SCIENCE CHINA PRESS

SCIENCE CHINA Life Sciences
life.scichina.com link.springer.com
https://doi.org/10.1007/s11427-023-2462-8

REVIEW

B cell development and antibody responses in human immune system mice: current status and future perspective

Tao Zhang[1,2], Wentao Liu[1,2*] & Yong-Guang Yang[1,2,3*]

[1]Key Laboratory of Organ Regeneration & Transplantation of the Ministry of Education, The First Hospital of Jilin University, Changchun 130061, China;
[2]National-Local Joint Engineering Laboratory of Animal Models for Human Diseases, Jilin University, Changchun 130061, China;
[3]International Center of Future Science, Jilin University, Changchun 130061, China

*Corresponding authors (Wentao Liu, email: liuwt@jlu.edu.cn; Yong-Guang Yang, email: yongg@jlu.edu.cn)

Received 24 July 2023; Accepted 28 September 2023; Published online 15 January 2024

Humanized immune system (HIS) mice have been developed and used as a small surrogate model to study human immune function under normal or disease conditions. Although variations are found between models, most HIS mice show robust human T cell responses. However, there has been unsuccessful in constructing HIS mice that produce high-affinity human antibodies, primarily due to defects in terminal B cell differentiation, antibody affinity maturation, and development of primary follicles and germinal centers. In this review, we elaborate on the current knowledge about and previous attempts to improve human B cell development in HIS mice, and propose a potential strategy for constructing HIS mice with improved humoral immunity by transplantation of human follicular dendritic cells (FDCs) to facilitate the development of secondary follicles.

humanized immune system mouse | humoral immunity | germinal center | B cell | follicular dendritic cell

Introduction

Human immune system (HIS) mice with a functional human lymphohematopoietic system can be in general categorized into three groups based on the human grafts transplanted into immunodeficient mice: the first involves transplantation of human peripheral blood mononuclear cells (PBMCs), the second is prepared by injection of human hematopoietic stem and progenitor cells (HSCs/HPCs), and the third is created by co-transplantation of fetal thymus and HSCs/HPCs (Manz and Di Santo, 2009; Rongvaux et al., 2013; Sun et al., 2020; Walsh et al., 2017). Currently, the commonly used HIS mice refer primarily to immunodeficient mice with engraftment of human HSCs/HPCs and differentiation and maturation of functional human immune cells, made by transplantation of human HSCs/HPCs or HSCs/HPCs plus thymic tissue (Ishikawa et al., 2005; Lan et al., 2006; Lan et al., 2004; Melkus et al., 2006; Mosier et al., 1988; Traggiai et al., 2004). Human HSC/HPC engraftment in mice results in the development of human T cells, B cells, myeloid cells (e.g., monocytes and dendritic cells (DCs)) (Ishikawa et al., 2005; Lan et al., 2006; Lan et al., 2004; Melkus et al., 2006; Traggiai et al., 2004), and, with the support of human IL-15, natural killer (NK) cells, leading to reconstitution of a functional human immune system (Herndler-Brandstetter et al., 2017; Huntington et al., 2009). HIS mice have been instrumental as an *in vivo* model for studying immune cell development and functions, modeling human diseases, and testing immunotherapies (Akkina, 2014; Allen et al., 2019; Kitsera et al., 2023; Rongvaux et al., 2013; Stripecke et al., 2020; Sun et al., 2020; Tan et al., 2017).

Although HIS mice show efficient human B cell development from HSCs to immature B cells and central B cell tolerance in the bone marrow, there is a severe defect in the late development stage of human B cells. Furthermore, the humoral immune response in HIS mice is more like the extrafollicular response with low somatic hypermutation (SHM) and class switch recombination (CSR) (Table 1) (Li et al., 2018; Waltari et al., 2018) due to the lack of germinal centers (GCs) (Akkina, 2014; Martinez-Torres et al., 2014; Seung and Tager, 2013; Villaudy et al., 2014), despite that HIS mice may produce antigen-specific antibodies following antigen immunization (Tonomura et al., 2008), xenotransplantation (Habiro et al., 2009) and viral infections (Sefik et al., 2022; Wahl et al., 2019; Wang et al., 2022). As a result, HIS mice have not been very useful for evaluating human vaccines or producing therapeutic human antibodies. This review dissects and summarizes the previous findings about and attempts to improve human B cell development and function in HIS mice, followed by discussion on the potential strategies to construct HIS mouse models with secondary follicle generation and improved antigen-specific high-affinity human antibody production.

Human immunoglobulin gene rearrangement and B cell tolerance in HIS mice

After being transplanted into immunodeficient mice, human HSCs could migrate to and engraft in the mouse bone marrow (Lapidot, 2001; Peled et al., 1999), then differentiate into immature B cells with newly generated IgM B cell receptors (BCRs) (Watanabe et al., 2009). Several studies have confirmed that HIS mice contain a wide variety of human IgM^+ naive B cell clones. By sequencing of VH regions of human B cells from HIS

Table 1. Humoral immunity characteristics in representative HIS mice and healthy human

HIS mice *vs.* human	Human graft	Serum IgG level	CSR (% IgG$^+$ memory B in B cells)	SHM (number of mutations)	Ref.
BRG mice having the SIRPα^{NOD} allele (BRGS)	HSCs	2–3[a)] μg mL^{-1}	0.36%[b)] in lymph node	1.73[b)] per IGHV in IgG$^+$/IgA$^+$ memory B cells	(Li et al., 2018)
BRG mice having the SIRPα$^{h/m}$ IL-6$^{h/h}$ allele	HSCs	(319.3±31.8) μg mL^{-1}	5%[a)] in spleen	1.16[a)] per IGHV in IgG$^+$ memory B cells	(Yu et al., 2017)
TSLP-transgenic BRGS mice	HSCs	1,020[a)] μg mL^{-1}	4.26%[b)] in lymph node	1.19[b)] per IGHV in IgG$^+$/IgA$^+$ memory B cells	(Li et al., 2018)
NSG mice	Thy/bone/spleen/HSCs	10–20[a)] μg mL^{-1}	N/A	N/A	(Chung et al., 2015)
Human	N/A	(11.2±2.5) mg mL^{-1}	7.3±3.3 in blood	22±8 per IGHV in IgG$^+$ memory B cells	(Fecteau et al., 2006; Gonzalez-Quintela et al., 2008)

a) The estimated mean or average range gathered from the results. b) The average values provided in the article.

mice generated via human HSC transplantation in irradiated Balb/c Rag2$^{-/-}$IL-2Rγ$^{-/-}$ (BRG) newborn mice, previous studies showed that human IgM BCR repertoires expressed by human B cells in HIS mice are indistinguishable from those of human peripheral blood B cells (Becker et al., 2010). It was also reported that B-cell repertoires of IgM$^+$IgD$^+$CD27$^-$ naive human B cells from NOD/SCID IL-2Rγ$^{-/-}$ (NSG) mice engrafted human umbilical cord blood CD34$^+$ HSCs are also indistinguishable from those of humans (Ippolito et al., 2012). Furthermore, autoreactive B cells were found to be effectively deleted, as shown by loss of BCRs with autoreactive V genes, during human B cell development from immature to naive B cell stages in HIS mice, similar to autoreactive B cell deletion in humans (Ippolito et al., 2012). This finding was further confirmed by studies analyzing the affinity of BCRs to multiple autoantigens, in which the frequencies of poly- and auto-reactive CD19$^+$CD27$^-$CD10$^+$IgM^{high}CD21^{low} new emigrant human B cells from HIS mice were found similar to those of human blood B cells (Cantaert et al., 2015; Schickel et al., 2016). Using HIS mice grafted with human HSCs and autologous thymic tissues, a recent study found that human regulatory T (Treg) cells developing in the autologous thymus graft can be stimulated by autoantigen-loaded B cells in an MHC-II-dependent manner and, in turn, inhibit the accumulation of autoreactive B cells, indicating an important role for Treg cells in the induction of B cell tolerance (Chen et al., 2022).

The above-mentioned studies indicate that immunoglobulin gene rearrangements and central and peripheral negative selection of human B cells in HIS mice are similar to what was reported for humans. Thus, HIS mice provide a useful *in vivo* model for understanding the development and function of human naive B cells, e.g., identifying the role and mechanism of activation-induced cytidine deaminase (AID) in mediating human central B cell tolerance (Cantaert et al., 2015). Furthermore, the application of HIS mice was further extended by their amenability to genetic modification. For example, HIS mice with transgenic expression of an anti-human Igκ antibody as a neo-self-antigen have been successfully used in defining the characteristics of autoreactive human B cells undergoing tolerance and mechanisms mediating human B cell tolerance (Table 2) (Alves da Costa et al., 2021; Lang et al., 2016).

Lack of FDCs limits lymphoid follicle formation in HIS mice

In the human body, immature B cells leave the bone marrow, circulate through peripheral blood to the spleen, then mature in the primary lymphoid follicles (Figure 1B) (Carsetti et al., 2004; Corcoran and Nutt, 2016; Pieper et al., 2013). However, previous studies have shown that HIS mice, made with human HSCs alone or along with autologous thymic tissue, do not have typical lymphoid follicle structures (Blümich et al., 2021; Karpel et al., 2015). Immunohistochemical analysis revealed that the lymph nodes of HIS mice were repopulated by human T cells and B cells, but B cells aggregated loosely and did not form lymphoid follicle structures (Blümich et al., 2021). Furthermore, human T cells were found to aggregate around murine splenic arterioles and form periarteriolar lymphoid sheaths (PALS)-like structures, and B cells arranged around T cells without forming typical lymphoid follicles (Figure 1A) (Blümich et al., 2021; Karpel et al., 2015). In line with these findings, only a small number of CD138$^+$ plasma cells were detected in the spleen of HIS mice (Singh et al., 2012).

This loose aggregation pattern of T and B cells was also observed in FDC-impaired mice (Wang et al., 2011). In normal primary follicles, FDCs maintain a CXCL13 gradient to recruit B cells and organize them into lymphoid follicles (Ansel et al., 2000; Wang et al., 2011). FDCs differentiate from mesenchymal precursor cells (MPCs) with the stimulation from lymphoid tissue inducer (LTi) cells and lymphocytes (Bénézech et al., 2010; Koning and Mebius, 2012) (see below for details). Thus, FDCs could only be of mouse origin in human HSC-transplanted mice, but immunodeficient mice are deficient in FDCs due to the lack of lymphocytes or LTi cells. Furthermore, mouse FDCs were not detected in the HIS mice following human immune reconstitution (Takahashi et al., 2017), indicating a failure of human LTi cells and lymphocytes to stimulate mouse FDC differentiation and/or keep their survival. Thus, lacking FDCs is likely a key factor responsible for the limited lymphoid follicle formation in HIS mice.

The humoral immunity in HIS mice likes extrafollicular B cell responses

Although ample human B cells can be generated in HIS mice, their maturation is blocked, resulting in a high frequency of transitional B cells in lymphoid organs and blood (Biswas et al., 2011; Jangalwe et al., 2016; Watanabe et al., 2009). The absence of typical primary follicles and germinal centers indicates that the humoral immunity observed in HIS mice is likely driven by extrafollicular B cells. The extrafollicular B cell response occurs typically in the early stage of anti-pathogen responses mediated by the rapidly produced short-lived plasma cells (Lam et

https://doi.org/10.1007/s11427-023-2462-8

Table 2. Cross-reactivity of mouse cytokines and chemokines essential for B cell development and function

Mouse protein	Role in B cell development and function	Activity on human
IL-7	Support human LTi cell survival and differentiation (Chappaz et al., 2010; Meier et al., 2007). Promote pro-B cell proliferation, survival, and maturation (Funk et al., 1993).	Yes (Barata et al., 2006)
SCF	Support LTi cell survival and differentiation (Chappaz et al., 2010). Promote pro-B cell proliferation and survival (Funk et al., 1993).	Yes (Xu et al., 1998)
CXCL12	Restricting the entry of self-reactive immature B cells into the periphery (Alves da Costa et al., 2021). Recruit GC B cells to the dark zone (Allen et al., 2004). Control the settlement of human plasma cells (Nakayama et al., 2003).	Yes (Lapidot, 2001; Peled et al., 1999)
BAFF	Support transitional B cell survival (Rowland et al., 2010).	No (Schmidt et al., 2008)
IL-6	Support plasma cell differentiation (Jourdan et al., 2014).	No (Coulie et al., 1989)
IL-15	Support GC B cell proliferation and differentiation (Park et al., 2004).	Three orders of magnitude less effective than human IL-15 (Eisenman et al., 2002)
CXCL13	Recruit CXCR5$^+$ T/B cells to form primary follicle and GC (De Silva and Klein, 2015; King et al., 2008).	Supposed to have no or insufficient cross-reaction (Dai et al., 2021)

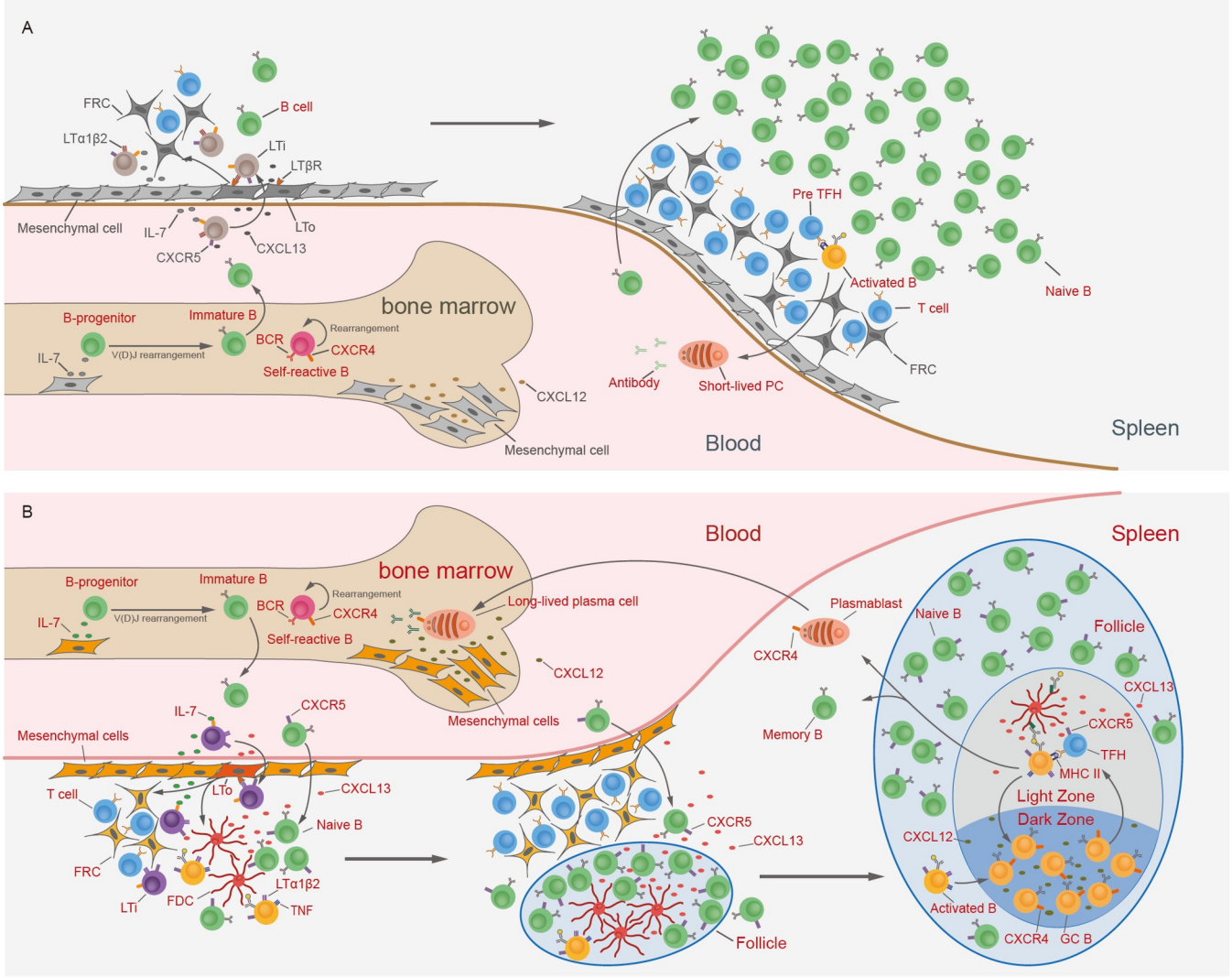

Figure 1. Human B cell development and maturation in HIS mice and humans. A, In LTi-cell repopulated HIS mice, human B cell maturation is blocked at the transitional stage, without primary follicle and GC development. The humoral response in HIS mice resembles the extrafollicular response, characterized by a limited production of class-switched antibodies and short-lived plasma cells. B, In the human body, FDCs differentiate from LTo cells under the stimulation from LTi cells and B cells. FDCs then recruit B cells to form lymphoid follicles by secreting CXCL13. GCs are formed through interactions between antigen-loaded FDCs, activated B cells and TFH cells. The Long-lived plasma cells produced in the GCs migrate to the bone marrow via the CXCL12-CXCR4 axis.

al., 2020). The humoral immune response in HIS mice has similar characteristics to the extrafollicular B cell response with low SHM, low-affinity maturation, and high-frequency autoreactive antibody production (Chang et al., 2012; Jacob and Kelsoe, 1992; MacLennan et al., 2003; McHeyzer-Williams et al., 1993). Previous studies have shown that human follicular helper T (TFH) cells, which are known to play an essential role in extrafollicular B cell responses by providing CD40 and IL-21 stimulatory signals that amplify the responses and induce small amounts of class-switched, low SHM antibody production (Lee et al., 2011; Sweet et al., 2011; Taylor et al., 2012), can develop in HIS mice (Godot et al., 2020; Li et al., 2018; Vecchione et al., 2022). Thus, HIS mice are considered useful in modeling human early anti-pathogen antibody responses.

Autoimmune diseases with excessive inflammatory reactions are often accompanied by disordered extrafollicular B cell responses (Elsner and Shlomchik, 2020). For example, systemic lupus erythematosus (SLE) has a typical extrafollicular B cell response (Jenks et al., 2019; Jenks et al., 2018), and the pathology of SLE is dominated mainly by producing pathogenic B cells and autoantibodies (Jenks et al., 2018; Nakano et al., 2008). Thus, HIS mice may also provide an important model for studying autoimmune diseases. In support of this possibility, the HIS mouse SLE model induced by pristane injection was found to recapitulate the key features of SLE patients, including lupus nephritis, pulmonary serositis, and an increase of human autoantibodies (Gunawan et al., 2017).

Mouse LTi cell repopulation cannot restore mouse FDCs in HIS mice

The IL-2Rγc mutation is a common choice for constructing highly immunodeficient mice. However, IL-2Rγc is a composition of the IL-7 receptor heterodimeric complex (Noguchi et al., 1993), and the absence of the IL-7 receptor signal blocks the development of LTi cells that are essential for generating the secondary lymphoid organ (Huang and Luther, 2012). Two transgenic mouse strains have been developed to restore LTi cell development in IL-2Rγ^{null} mice. In the first model, LTi cell number and lymph node development were restored in NOD/SCID IL-2Rγ^{null} mice by LTi cell-specific expression of IL-2Rγc (Takahashi et al., 2017). However, mouse FDCs were undetectable in the lymph nodes of these mice following human CD34$^+$ cell transplantation, and no improvement in primary follicle or GC formation was detected in these HIS mice (Takahashi et al., 2017). The enlarged lymph nodes observed in these mice are believed to be resulted from the improved development of other lymphoid tissue stromal cells, such as fibroblastic reticular cells (FRCs) that can develop independently of lymphocytes (Balogh et al., 2004). In another model, the development of LTi cells and lymph nodes was restored in Rag2$^{-/-}$IL-2Rγ$^{-/-}$ mice by transgenic overexpression of thymic stromal lymphopoietin (TSLP) that has similar bioactivity with IL-7 in lymphopoiesis (Chappaz and Finke, 2010; Li et al., 2018), and like the model described above, this approach also failed to improve mouse FDC development (Chappaz and Finke, 2010). Although HIS mice made using these mice exhibited improved human humoral immunity, as shown by improved lymph node development, more IgG antibody and mature B cell generation (Li et al., 2018), the SHM frequency in these HIS mice is still much lower than that in humans (Table 1).

As B cells are necessary for the survival and maintenance of FDCs in lymphoid follicles (Fu et al., 1998), we speculate that B cell deficiency is responsible for the absence of mouse FDCs in LTi cell-restored immunodeficient mice (Chappaz and Finke, 2010). In support of this possibility, transplantation of mouse B cells effectively restored mouse FDC networks in SCID mice with normal LTi cells (Yoshida et al., 1995). Although HIS mice have functional B cells, human B cells may not maintain mouse FDCs due to poor or no cross-species reactivity of mouse FDCs to human tumor necrosis factors (TNF) and lymphotoxin (LT) α1β2. Taken together, we propose that mouse LTi cells are unable to restore mouse FDCs in HIS mice.

Mouse FDC reconstitution is unlikely to result in the improved formation of primary follicles or germinal center in HIS mice

The lack of FDCs is a key factor causing incomplete humoral immunity in HIS mice. Although attempts were made to improve secondary lymphoid tissue development in HIS mice by restoring mouse FDCs (Li et al., 2018; Takahashi et al., 2017), this approach may not efficiently solve the problem for the following reasons. First, there is a lack of cross-species reactivity between cytokines and chemokines produced by mouse FDCs on human B cells (Table 2). Specifically, the recruitment of B cells and TFH cells for the formation of primary follicles and germinal centers (GCs) relies on FDC-derived CXCL13 (De Silva and Klein, 2015; King et al., 2008). Although there is no direct evidence demonstrating the lack of cross-reactivity of between mouse CXCL13 and human CXCR5, the low amino acid identity (40%) between mouse and human CXCL13 (Dai et al., 2021) indicates a likelihood of no or insufficient cross-reaction between mouse CXCL13 and human CXCR5. Moreover, in GCs, IL-6, IL-15 and BAFF produced by FDCs are essential in promoting B cell survival, proliferation and differentiation (Jourdan et al., 2014; Park et al., 2004; Rowland et al., 2010; Schmidt et al., 2008). However, none of these cytokines of the mouse is effective on human cells (Coulie et al., 1989; Eisenman et al., 2002; Schmidt et al., 2008).

Second, FDCs trap and retain unprocessed antigens through Fc and complement receptors (Heesters et al., 2016; Roozendaal and Carroll, 2007; van der Poel et al., 2019). Although mouse FDCs may load the immune complexes formed by mouse antibodies and antigens and then present the antigens to human B cells (El Shikh et al., 2009; Fakher et al., 2001), HIS mice do not have mouse antibodies, and there is no evidence that mouse FDCs can trap and retain the immune complexes composed of human antibodies and antigens and then present to human B cells. On the other hand, naive B cells are essential in transporting antigens to FDCs (Heesters et al., 2014). Naive B cells also activate FDCs and promote the development of secondary follicles when transporting immune complexes to FDCs (El Shikh et al., 2006). However, it has not been demonstrated that human B cells can transport immune complexes to mouse FDCs. Thus, mouse FDC reconstitution is unlikely to be an effective approach to improving the formation of primary follicles or GCs in HIS mice.

Human FDC reconstitution has the potential to restore the secondary follicles in HIS mice

In normal lymph organs, the secondary follicles are mainly

https://doi.org/10.1007/s11427-023-2462-8

composed of three types of cells: B cells, FDCs, and TFH cells (De Silva and Klein, 2015). HIS mice have abundant human B cells and functional PD-1$^+$CXCR5$^+$ human TFH cells (Godot et al., 2020; Li et al., 2018; Vecchione et al., 2022). Thus, the lack of secondary follicles in HIS mice is likely due to the absence of human FDCs. Although there is no direct evidence that human FDC reconstruction in HIS mice can restore secondary follicles, previous studies have shown human FDCs can survive in immunodeficient mice (Blades et al., 2002; Chung et al., 2015; Shih et al., 2000). Furthermore, transplantation of human spleen tissues as a source of human FDCs to HIS mice has been shown to be effective in reconstructing secondary follicles in HIS mice that were additionally transplanted with human fetal thymus, bone tissue and CD34$^+$ cells; termed TBS34N mice (Chung et al., 2015). In this model, the human fetal spleen grafts had a prominent lymphoid follicle structure with human FDCs (Chung et al., 2015). Unexpectedly, human FDCs were also detected in mouse spleen (Chung et al., 2015), indicating the existence of migratory FDC progenitors in these HIS mice. Additionally, GC-associated AID$^+$ human B cells and CD71$^+$BR3$^+$ activated human GC B cells were also detected in the mouse spleen, suggesting the development of GCs in these HIS mice (Chung et al., 2015). However, GC functions such as antibody affinity maturation have not been tested (Chung et al., 2015). Given that the serum IgG concentration was still three orders of magnitude less than that in humans (Table 1), GCs in these HIS mice were likely not fully functional. This could be due to the low number of human FDCs or their progenitors transplanted. Thus, transplantation of enriched human FDCs is expected to facilitate the development of primary and secondary follicles in HIS mice (Figure 2).

Human MPC transplantation may possibly be an alternative approach to achieve human humoral immunity in HIS mice. FDCs are derived from MPCs (Bénézech et al., 2010; Koning and Mebius, 2012; Krautler et al., 2012). In response to retinoic acid (RA), the vitamin A metabolite that is highly conserved in vertebrates, MPCs produce CXCL13 (van de Pavert et al., 2009) to recruit CXCR5$^+$ LTi cells, which then provide LTα1β2 to stimulate MPCs to differentiate into lymphoid tissue organizer (LTo) cells (Bénézech et al., 2010; Vondenhoff et al., 2009). With maturation, LTo cells produce more CXCL13 (Cupedo et al., 2004; Yoshida et al., 2002) to recruit activated CXCR5$^+$ B cells, which provide LTα1β2 and TNF to induce LTo cell differentiation into FDCs (Fu et al., 1998; Koning and Mebius, 2012). Human Group 3 innate lymphocytes (ILC3s) include LTi cells (CD56$^-$ NKp44$^-$), NCR$^-$ ILC3 (CD56$^+$NKp44$^-$), and NCR$^+$ ILC3 (CD56$^+$ NKp44$^+$) (Killig et al., 2014; Montaldo et al., 2015). Although there has been no direct evidence demonstrating the presence of LTi cells in HIS mice, HIS mice were reported to develop human ILC3s (Lopez-Lastra et al., 2017; Raykova et al., 2017). Furthermore, SCF and IL-7 are sufficient to induce LTi-cell differentiation from common ILC progenitors *in vitro* (Chappaz et al., 2010; Montaldo et al., 2014), and mouse IL-7 and SCF exhibit cross-species reactivity on human cells (Barata et al., 2006; Manz, 2007; Xu et al., 1998). Furthermore, because all ILC3s are differentiated from the same progenitors (Guia and Narni-Mancinelli, 2020), the development of human LTi cells is likely achievable in HIS mice. These observations support the use of human MPCs to improve the development of primary and secondary follicles (Figure 3), hence humoral immunity. Because MPCs are much easier than FDCs for collection and *in vitro* expansion, MPC transplantation may be more practical.

Concluding remarks

HIS mice hold a sub-functional humoral immune system, as shown by restricted human B cell maturation and production of low-affinity antibodies with limited SHM and CSR (Table 1), and these defects are caused by the lack of primary follicles and GCs. Nonetheless, currently available HIS mouse models have been proven useful in studies on the development and function of human naive B cells and, to a certain extent, antibody responses

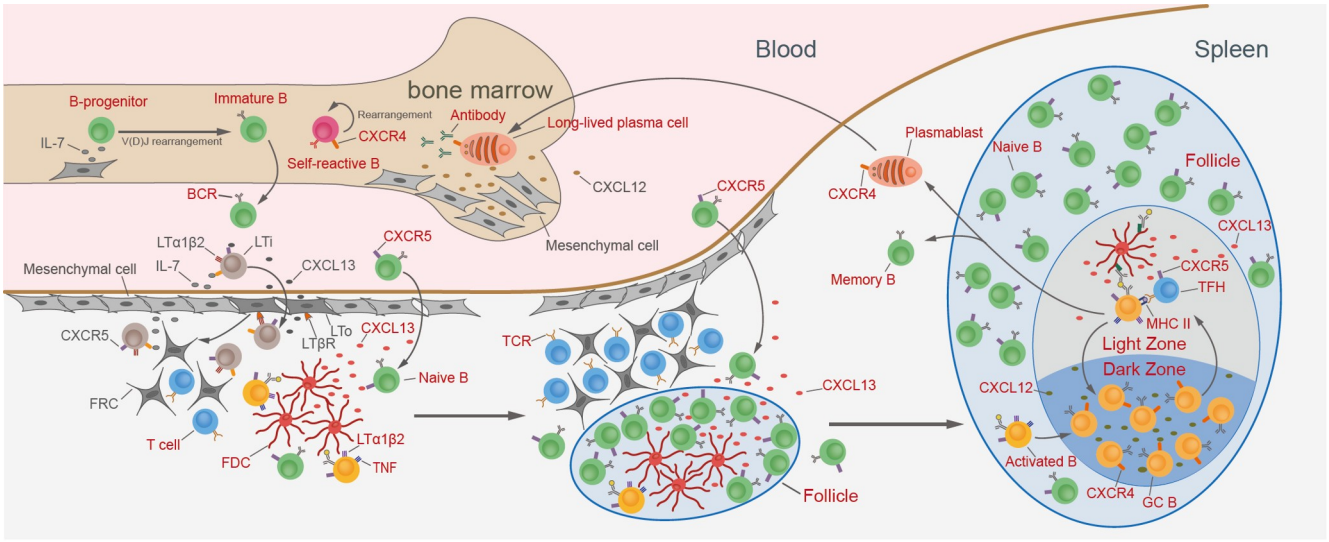

Figure 2. Human FDC transplantation restores human B cell development in LTi-cell repopulated HIS mice. The transplanted human FDCs secrete CXCL13 to recruit human B cells and form primary follicles. Mouse LTo cells secrete CXCL13 to recruit mouse CXCR5$^+$ LTi cells, while membrane-bound LTα1β2 on the mouse LTi cells promote differentiation of mouse LTo cell into FRCs. After antigen stimulation, activated human B cells and human TFH cells migrate into follicles where they form GCs with the assistance of human FDCs. Subsequently, newly generated human long-lived plasma cells are attracted by mouse CXCL12 and home to the bone marrow of mice. Human cell types and proteins are denoted in red while those of mouse origin are indicated in black.

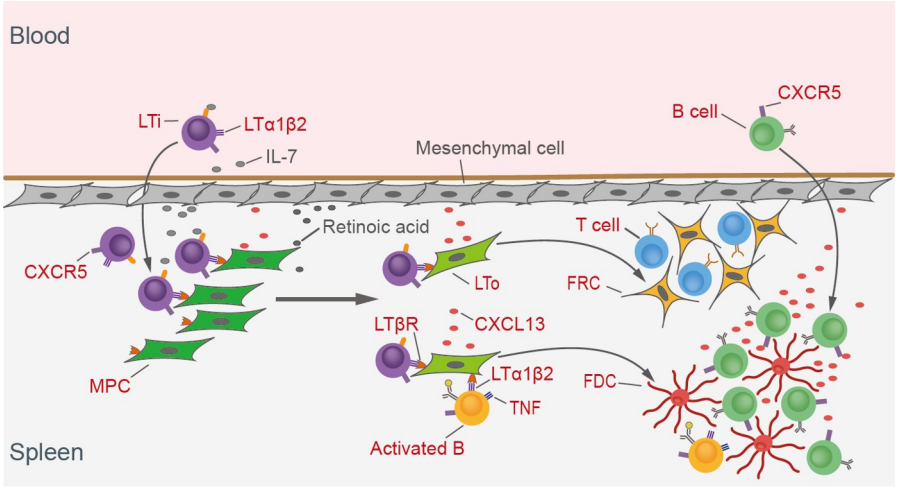

Figure 3. Transplanted human MPCs differentiate into FDCs and FRCs in HIS mice. In response to RA, human MPCs produce CXCL13 to recruit human LTi cells. Mouse mesenchymal cells secrete IL-7 to promote the survival of human LTi cells. Human LTi cells stimulate the differentiation of human MPC into LTo cells or further differentiate into FRCs. With maturation, LTo cells produce more CXCL13 to recruit CXCR5$^+$ B cells that induce LTo cell differentiation into FDCs by providing LTα1β2 and TNF.

under physiological and pathogenic conditions. However, these HIS mice are insufficient for characterizing human B cell SHM or CSR, testing vaccine efficacies, or producing fully-human therapeutic antibodies. Thus, further improvement of the human humoral immunity in HIS mice is highly attractive. Based on previous findings, we propose that the lack of human FDCs is the key factor resulting in the absence of lymphoid follicles and GCs (Figure 1). This possibility is further supported by the fact that transplantation of FDC/PMC-containing human lymphoid (lymph node or spleen) tissues is the most effective approach among previously reported efforts. This approach, however, still fails to significantly increase production of human IgG antibodies, likely due to the low number of FDCs/PMCs in the human lymphoid tissue graft. Thus, transplantation of enriched human FDCs or MPCs may have the potential to substantially improve the human humoral immune system in HIS mice.

Compliance and ethics

The author(s) declare that they have no conflict of interest.

Acknowledgement

This work was supported by the National Key Research and Development Program of China (2021YFA1100700), the National Natural Science Foundation of China (81941008), the Natural Science Foundation of Jilin Province, China (202000201191JC), the Department of Human Resource and Social Security of Jilin Province (2022DJ02), the Science Development of Jilin Province, China (20230505029ZP), and the Bethune Medical Department of Jilin University (2022JBGS01).

References

Akkina, R. (2014). Humanized mice for studying human immune responses and generating human monoclonal antibodies. Microbiol Spectr 2.

Allen, C.D.C., Ansel, K.M., Low, C., Lesley, R., Tamamura, H., Fujii, N., and Cyster, J.G. (2004). Germinal center dark and light zone organization is mediated by CXCR4 and CXCR5. Nat Immunol 5, 943–952.

Allen, T.M., Brehm, M.A., Bridges, S., Ferguson, S., Kumar, P., Mirochnitchenko, O., Palucka, K., Pelanda, R., Sanders-Beer, B., Shultz, L.D., et al. (2019). Humanized immune system mouse models: progress, challenges and opportunities. Nat Immunol 20, 770–774.

Alves da Costa, T., Peterson, J.N., Lang, J., Shulman, J., Liang, X., Freed, B.M., Boackle, S.A., Lauzurica, P., Torres, R.M., and Pelanda, R. (2021). Central human B cell tolerance manifests with a distinctive cell phenotype and is enforced via CXCR4 signaling in hu-mice. Proc Natl Acad Sci USA 118, e2021570118.

Ansel, K.M., Ngo, V.N., Hyman, P.L., Luther, S.A., Förster, R., Sedgwick, J.D., Browning, J.L., Lipp, M., and Cyster, J.G. (2000). A chemokine-driven positive feedback loop organizes lymphoid follicles. Nature 406, 309–314.

Balogh, P., Horváth, G., and Szakal, A.K. (2004). Immunoarchitecture of distinct reticular fibroblastic domains in the white pulp of mouse spleen. J Histochem Cytochem 52, 1287–1298.

Barata, J.T., Silva, A., Abecasis, M., Carlesso, N., Cumano, A., and Cardoso, A.A. (2006). Molecular and functional evidence for activity of murine IL-7 on human lymphocytes. Exp Hematol 34, 1132–1141.

Becker, P.D., Legrand, N., van Geelen, C.M.M., Noerder, M., Huntington, N.D., Lim, A., Yasuda, E., Diehl, S.A., Scheeren, F.A., Ott, M., et al. (2010). Generation of human antigen-specific monoclonal IgM antibodies using vaccinated "human immune system" mice. PLoS ONE 5, e13137.

Bénézech, C., White, A., Mader, E., Serre, K., Parnell, S., Pfeffer, K., Ware, C.F., Anderson, G., and Caamaño, J.H. (2010). Ontogeny of stromal organizer cells during lymph node development. J Immunol 184, 4521–4530.

Biswas, S., Chang, H., Sarkis, P.T.N., Fikrig, E., Zhu, Q., and Marasco, W.A. (2011). Humoral immune responses in humanized BLT mice immunized with West Nile virus and HIV-1 envelope proteins are largely mediated via human CD5$^+$ B cells. Immunology 134, 419–433.

Blades, M.C., Manzo, A., Ingegnoli, F., Taylor, P.R., Panayi, G.S., Irjala, H., Jalkanen, S., Haskard, D.O., Perretti, M., and Pitzalis, C. (2002). Stromal cell-derived factor 1 (CXCL12) induces human cell migration into human lymph nodes transplanted into SCID mice. J Immunol 168, 4308–4317.

Blümich, S., Zdimerova, H., Münz, C., Kipar, A., and Pellegrini, G. (2021). Human CD34$^+$ hematopoietic stem cell-engrafted NSG mice: morphological and immunophenotypic features. Vet Pathol 58, 161–180.

Cantaert, T., Schickel, J.N., Bannock, J.M., Ng, Y.S., Massad, C., Oe, T., Wu, R., Lavoie, A., Walter, J.E., Notarangelo, L.D., et al. (2015). Activation-induced cytidine deaminase expression in human B cell precursors is essential for central B cell tolerance. Immunity 43, 884–895.

Carsetti, R., Rosado, M.M., and Wardmann, H. (2004). Peripheral development of B cells in mouse and man. Immunol Rev 197, 179–191.

Chang, H., Biswas, S., Tallarico, A.S., Sarkis, P.T.N., Geng, S., Panditrao, M.M., Zhu, Q., and Marasco, W.A. (2012). Human B-cell ontogeny in humanized NOD/SCID γcnull mice generates a diverse yet auto/poly- and HIV-1-reactive antibody repertoire. Genes Immun 13, 399–410.

Chappaz, S., and Finke, D. (2010). The IL-7 signaling pathway regulates lymph node development independent of peripheral lymphocytes. J Immunol 184, 3562–3569.

Chappaz, S., Gärtner, C., Rodewald, H.R., and Finke, D. (2010). Kit ligand and IL7 differentially regulate Peyer's Patch and lymph node development. J Immunol 185, 3514–3519.

Chen, J.W., Schickel, J.N., Tsakiris, N., Sng, J., Arbogast, F., Bouis, D., Parisi, D., Gera, R., Boeckers, J.M., Delmotte, F.R., et al. (2022). Positive and negative selection shape the human naive B cell repertoire. J Clin Invest 132, e150985.

Chung, Y.S., Son, J.K., Choi, B., Park, J.B., Chang, J., and Kim, S.J. (2015). Transplantation of human spleen into immunodeficient NOD/SCID IL2Rγ null mice generates humanized mice that improve functional B cell development. Clin Immunol 161, 308–315.

Corcoran, L.M., and Nutt, S.L. (2016). Long-lived plasma cells have a sweet tooth.

Immunity 45, 3–5.
Coulie, P.G., Stevens, M., and Snick, J.V. (1989). High- and low-affinity receptors for murine interleukin 6. Distinct distribution on B and T cells. Eur J Immunol 19, 2107–2114.
Cupedo, T., Lund, F.E., Ngo, V.N., Randall, T.D., Jansen, W., Greuter, M.J., de Waal-Malefyt, R., Kraal, G., Cyster, J.G., and Mebius, R.E. (2004). Initiation of cellular organization in lymph nodes is regulated by non-B cell-derived signals and is not dependent on CXC chemokine ligand 13. J Immunol 173, 4889–4896.
Dai, G., Wanek, A., Eddens, T., Volden, P., and Kolls, J.K. (2021). Toward a humanized mouse model of Pneumocystis pneumonia. JCI Insight 6, e139573.
De Silva, N.S., and Klein, U. (2015). Dynamics of B cells in germinal centres. Nat Rev Immunol 15, 137–148.
Eisenman, J., Ahdieh, M., Beers, C., Brasel, K., Kennedy, M.K., Le, T., Bonnert, T.P., Paxton, R.J., and Park, L.S. (2002). Interleukin-15 interactions with interleukin-15 receptor complexes: characterization and species specificity. Cytokine 20, 121–129.
El Shikh, M., El Sayed, R., Szakal, A., and Tew, J. (2006). Follicular dendritic cell (FDC)-FcγRIIB engagement *via* immune complexes induces the activated FDC phenotype associated with secondary follicle development. Eur J Immunol 36, 2715–2724.
El Shikh, M.E.M., El Sayed, R.M., Szakal, A.K., and Tew, J.G. (2009). T-independent antibody responses to T-dependent antigens: a novel follicular dendritic cell-dependent activity. J Immunol 182, 3482–3491.
Elsner, R.A., and Shlomchik, M.J. (2020). Germinal center and extrafollicular B cell responses in vaccination, immunity, and autoimmunity. Immunity 53, 1136–1150.
Fakher, M., Wu, J., Qin, D., Szakal, A.K., and Tew, J.G. (2001). Follicular dendritic cell accessory activity crosses MHC and species barriers. Eur J Immunol 31, 176–185.
Fecteau, J.F., Côté, G., and Néron, S. (2006). A new memory CD27^{-}IgG^{+} B cell population in peripheral blood expressing V_H genes with low frequency of somatic mutation. J Immunol 177, 3728–3736.
Fu, Y.X., Huang, G., Wang, Y., and Chaplin, D.D. (1998). B lymphocytes induce the formation of follicular dendritic cell clusters in a lymphotoxin α-dependent fashion. J Exp Med 187, 1009–1018.
Funk, P.E., Varas, A., and Witte, P.L. (1993). Activity of stem cell factor and IL-7 in combination on normal bone marrow B lineage cells. J Immunol 150, 748–752.
Godot, V., Tcherakian, C., Gil, L., Cervera-Marzal, I., Li, G., Cheng, L., Ortonne, N., Lelievre, J.D., Pantaleo, G., Fenwick, C., et al. (2020). TLR-9 agonist and CD40-targeting vaccination induces HIV-1 envelope-specific B cells with a diversified immunoglobulin repertoire in humanized mice. PLoS Pathog 16, e1009025.
Gonzalez-Quintela, A., Alende, R., Gude, F., Campos, J., Rey, J., Meijide, L.M., Fernandez-Merino, C., and Vidal, C. (2008). Serum levels of immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship with alcohol consumption, smoking and common metabolic abnormalities. Clin Exp Immunol 151, 42–50.
Guia, S., and Narni-Mancinelli, E. (2020). Helper-like innate lymphoid cells in humans and mice. Trends Immunol 41, 436–452.
Gunawan, M., Her, Z., Liu, M., Tan, S.Y., Chan, X.Y., Tan, W.W.S., Dharmaraaja, S., Fan, Y., Ong, C.B., Loh, E., et al. (2017). A novel human systemic lupus erythematosus model in humanised mice. Sci Rep 7, 16642.
Habiro, K., Sykes, M., and Yang, Y.G. (2009). Induction of human T-cell tolerance to pig xenoantigens via thymus transplantation in mice with an established human immune system. Am J Transplant 9, 1324–1329.
Heesters, B.A., Myers, R.C., and Carroll, M.C. (2014). Follicular dendritic cells: dynamic antigen libraries. Nat Rev Immunol 14, 495–504.
Heesters, B.A., van der Poel, C.E., Das, A., and Carroll, M.C. (2016). Antigen presentation to B cells. Trends Immunol 37, 844–854.
Herndler-Brandstetter, D., Shan, L., Yao, Y., Stecher, C., Plajer, V., Lietzenmayer, M., Strowig, T., de Zoete, M.R., Palm, N.W., Chen, J., et al. (2017). Humanized mouse model supports development, function, and tissue residency of human natural killer cells. Proc Natl Acad Sci USA 114, E9626–E9634.
Huang, H.Y., and Luther, S.A. (2012). Expression and function of interleukin-7 in secondary and tertiary lymphoid organs. Semin Immunol 24, 175–189.
Huntington, N.D., Legrand, N., Alves, N.L., Jaron, B., Weijer, K., Plet, A., Corcuff, E., Mortier, E., Jacques, Y., Spits, H., et al. (2009). IL-15 trans-presentation promotes human NK cell development and differentiation *in vivo*. J Exp Med 206, 25–34.
Ippolito, G.C., Hoi, K.H., Reddy, S.T., Carroll, S.M., Ge, X., Rogosch, T., Zemlin, M., Shultz, L.D., Ellington, A.D., VanDenBerg, C.L., et al. (2012). Antibody repertoires in humanized NOD-scid-IL2Rγnull mice and human B cells reveals human-like diversification and tolerance checkpoints in the mouse. PLoS ONE 7, e35497.
Ishikawa, F., Yasukawa, M., Lyons, B., Yoshida, S., Miyamoto, T., Yoshimoto, G., Watanabe, T., Akashi, K., Shultz, L.D., and Harada, M. (2005). Development of functional human blood and immune systems in NOD/SCID/IL2 receptor γ chainnull mice. Blood 106, 1565–1573.
Jacob, J., and Kelsoe, G. (1992). In situ studies of the primary immune response to (4-hydroxy-3-nitrophenyl)acetyl. II. A common clonal origin for periarteriolar lymphoid sheath-associated foci and germinal centers. J Exp Med 176, 679–687.
Jangalwe, S., Shultz, L.D., Mathew, A., and Brehm, M.A. (2016). Improved B cell development in humanized NOD *-scid IL2Rγ^{null}* mice transgenically expressing human stem cell factor, granulocyte-macrophage colony-stimulating factor and interleukin-3. Immun Inflam Dis 4, 427–440.
Jenks, S.A., Cashman, K.S., Woodruff, M.C., Lee, F.E., and Sanz, I. (2019). Extrafollicular responses in humans and SLE. Immunol Rev 288, 136–148.
Jenks, S.A., Cashman, K.S., Zumaquero, E., Marigorta, U.M., Patel, A.V., Wang, X., Tomar, D., Woodruff, M.C., Simon, Z., Bugrovsky, R., et al. (2018). Distinct effector B cells induced by unregulated Toll-like receptor 7 contribute to pathogenic responses in systemic lupus erythematosus. Immunity 49, 725–739.e6.
Jourdan, M., Cren, M., Robert, N., Bolloré, K., Fest, T., Duperray, C., Guilloton, F., Hose, D., Tarte, K., and Klein, B. (2014). IL-6 supports the generation of human long-lived plasma cells in combination with either APRIL or stromal cell-soluble factors. Leukemia 28, 1647–1656.
Karpel, M.E., Boutwell, C.L., and Allen, T.M. (2015). BLT humanized mice as a small animal model of HIV infection. Curr Opin Virol 13, 75–80.
Killig, M., Glatzer, T., and Romagnani, C. (2014). Recognition strategies of group 3 innate lymphoid cells. Front Immunol 5, 142.
King, C., Tangye, S.G., and Mackay, C.R. (2008). T follicular helper (T_{FH}) cells in normal and dysregulated immune responses. Annu Rev Immunol 26, 741–766.
Kitsera, M., Brunetti, J.E., and Rodríguez, E. (2023). Recent developments in NSG and NRG humanized mouse models for their use in viral and immune research. Viruses 15, 478.
Koning, J.J., and Mebius, R.E. (2012). Interdependence of stromal and immune cells for lymph node function. Trends Immunol 33, 264–270.
Krautler, N.J., Kana, V., Kranich, J., Tian, Y., Perera, D., Lemm, D., Schwarz, P., Armulik, A., Browning, J.L., Tallquist, M., et al. (2012). Follicular dendritic cells emerge from ubiquitous perivascular precursors. Cell 150, 194–206.
Lam, J.H., Smith, F.L., and Baumgarth, N. (2020). B cell activation and response regulation during viral infections. Viral Immunol 33, 294–306.
Lan, P., Tonomura, N., Shimizu, A., Wang, S., and Yang, Y.G. (2006). Reconstitution of a functional human immune system in immunodeficient mice through combined human fetal thymus/liver and CD34^{+} cell transplantation. Blood 108, 487–492.
Lan, P., Wang, L., Diouf, B., Eguchi, H., Su, H., Bronson, R., Sachs, D.H., Sykes, M., and Yang, Y.G. (2004). Induction of human T-cell tolerance to porcine xenoantigens through mixed hematopoietic chimerism. Blood 103, 3964–3969.
Lang, J., Ota, T., Kelly, M., Strauch, P., Freed, B.M., Torres, R.M., Nemazee, D., and Pelanda, R. (2016). Receptor editing and genetic variability in human autoreactive B cells. J Exp Med 213, 93–108.
Lapidot, T. (2001). Mechanism of human stem cell migration and repopulation of NOD/SCID and B2mnull NOD/SCID mice. Ann New York Acad Sci 938, 83–95.
Lee, S.K., Rigby, R.J., Zotos, D., Tsai, L.M., Kawamoto, S., Marshall, J.L., Ramiscal, R. R., Chan, T.D., Gatto, D., Brink, R., et al. (2011). B cell priming for extrafollicular antibody responses requires Bcl-6 expression by T cells. J Exp Med 208, 1377–1388.
Li, Y., Masse-Ranson, G., Garcia, Z., Bruel, T., Kök, A., Strick-Marchand, H., Jouvion, G., Serafini, N., Lim, A.I., Dusseaux, M., et al. (2018). A human immune system mouse model with robust lymph node development. Nat Methods 15, 623–630.
Lopez-Lastra, S., Masse-Ranson, G., Fiquet, O., Darche, S., Serafini, N., Li, Y., Dusséaux, M., Strick-Marchand, H., and Di Santo, J.P. (2017). A functional DC cross talk promotes human ILC homeostasis in humanized mice. Blood Adv 1, 601–614.
MacLennan, I.C.M., Toellner, K., Cunningham, A.F., Serre, K., Sze, D.M., Zúñiga, E., Cook, M.C., and Vinuesa, C.G. (2003). Extrafollicular antibody responses. Immunol Rev 194, 8–18.
Manz, M.G. (2007). Human-hemato-lymphoid-system mice: opportunities and challenges. Immunity 26, 537–541.
Manz, M.G., and Di Santo, J.P. (2009). Renaissance for mouse models of human hematopoiesis and immunobiology. Nat Immunol 10, 1039–1042.
Martinez-Torres, F., Nochi, T., Wahl, A., Garcia, J.V., and Denton, P.W. (2014). Hypogammaglobulinemia in BLT humanized mice—an animal model of primary antibody deficiency. PLoS ONE 9, e108663.
McHeyzer-Williams, M.G., McLean, M.J., Lalor, P.A., and Nossal, G.J. (1993). Antigen-driven B cell differentiation *in vivo*. J Exp Med 178, 295–307.
Meier, D., Bornmann, C., Chappaz, S., Schmutz, S., Otten, L.A., Ceredig, R., Acha-Orbea, H., and Finke, D. (2007). Ectopic lymphoid-organ development occurs through interleukin 7-mediated enhanced survival of lymphoid-tissue-inducer cells. Immunity 26, 643–654.
Melkus, M.W., Estes, J.D., Padgett-Thomas, A., Gatlin, J., Denton, P.W., Othieno, F.A., Wege, A.K., Haase, A.T., and Garcia, J.V. (2006). Humanized mice mount specific adaptive and innate immune responses to EBV and TSST-1. Nat Med 12, 1316–1322.

Montaldo, E., Juelke, K., and Romagnani, C. (2015). Group 3 innate lymphoid cells (ILC3s): origin, differentiation, and plasticity in humans and mice. Eur J Immunol 45, 2171–2182.
Montaldo, E., Teixeira-Alves, L.G., Glatzer, T., Durek, P., Stervbo, U., Hamann, W., Babic, M., Paclik, D., Stölzel, K., Gröne, J., et al. (2014). Human RORγt^{+}CD34^{+} cells are lineage-specified progenitors of group 3 RORγt^{+} innate lymphoid cells. Immunity 41, 988–1000.
Mosier, D.E., Gulizia, R.J., Baird, S.M., and Wilson, D.B. (1988). Transfer of a functional human immune system to mice with severe combined immunodeficiency. Nature 335, 256–259.
Nakano, S., Morimoto, S., Suzuki, J., Nozawa, K., Amano, H., Tokano, Y., and Takasaki, Y. (2008). Role of pathogenic auto-antibody production by Toll-like receptor 9 of B cells in active systemic lupus erythematosus. Rheumatology 47, 145–149.
Nakayama, T., Hieshima, K., Izawa, D., Tatsumi, Y., Kanamaru, A., and Yoshie, O. (2003). Cutting edge: profile of chemokine receptor expression on human plasma cells accounts for their efficient recruitment to target tissues. J Immunol 170, 1136–1140.
Noguchi, M., Nakamura, Y., Russell, S.M., Ziegler, S.F., Tsang, M., Cao, X., and Leonard, W.J. (1993). Interleukin-2 receptor γ chain: a functional component of the interleukin-7 receptor. Science 262, 1877–1880.
Park, C.S., Yoon, S.O., Armitage, R.J., and Choi, Y.S. (2004). Follicular dendritic cells produce IL-15 that enhances germinal center B cell proliferation in membrane-bound form. J Immunol 173, 6676–6683.
Peled, A., Petit, I., Kollet, O., Magid, M., Ponomaryov, T., Byk, T., Nagler, A., Ben-Hur, H., Many, A., Shultz, L., et al. (1999). Dependence of human stem cell engraftment and repopulation of NOD/SCID mice on CXCR4. Science 283, 845–848.
Pieper, K., Grimbacher, B., and Eibel, H. (2013). B-cell biology and development. J Allergy Clin Immunol 131, 959–971.
Raykova, A., Carrega, P., Lehmann, F.M., Ivanek, R., Landtwing, V., Quast, I., Lünemann, J.D., Finke, D., Ferlazzo, G., Chijioke, O., et al. (2017). Interleukins 12 and 15 induce cytotoxicity and early NK-cell differentiation in type 3 innate lymphoid cells. Blood Adv 1, 2679–2691.
Rongvaux, A., Takizawa, H., Strowig, T., Willinger, T., Eynon, E.E., Flavell, R.A., and Manz, M.G. (2013). Human hemato-lymphoid system mice: current use and future potential for medicine. Annu Rev Immunol 31, 635–674.
Roozendaal, R., and Carroll, M.C. (2007). Complement receptors CD21 and CD35 in humoral immunity. Immunol Rev 219, 157–166.
Rowland, S.L., Leahy, K.F., Halverson, R., Torres, R.M., and Pelanda, R. (2010). BAFF receptor signaling aids the differentiation of immature B cells into transitional B cells following tonic BCR signaling. J Immunol 185, 4570–4581.
Schickel, J.N., Kuhny, M., Baldo, A., Bannock, J.M., Massad, C., Wang, H., Katz, N., Oe, T., Menard, L., Soulas-Sprauel, P., et al. (2016). PTPN22 inhibition resets defective human central B cell tolerance. Sci Immunol 1.
Schmidt, M.R., Appel, M.C., Giassi, L.J., Greiner, D.L., Shultz, L.D., and Woodland, R.T. (2008). Human BLyS facilitates engraftment of human PBL derived B cells in immunodeficient mice. PLoS ONE 3, e3192.
Sefik, E., Qu, R., Junqueira, C., Kaffe, E., Mirza, H., Zhao, J., Brewer, J.R., Han, A., Steach, H.R., Israelow, B., et al. (2022). Inflammasome activation in infected macrophages drives COVID-19 pathology. Nature 606, 585–593.
Seung, E., and Tager, A.M. (2013). Humoral immunity in humanized mice: a work in progress. J Infect Dis 208, S155–S159.
Shih, C.C., Hu, J., Arber, D., LeBon, T., and Forman, S.J. (2000). Transplantation and growth characteristics of human fetal lymph node in immunodeficient mice. Exp Hematol 28, 1046–1053.
Singh, M., Singh, P., Gaudray, G., Musumeci, L., Thielen, C., Vaira, D., Vandergeeten, C., Delacroix, L., Van Gulck, E., Vanham, G., et al. (2012). An improved protocol for efficient engraftment in NOD/LTSZ-SCIDIL-2RγNULL mice allows HIV replication and development of anti-HIV immune responses. PLoS ONE 7, e38491.
Stripecke, R., Münz, C., Schuringa, J.J., Bissig, K., Soper, B., Meeham, T., Yao, L., Di Santo, J.P., Brehm, M., Rodriguez, E., et al. (2020). Innovations, challenges, and minimal information for standardization of humanized mice. EMBO Mol Med 12, e8662.
Sun, L., Jin, C.H., Tan, S., Liu, W., and Yang, Y.G. (2020). Human immune system mice with autologous tumor for modeling cancer immunotherapies. Front Immunol 11, 591669.
Sweet, R.A., Ols, M.L., Cullen, J.L., Milam, A.V., Yagita, H., and Shlomchik, M.J. (2011). Facultative role for T cells in extrafollicular Toll-like receptor-dependent autoreactive B-cell responses *in vivo*. Proc Natl Acad Sci USA 108, 7932–7937.
Takahashi, T., Katano, I., Ito, R., Goto, M., Abe, H., Mizuno, S., Kawai, K., Sugiyama, F., and Ito, M. (2017). Enhanced antibody responses in a novel NOG transgenic mouse with restored lymph node organogenesis. Front Immunol 8, 2017.
Tan, S., Li, Y., Xia, J., Jin, C.H., Hu, Z., Duinkerken, G., Li, Y., Khosravi Maharlooei, M., Chavez, E., Nauman, G., et al. (2017). Type 1 diabetes induction in humanized mice. Proc Natl Acad Sci USA 114, 10954–10959.
Taylor, J.J., Pape, K.A., and Jenkins, M.K. (2012). A germinal center-independent pathway generates unswitched memory B cells early in the primary response. J Exp Med 209, 597–606.
Tonomura, N., Habiro, K., Shimizu, A., Sykes, M., and Yang, Y.G. (2008). Antigen-specific human T-cell responses and T cell-dependent production of human antibodies in a humanized mouse model. Blood 111, 4293–4296.
Traggiai, E., Chicha, L., Mazzucchelli, L., Bronz, L., Piffaretti, J.C., Lanzavecchia, A., and Manz, M.G. (2004). Development of a human adaptive immune system in cord blood cell-transplanted mice. Science 304, 104–107.
van de Pavert, S.A., Olivier, B.J., Goverse, G., Vondenhoff, M.F., Greuter, M., Beke, P., Kusser, K., Höpken, U.E., Lipp, M., Niederreither, K., et al. (2009). Chemokine CXCL13 is essential for lymph node initiation and is induced by retinoic acid and neuronal stimulation. Nat Immunol 10, 1193–1199.
van der Poel, C.E., Bajic, G., Macaulay, C.W., van den Broek, T., Ellson, C.D., Bouma, G., Victora, G.D., Degn, S.E., and Carroll, M.C. (2019). Follicular dendritic cells modulate germinal center B cell diversity through FcγRIIB. Cell Rep 29, 2745–2755.e4.
Vecchione, A., Madley, R., Danzl, N., Borsotti, C., Marharlooei, M.K., Li, H.W., Nauman, G., Ding, X., Ho, S.H., Fousteri, G., et al. (2022). T1D patient-derived hematopoietic stem cells are programmed to generate Tph, Tfh, and autoimmunity-associated B cell subsets in human immune system mice. Clin Immunol 240, 109048.
Villaudy, J., Schotte, R., Legrand, N., and Spits, H. (2014). Critical assessment of human antibody generation in humanized mouse models. J Immunol Methods 410, 18–27.
Vondenhoff, M.F., Greuter, M., Goverse, G., Elewaut, D., Dewint, P., Ware, C.F., Hoorweg, K., Kraal, G., and Mebius, R.E. (2009). LTβR signaling induces cytokine expression and up-regulates lymphangiogenic factors in lymph node anlagen. J Immunol 182, 5439–5445.
Wahl, A., De, C., Abad Fernandez, M., Lenarcic, E.M., Xu, Y., Cockrell, A.S., Cleary, R. A., Johnson, C.E., Schramm, N.J., Rank, L.M., et al. (2019). Precision mouse models with expanded tropism for human pathogens. Nat Biotechnol 37, 1163–1173.
Walsh, N.C., Kenney, L.L., Jangalwe, S., Aryee, K.E., Greiner, D.L., Brehm, M.A., and Shultz, L.D. (2017). Humanized mouse models of clinical disease. Annu Rev Pathol Mech Dis 12, 187–215.
Waltari, E., Jia, M., Jiang, C.S., Lu, H., Huang, J., Fernandez, C., Finzi, A., Kaufmann, D.E., Markowitz, M., Tsuji, M., et al. (2018). 5′ rapid amplification of cDNA ends and illumina MiSeq reveals B cell receptor features in healthy adults, adults with chronic HIV-1 infection, cord blood, and humanized mice. Front Immunol 9, 628.
Wang, X., Cho, B., Suzuki, K., Xu, Y., Green, J.A., An, J., and Cyster, J.G. (2011). Follicular dendritic cells help establish follicle identity and promote B cell retention in germinal centers. J Exp Med 208, 2497–2510.
Wang, Y., Wang, L., Fu, C., Wang, X., Zuo, S., Shu, C., Shan, Y., He, J., Zhou, Q., Li, W., et al. (2022). Exploration of human lung-resident immunity and response to respiratory viral immunization in a humanized mouse model. J Immunol 208, 420–428.
Watanabe, Y., Takahashi, T., Okajima, A., Shiokawa, M., Ishii, N., Katano, I., Ito, R., Ito, M., Minegishi, M., Minegishi, N., et al. (2009). The analysis of the functions of human B and T cells in humanized NOD/shi-scid/γcnull (NOG) mice (hu-HSC NOG mice). Int Immunol 21, 843–858.
Xu, M., Tsuji, K., Ueda, T., Mukouyama, Y., Hara, T., Yang, F.C., Ebihara, Y., Matsuoka, S., Manabe, A., Kikuchi, A., et al. (1998). Stimulation of mouse and human primitive hematopoiesis by murine embryonic aorta-gonad-mesonephros-derived stromal cell lines. Blood 92, 2032–2040.
Yoshida, H., Naito, A., Inoue, J.I., Satoh, M., Santee-Cooper, S.M., Ware, C.F., Togawa, A., Nishikawa, S., and Nishikawa, S.I. (2002). Different cytokines induce surface lymphotoxin-αβ on IL-7 receptor-α cells that differentially engender lymph nodes and Peyer's patches. Immunity 17, 823–833.
Yoshida, K., Kaji, M., Takahashi, T., van den Berg, T.K., and Dijkstra, C.D. (1995). Host origin of follicular dendritic cells induced in the spleen of SCID mice after transfer of allogeneic lymphocytes. Immunology 84, 117–126.
Yu, H., Borsotti, C., Schickel, J.N., Zhu, S., Strowig, T., Eynon, E.E., Frleta, D., Gurer, C., Murphy, A.J., Yancopoulos, G.D., et al. (2017). A novel humanized mouse model with significant improvement of class-switched, antigen-specific antibody production. Blood 129, 959–969.