injury from radiation, chemotherapy, infection, and graft-versus-host disease following bone marrow transplantation (Adkins et al., 1988; Rossi et al., 2002; Ye et al., 2004; Mackall et al., 1995). Therefore, there is a need for the development of strategies to enhance or restore TECs. Administration of keratinocyte growth factor or sex steroid ablation has been shown to increase the number of TECs, resulting in enhanced thymopoiesis (Kelly et al., 2008; Min et al., 2002; Rossi et al., 2007; Min et al., 2007; Alpdogan et al., 2006). Additionally, transplantation of cultured thymus fragments has been used to provide the thymic microenvironment for T-cell regeneration in patients and experimental animals with T-cell deficiencies or as a method for the induction of tolerance in organ transplantation (Markert et al., 2003; Hong et al., 1979; Yamada et al., 2000; Kamano et al., 2004). However, the applications of cultured thymus fragments are limited by tissue availability.

During development in mice, the thymus initially arises from the third pharyngeal pouch (Anderson et al., 2006). Previous studies have suggested a dual origin for thymic epithelium, with cortical epithelium deriving from ectoderm and medullary epithelium deriving from endoderm (Manley, 2000). However, recent functional data strongly supports the theory that thymic epithelium is derived from a single germ layer, the endoderm (Manley, 2000; Rodewald, 2008; Blackburn & Manley 2004; Zhang et al., 2007). This single endoderm-origin model is consistent with data suggesting a common progenitor gives rise to both types of TECs (Gordon et al., 2004; Bleul et al., 2006). The thymic epithelial progenitors (TEPs) in the embryonic thymus have been reported to be MTS24+ cells due to the finding that purified MTS24+ cells can reconstitute a functional thymic epithelial microenvironment capable of supporting T-cell development *in vivo* (Markert et al., 2003; Hong et al., 1979). However, another recent study showed that thymic architecture could be formed *in vivo* by a large number of MTS24- cells (Yamada et al., 2000). While the expression of a common surface marker on these progenitor cells remains controversial, ontogenetic analysis of epithelial cells during thymic development has shown that TEPs co-express cytokeratins (k) 5 and K8,, then proliferate and differentiate into mature K5-K8+ cTECs and K5+k8- mTECs (Anderson et al., 2006; Klug et al., 2002). However, because cytokeratins are intracellular antigens, which requires that cells are permeabilized before antibody staining and analysis, the patterns of the cytokeratin expression allow only phenotypic analysis, not the isolation of live cells for functional studies. Recently, Rossi et al reported that a fraction

of MTS24⁺ cells in the embryonic thymus expressed the cell surface marker, EpCAM1 (Rossi et al., 2006). Importantly, a single EpCAM1⁺ cell isolated from the embryonic thymus could develop into both types of TECs *in vivo* (Rossi et al., 2006). The identification and characterization of TEPs has important clinical implications for restoring thymic function. However, use of TEPs for this purpose has been restricted thus far by the limited availability of such cells.

2. Generation of thymic epithelial progenitors from mouse embryonic stem cells

It is well known that embryonic stem cells (ESCs) have the dual ability to propagate indefinitely *in vitro* in an undifferentiated state and to differentiate into many types of cells that derive from all three germ layers (Murry & Keller 2008). We have investigated whether mouse ESCs can be selectively induced to generate TEPs *in vitro*. By using both three-dimension embryoid body formation and two-dimension monolayer culture systems in the presence of four growth factors [fibroblast growth factor (FGF)-7, FGF-10, bone morphogenetic protein 4 and epithelial growth factor], we have shown for the first time, that murine ESCs (mESCs) can be selectively induced to differentiate into TEPs (Lai & Jin, 2009). Under these culture conditions, EpCAM1⁺ cells can be generated from mESCs (Lai & Jin, 2009). Importantly, most of the mESC-derived EpCAM1⁺ cells co-expressed K5 and K8, a phenotype of TEPs (Gordon et al., 2004; Bleul, 2006; Rossi et al., 2006). The EpCAM1⁺ cells also expressed the Pax1, Pax9, FoxN1, and Plet1 genes that are known to be highly expressed in TEPs from the embryonic thymus (Manley, 2000). Together, these findings indicate that the mESC-derived EpCAM1⁺ cells contained TEPs.

To determine whether the mESC-derived EpCAM1⁺ cells could differentiate into cTECs and mTECs, and form normal thymic architecture, we purified cultured mESC-derived EpCAM1⁺ cells and mixed these cells with CD4-CD8-CD45⁺ immature thymocytes from adult mice. The mixtures were subjected to cell reaggregation *in vitro*, and then were transplanted under the kidney capsule of syngeneic mice. Six weeks later, the grafts were examined by immunohistochemical staining. We found that discrete K8⁺K5⁻ cortical and K8⁻K5⁺ medullary epithelial areas were present in the grafts. Some of the cells co-expressed K8 and K5, suggesting they were residual, or self-replicating, TEPs (Lai & Jin, 2009). In controls, transplantation of CD4-CD8-CD45⁺ immature thymocytes and/or mESC-derived EpCAM1⁻ cells could not form normal thymic architecture *in vivo*. Further analysis showed that all stages of T cells were generated in the EpCAM1⁺, but not in the EpCAM1⁻ cell grafts (Lai & Jin, 2009). These data suggest that the mESC-derived EpCAM1⁺ cells can form normal thymic architecture that supports T-cell development *in vivo*.

To further confirm that the mESC-derived TEPs can give rise to both cTECs and mTECs *in vivo*, we injected a single EGFP⁺ EpCAM1⁺ cell into irradiated thymic fragments that were then implanted under the kidney capsule of syngeneic mice. We examined the grafts six weeks later and found that EGFP⁺ EpCAM1⁺-derived cells were comprised of K5⁺K8⁺ TEPs, K5-K8⁺ cTECs, and K5⁺K8⁻ mTECs (Lai & Jin, 2009). These results further suggest the mESC-derived TEPs are able to differentiate into both types of TECs and to self-renew *in vivo*.

We then determined whether transplantation of ESC-derived EpCAM1⁺ cells could enhance thymopoiesis following bone marrow transplant (BMT). Because the mESC-derived

EpCAM1⁺ cells cannot efficiently migrate from the blood into the thymus (Lai & Jin, 2009), we injected the EpCAM1⁺ cells intrathymically (i.t.) into irradiated syngeneic mice followed by intravenous (i.v.) injection of T cell deleted (TCD)-BM. Either mESC-derived EpCAM1⁻ cells or PBS were transplanted as controls. One month after transfer, thymic cellularity was analyzed. We found that the number of thymocytes in the EpCAM1⁻ cell- or PBS-treated BMT mice was significantly reduced, as compared to that in the normal non-BMT control mice. In contrast, the number of thymocytes in the EpCAM1⁺ cell-treated mice approximated that of normal, non-BMT control mice. Further analysis showed that the relative distribution of thymocyte subsets in the EpCAM1⁺ cell-treated mice was comparable to that of the normal non-BMT controls (Lai & Jin, 2009). Importantly, the number of TECs in the EpCAM1⁺ cell-treated mice was significantly increased (as compared to EpCAM1⁻ cell- or PBS-treated mice), and about two thirds of TECs were derived from mESCs. Further analysis revealed that the mESC donor-origin TECs expressed CCL25, delta-like Notch ligands, and MHC I and MHC II molecules (Lai & Jin, 2009). All of these proteins are involved in attracting T-cell progenitors to the thymus, and/or in supporting T-cell development within the thymus.

We then analyzed peripheral T cells in these recipients and found that the numbers of total and naïve CD4⁺ and CD8⁺ T-cells in the spleens of the EpCAM1⁺ cell-treated BMT mice were significantly higher than those in the EpCAM1⁻ cell- or PBS-treated BMT mice (Lai & Jin, 2009; and Figure 1). We also evaluated the functions of these peripheral T cells and found that splenic T cells from EpCAM1⁺ cell-treated BMT mice had a higher rate of proliferation in response to T cell mitogen or alloantigen stimulation than those from

Fig. 1. Mouse ESC-derived EpCAM1⁺ cell treatment increases the numbers of total and naïve CD8⁺ T cells after syngeneic BMT. Lethally irradiated syngeneic mice were injected intrathymically with 5X10⁴ mESC-derived EpCAM1⁺, EpCAM1⁻ cells, or PBS, and injected i.v. with TCD-BM (2X10⁶). One month later, the numbers of total CD8⁺ T cells and naïve CD8⁺ T cells (CD62^{hi}CD44^{lo}CD8⁺) were analyzed by flow cytometry. Data are presented as means ± standard deviation (S.D.) from 4-6 mice per group. * P<0.05 compared to PBS-treated BMT mice.

EpCAM1⁻ cell-, or PBS-treated BMT mice (Lai & Jin, 2009). Furthermore, a significantly higher percentage of splenic CD4⁺ and CD8⁺ T cells from the EpCAM1⁺ cell-treated BMT were able to produce interferon (IFN)- γ , tumor necrosis factor- α (TNF α), and interleukin-2 (IL-2) than those from EpCAM1⁻ cell-, or PBS-treated BMT mice (Lai & Jin, 2009; and Figure 2). To determine whether the induction of antigen-specific T cell-mediated immunity was intact in the EpCAM1⁺ cell-treated BMT mice, groups of BMT recipients were vaccinated with ovalbumin (OVA) in complete Freund's adjuvant 2 weeks after BMT. OVA-specific T cell responses in these mice were evaluated 2 weeks after vaccination. As shown in Figure 3, T cells purified from OVA-vaccinated, EpCAM1⁺ cell-treated mice exhibited higher rates of proliferation in response to *in vitro* stimulation with OVA, as compared to T cells purified from vaccinated PBS or EpCAM1⁻ cell-treated mice.

These results suggest that mESCs can be selectively induced to differentiate into EpCAM1⁺ cells with the phenotypes and genotypes of TEPs. When placed *in vivo*, these mESC-derived EpCAM1⁺ cells develop into both cTECs and mTECs, reconstitute the normal thymic architecture, and enhance thymopoiesis, resulting in increased numbers and functions of T cells in the periphery.

Fig. 2. Significantly higher fractions of splenic T cells from the mESC-derived EpCAM1⁺ cell-treated BMT recipients are able to produce TNF α and IL-2 after stimulation. Lethally irradiated, syngeneic mice were injected intrathymically with mESC-derived EpCAM1⁺, EpCAM1⁻ cells, or PBS, and injected i.v. with TCD-BM as in Figure 1. One month later, splenocytes were stimulated with PMA and ionomycin and stained for cell surface markers and intracellular cytokines using antibodies against CD4, CD8, IL-2, and TNF α . The percentages of IL-2 and TNF α positive cells in (A) CD4⁺ and (B) CD8⁺ T cells were determined by flow cytometry. Data are presented as means + S.D. from 4-6 mice per group. * P<0.05 compared to PBS-treated BMT mice.

Fig. 3. Antigen-specific T cell-mediated immunity was in EpCAM1⁺ cell-treated BMT mice. Lethally irradiated syngeneic mice were injected intrathymically with mESC-derived EpCAM1⁺, EpCAM1⁻ cells, or PBS, and injected i.v. with TCD-BM as for Figure 1. The recipients were vaccinated with 50 µg of OVA emulsified in Complete Freund's Adjuvant two weeks after BMT. Two weeks later, freshly isolated CD3⁺ cells were cultured in the presence of irradiated normal splenocytes + OVA for 4 days. T cell proliferation was determined by [3H] thymidine incorporation. Data are presented as means + S.D. from 4-6 mice per group. * P<0.05 compared to PBS-treated BMT mice.

3. Future directions

The generation of ESC-derived TEPs has important applications at both basic and translational levels. Although some molecules have been implicated in early thymic organogenesis, molecules involved in the development of TEPs and TECs remain poorly defined mainly due to the lack of a suitable system for these studies. Our demonstration that mESCs can be selectively induced to generate TEPs *in vitro* provides a powerful model with which to study the molecules associated with the development and differentiation of TEPs and TECs. These studies are important not only for gaining a better understanding of the mechanisms underlying thymic development, but also for strategies aimed at maximizing the generation of ESC-derived TEPs and regenerating adult TEPs and TECs.

With modern advances in medicine, our average lifespan is increasing. Currently, individuals aged 60 years and older constitute about 10% of the total world population, and this segment of the population is projected to increase to approximately 22% - 25% by 2050 (Dorshkind et al., 2009). However, advanced age is often accompanied by chronic diseases that have a significant impact on both an individual's quality of life and on the health-care systems that treat those patients (Dorshkind et al., 2009). Aging affects several organ systems and the immune system is one of the systems most significantly affected. Thymic involution is a hallmark of immune system aging, and this results in decreased numbers and functional capacities of T-cells, which in turn leads to increased rates of infections,

autoimmunity, and cancers (Dorshkind et al., 2009; Zediak and Bhandoola., 2005; Lynch., 2009; Taub and Longo., 2005). It is important to determine whether transplantation of ESC-derived TEPs can be used to prevent or reverse age-dependent thymic involution. It will also be important to determine whether transplantation of ESC-derived TEPs can enhance T cell regeneration after chemotherapy and radiotherapy for cancer patients, as well as after preparative regimens for foreign tissue and organ transplants. If successful, human ESC-derived TEPs might one day be used in the treatment of these patients.

Other ESC-derived cells have the potential to be used in the treatment of various degenerative diseases. However, one of the major challenges in ESC-based therapies is the potential for ESC-derived tissues to be rejected by the host immune response (Li et al., 2004; Hyslop et al., 2005; Chidgey et al., 2008). Several studies have shown that the inherent immune privileged status of ESCs was insufficient to prevent rejection across a multiple minor histocompatibility mis-match, even when the major histocompatibility complexes were the same (Li et al., 2004; Hyslop et al., 2005; Chidgey et al., 2008). Therefore, strategies to induce tolerance to ESC-based transplants will be required. Although current strategies to establish tolerance to foreign grafts by inhibiting pre-existing host T cells has achieved some success, these strategies often lead to immune deficiency (Chidgey et al., 2008). Therefore, strategies to induce donor-specific tolerance in the host, whilst maintaining generalized immunocompetence, are required. The best way to induce ESC-specific tolerance would be to use the same thymus-induced tolerance mechanisms that cause potentially autoreactive T cells to be deleted in the thymus. However, to achieve this the thymus must be functional and ESC antigens have to be incorporated into the thymus. As mentioned above, the thymus is subjected to age-dependent involution that affects its functions. ESC-derived TEPs should provide a powerful tool to prevent rejection of the ESC-derived tissues by supporting both restoration of thymic function and incorporation of the ESC antigens into the thymus.

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