ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.248
Asthma Allergy Immunol 2023;21:82-88

REVIEW

Received: 11.04.2023 • Accepted: 08.05.2023
Online Published: 21.06.2023

Thymic Development, Inborn Errors of Immunity with Thymic Dysfunction and Thymic Transplantation

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ABSTRACT

The thymus is an organ that plays a critical role in the production of T-cells, which are important for immune functions. Serious consequences can arise if thymic homeostasis is not properly regulated. Therefore, it is necessary to fully understand the thymic environment that induces and supports T-cell development. The most severe thymic defects causing thymic aplasia, as well as disorders affecting the development and function of thymic stromal cells, result in immunodeficiency and autoimmunity. Thymic transplantation can save the lives of athymic patients with severe T-cell lymphopenia and provide the necessary immune reconstitution to prevent infectious complications. Early diagnosis and prophylactic treatments will reduce the frequency of infections in affected individuals as the use of neonatal screening programs for T-cell deficiencies becomes more widespread.

Keywords: Thymus, Di George Syndrome, FOXN1, PAX1, cultured thymic tissue transplantation

THYMIC DEVELOPMENT

Pharyngeal arches are essential for head and neck development in humans. The internal part of the pharyngeal arches contains endoderm, while the external part contains ectoderm. Each arch has tissues originating from the mesoderm and neural crest. The thymus and parathyroid glands develop from the endoderm of the third pharyngeal pouch. The thymus is the necessary organ for T-cell development (1, 2). Many genes regulate the formation and pattern of pharyngeal arches as well as the development of the thymus. During the very early phase, various transcription factors such as HOXA3, PAX1, PAX9, EYA1, SIX1, and TBX1 are involved and after this phase, the thymus and parathyroid continue to develop as two different organs. FOXN1 is required for thymic development and especially for the development of cortical TEC (cTEC) and medullary TEC (mTEC) from thymic epithelial cell (TEC) precursors. GCM2 is responsible for parathyroid development (3).

The thymus contains many cell types, including stromal cells and immune cells, which are important for both T-cell development and thymic homeostasis. During the 7-8th embryonic weeks, early thymus-seeding precursors originate initially from the aorta-gonad-mesonephros region and later from the fetal liver and bone marrow (4). During T-cell development, early thymic precursors (ETPs) from the bone marrow migrate to the thymus and receive Notch signals from cTECs, leading to T-lineage differentiation. Bone marrow-derived ETPs migrate through the corticomedullary junction and are located in the outer cortex. ETPs are important for the development of the cortical microenvironment. These early progenitor cells are CD4 and CD8 negative (double-negative). Their TCRs have not yet undergone V(D)J recombination. After this double negative cell stage, cells progress to the double-positive (DP) stage. The cells that generate gamma-delta TCRs become γδ T-cells. However, most of the cells become double-positive after generating TCR alpha gene loci and are later presented with self-antigens by cTECs with MHC complexes. Appropriate TCR-MHC interaction allows for the transition of αβ T-cells to other developmental stages. 95% of DP cells die because they do not provide appropriate MHC interaction. After positive

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selection, DP cells pass towards the thymic medulla. In the thymic medulla, mTECs present self-antigens through MHC molecules. Negative selection occurs when there is a strong TCR-MHC interaction and it provides self-tolerance. While there is a substantial amount of cell death every day during the selection of many self-antigens in mTECs under the regulation of the autoimmune regulator gene (AIRE), other cell types in the thymus maintain thymus homeostasis (3).

Positive selection occurs in the thymic cortex by the interaction of TCR of DP thymocytes and MHC of cTEC. Nonreactive cells are removed. The cortex experiences the first wave of negative selection, which eliminates autoreactive T-cells. The remaining T-cells differentiate into single positive cells that migrate to the medulla. In the thymic medulla, single positive TCRαβ-expressing cells and MHC of mTEC interaction occurs, and autoreactive cells are eliminated as indicated above. T-cells with receptors that recognize self-tissue restricted antigens (TRA) will either be deleted or develop down the pathway of regulatory T-cells (Tregs) (5, 6). Only 3-5% of developing thymocytes become mature CD4+ or CD8+T-cells and leave the thymus for effector functions in the periphery (7).

This two-stage selection is repeated every day in the thymus. Aging of the thymus, radiation, and inflammatory stress cause thymus damage and reduce the thymic functions.

CELLS IN THE THYMUS

Thymocytes are the main cellular component of the thymus. Other cells in the thymus include dendritic cells, macrophages, B cells, and NK cells (8). Thymic epithelial cells (TECs), cTECs in the cortex, and mTECs in the medulla form the stromal component of the thymus that express AIRE. Other stromal cells include mesenchymal and endothelial cells (9).

Thymic Dendritic Cells (DCs)

Thymic DCs make up 0.5% of the cells in the thymus and are located in the thymic medulla. They are important in negative selection. There are three different groups of dendritic cells: plasmacytoid dendritic cells (pDCs), CD8+ signal regulatory protein α (SIRPα)-DCs, and CD8-SIRPα+ DCs. pDCs and SIRPα+ DCs are migratory cells originating from the bone marrow that migrate from the periphery to the thymus and have antigen-carrying capacity from the periphery to the thymus. It is unknown which kind of thymic DC carries a particular antigen. SIRPα+ DCs are located in the corticomedullary perivascular space, CD8+ DCs in the medulla, and pDCs in the corticomedullary junction (9).

Thymic DCs express high levels of MHC class I and II molecules and play a role in central tolerance and clonal deletion. Studies in mice have shown that SIRPα+ DCs are important in Treg development by carrying antigens from the blood. In recent years, a new CD14+ SIRPα+ monocyte DC (moDC) subgroup has been found to have important functions in Treg development in the thymus. Induction of the TLR9/MyD88 pathway in mTECs leads to the synthesis and secretion of chemokines that promote the accumulation of moDCs in the thymus (9).

Thymic Macrophages

Cells that fail positive or negative selection during T-cell development die by apoptosis, accounting for 95% of the daily turnover of thymic cells. Thymic macrophages are responsible for the clearance of these dead cells.

With the advent of single-cell RNA sequencing technology, it has become possible to subtype thymic macrophages. Two MQ subtypes have been identified; Timd4+ macrophages are located in the cortex and are involved in the efferocytosis of apoptotic thymocytes, while CX3CR1+ macrophages are located in the corticomedullary junction and are involved in T-cell negative selection (9).

Mesenchymal Cells

Mesenchymal cells include fibroblasts and pericytes. They are located in the thymic capsule and septa. They are neural crest-derived cells and are involved in the early stages of thymic organogenesis. They regulate lymphocyte trafficking and have a role in the growth and survival of TECs (9).

Thymic Endothelial Cells

Thymic endothelial cells are the vascular cells in the thymus and they are located in the perivascular space at the corticomedullary junction. They are important in the homing of ETPs (9).

THYMIC APLASIA and HYPOPLASIA

Thymic aplasia and hypoplasia can occur as a result of intrinsic disorders in the development and/or function of thymic stromal cells or diseases that impair or have a negative effect on thymocyte formation or maturation. In addition, non-genetic factors such as maternal diabetes,

prenatal exposure to alcohol, and retinoic acid can also cause thymic defects (10, 11).

The diseases and conditions that cause a thymic defect are summarized in Table I.

Table I: Thymic disorders.

Gene	Inheritance	Pathogenic effect	Non-immunological features
Diseases Affecting Thymic Organogenesis			
TBX1	AD	Formation of pharyngeal arch artery and pharyngeal segmentation Potential impact on how the parathyroid develops	22q11.2 deletion syndrome: Developmental delay, ear anomalies, hearing loss, velopalatal insufficiency and cleft lip and/or palate Di George Syndrome: congenital heart defects, hypoparathyroidism
TBX2	AD	Unknown	DGS like findings
CHD7 (CHARGE Syndrome)	AD	Formation of pharyngeal arch artery and sac formation, development of TEC	Coloboma of eye, cardiac defects, choanal atresia, growth and/or developmental delay, genital anomalies and ear anomalies and/or hearing loss
Chromosome 10p deletion	AD		Cardiac defects hypoparathyroidism/hypocalcemia, facial dysmorphism, growth and developmental delay, hearing loss, genitourinary anomalies
FOXI3, Chromosome 2p11.2 microdeletion	AD	Pharyngeal segmentation	DGS like findings
Diseases Affecting the Development of TEC			
FOXN1	AR, biallelic	Development, differentiation and maintenance of TECs during the embryonic period and postnatally	Congenital alopecia, nail dystrophy, athymia
FOXN1	AD	Development, differentiation and maintenance of TECs during the embryonic period and postnatally	Nail dystrophy, recurrent respiratory tract infections, atopic dermatitis
PAX1	AR biallelic LOF	Expressed in the pharyngeal sacs and TECs in the early period. Offers a favorable setting for T cell maturation.	Facial dysmorphism, ear anomalies, hearing loss, branchial cysts and fistulas, shoulder girdle anomalies and mild intellectual disability
EXTL3	AR	Development of hematopoietic precursors and thymic stromal cells development	Skeletal dysplasia, neurodevelopmental delay
Diseases Affecting TEC Function, Lymphostromal Crosstalk			
AIRE	AR or AD		Chronic mucocutaneous candidiasis, alopecia, enteropathy, dental enamel hypoplasia, multiple autoimmunity
RAG1, RAG2	AR	AIRE dysfunction and signaling	Severe combined or combined immunodeficiency
PRKDC	AR	AIRE dysfunction and signaling	Severe combined or combined immunodeficiency
NFKB2	AD	Impaired AIRE signaling	Recurrent sinopulmonary infections, alopecia, endocrine features
TTC7A	AR	Thymic stromal cell dysfunction	Immunodeficiency, intestinal atresia, severe enteropathy
Non-genetic Causes of Thymic Hypoplasia			
-Maternal diabetes -Intrauterine exposure to retinoic acid -Fetal alcohol syndrome			

1. Diseases Affecting Thymic Organogenesis

a. Di George Syndrome (DGS)

The most common defect that affects stromal cell development is Di George syndrome. The disease has a wide range of clinical symptoms. Approximately half of the patients have congenital heart disease, which is the most common cause of death. The thymus is either aplastic or hypoplastic. About half of the patients have hypocalcemia due to hypoparathyroidism. There are also dysmorphic features on the face, such as hypertelorism, low-set ears, a fish-like mouth, velopharyngeal insufficiency, a cleft palate, and a bifid uvula. With advancing age, the risk for growth retardation, kidney disease, autoimmunity, atopy, psychiatric problems, and malignancy increases.

The degree of immunodeficiency seen in Di George syndrome varies. Only 0.5% of patients have a complete absence of the thymus resulting in severe combined immunodeficiency (12, 13).

The prevalence of the 22q11.21 microdeletion is estimated to be between 1/3000 and 1/6000, and it is the most common chromosomal microdeletion syndrome (14). 90% of patients have a heterozygous 22q11.2 deletion. In 90% of the deletions, a 3 mb deletion is observed, affecting 100 genes; in 10%, there is a 1.5 mb deletion, affecting 50 genes. In both deletions, the T-box family of the TF (TBX1) gene is affected. There is no correlation between the size of the deletion and the phenotype. Pathological examination of the thymus in the patients has shown a smaller thymus with a less pronounced medullary compartment.

AIRE expression is reduced in the medulla, resulting in a defect in the negative selection of self-reactive T-cells. The thymic output decreases. TREC, naive T-cells, RTE, and Treg cells are low.

The TBX gene is important in thymic organogenesis. Pathogenic variants inherited in an autosomal dominant manner in the TBX1 or TBX2 gene constitute a small portion of DGS cases. TBX1 controls the expression of 2000 genes through epigenetic modifications. TBX2 forms a regulatory network with TBX1 and TBX3 (4). The autosomal dominant TBX2 variant is associated with syndromic cardiovascular and developmental skeletal disorders and thymic hypoplasia.

b. Chromosome 10p deletion

It causes symptoms similar to Di George syndrome. The thymus is hypoplastic. The condition may be accompanied by heart defects, hypoparathyroidism/hypocalcemia, facial dysmorphia, developmental delay, growth retardation, hearing loss, and genitourinary anomalies. There is T-cell lymphopenia.

c. CHARGE Syndrome

The first letters of the following headings form an acronym for the disease: **C**oloboma, **H**eart defects, **A**tresia of choana, **R**etarded development, **G**enital/urinary abnormalities, and **E**ar abnormalities/deafness. It occurs due to a gene mutation in the chromodomain helicase DNA binding protein (CHD7). CHD7 encodes a molecule involved in chromatin remodeling. This molecule is expressed in TECs and mesenchymal cells in the thymus. CHD7 controls FOXN1 expression and TEC function in early organogenesis (15, 16).

d. FOXI3 Mutation

Recently, findings of DGS (T-cell lymphopenia and hypocalcemia present, cardiac defects absent) have been described in 5 families. It occurs due to a microdeletion in 2p11.2 (17, 18).

2. Diseases Affecting the Development of TEC

a. FOXN1 Mutation

FOXN1 is a member of the transcription factor family that is expressed in epithelial cells in the skin and thymus. It is required for the development, differentiation, and maintenance of TECs, as well as the growth and differentiation of skin and epithelial cells, during the embryonic period and postnatally (19). Biallelic loss-of-function (LOF) mutations in FOXN1 result in the nude severe combined immunodeficiency (SCID) phenotype (20). It has been described in 10 cases with congenital alopecia universalis, nail dystrophy, and SCID findings (21, 22). Thymic transplantation is necessary (23).

Recently, heterozygous LOF mutations in FOXN1 have been identified in 20 children and adults. T-cell lymphopenia (especially CD8) and low TREC were observed in the patients. Consistent with the nude SCID phenotype, several pediatric and adult patients with heterozygous FOXN1 mutations also had nail dystrophy, hair thinning or hair loss, and symptoms of atopic dermatitis (11).

b. PAX1 Mutation

The paired box family of the TF (PAX1) gene is expressed in the third pharyngeal pouch and is important in thymic organogenesis. PAX1 expression in the thymic epithelium creates a favorable environment for T-cell maturation (24). Autosomal recessive PAX1 mutations result in the Otofaciocervical Syndrome Type 2 (OTFCS2) with dysmorphic facial features, ear anomalies, hearing loss, and skeletal malformations of the vertebrae and shoulder. Patients have a T-B+NK+ SCID phenotype and require thymus transplantation (25, 26).

c. EXTL3 Mutation

The exostosin-like glycosyltransferase 3 (EXTL3) gene encodes a glycosyltransferase involved in the biosynthesis of heparan sulfate proteoglycans (HSPG). HSPG is important in the development of hematopoietic precursors and thymic stromal cells. Patients may present with skeletal dysplasia and neurodevelopmental delay. It causes a syndromic combined immunodeficiency with T-cell lymphopenia.

3. Defects in Hematopoietic Cells

Biallelic *AIRE* mutations result in problems with negative selection of autoreactive thymocytes and cause autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia (APECED), also known as autoimmune polyglandular syndrome 1 (APS 1). Impairment in T-cell selection leads to the formation of various autoantibodies, including anti-IL-17 autoantibodies associated with chronic mucocutaneous candidiasis (CMC) and autoantibodies against type 1 IFN, which cause severe SARS-CoV2 infection. AIRE deficiency in macrophages leads to impaired phagocytosis of Candida by reducing the expression of Dectin-1 and Dectin-2, causing CMC. Hypoparathyroidism and adrenal insufficiency are the most common endocrinopathies, but the clinical manifestations of APECED is broader than previously recognized, including significant non-endocrine findings (4). Moreover, it has been discovered that dominant-negative single allele AIRE mutations might cause a milder predisposition to autoimmune disease (27).

Hypomorphic *RAG* or *PRKDC* mutations impair AIRE function and AIRE signaling, resulting in impaired crosstalk between mTEC and thymocytes. Similarly, impaired AIRE signaling has been proposed in early-onset common variable immunodeficiency due to heterozygous *NFKB2* mutations, for which autoimmune features, including alopecia, hypopituitarism, and serum autoantibodies, have been reported alongside a susceptibility to infections and hypogammaglobulinemia (4).

A tetratricopeptide repeat domain-containing protein (*TTC7A*) is expressed in TEC, hematopoietic cells, and intestinal epithelial cells. Patients with the *TTC7A* mutation present with immunodeficiency, intestinal atresia, and severe enteropathy symptoms. These patients may also have thymic stromal dysfunction. *TTC7A* regulates the dynamics of the actin cytoskeleton in lymphocytes and is highly expressed in TECs (28). Although the effect of *TTC7A* mutations on TECs has not been fully investigated, postmortem examination of thymic tissue in these patients reveals dysplastic changes and blurred corticomedullary junctions, indicating thymic structural abnormalities. The benefit of hematopoietic stem cell transplantation (HSCT) for patients and the development of naive T-cells after HSCT suggest that thymic dysfunction in these patients is mainly secondary to lymphodepletion rather than a primary TEC defect (4).

X-linked SCID (*IL2RG* defect) leads to a significant reduction in thymocytes. The pathological examination of thymus has shown a loss of corticomedullary differentiation and absence of Hassall's corpuscles. *ADA* deficiency causes early thymic involution. In reticular dysgenesis, the thymus is severely hypoplastic, and Hassall's corpuscles are absent. In ataxia-telangiectasia, TCRγδ T-cells are increased and the thymus is hypoplastic, and Hassall's corpuscles are absent. *CD3D, 3E, 3Z* gene defects result in a block in the pre-TCR expression stage. MHC class II is required for TEC and thymic DC antigen presentation. In MHC class II deficiency, problems arise in positive and negative selection. Thymic medulla and AIRE+TECs are reduced in biopsies (10).

4. Non-Genetic Causes of Thymic Hypoplasia

Mothers of patients with thymic developmental defects should be asked about potential teratogens, including diabetes, isotretinoin (retinoic acid) exposure, and alcohol consumption during pregnancy (29). Some diabetic infants have congenital athymia without any identifiable genetic defect (30). Although some experimental studies suggest that hyperglycemia is teratogenic in diabetic pregnancies, the underlying mechanism is not fully understood.

Intrauterine exposure to retinoic acid alters TBX1 and/or PAX1 expression. This can cause thymic aplasia, hypoplasia, or ectopia (31).

Facial anomalies and immune system disorders are common features of fetal alcohol syndrome and Di George syndrome. Studies in mouse models show that ethanol exposure negatively affects thymic development (32).

TREATMENT

Cultured Thymus Tissue Implantation

Thymic tissue for thymic transplantation is obtained from infants who undergo cardiothoracic surgery for congenital heart disease with a sternotomy. During surgery, the thymus is taken out to expose the heart. After being taken out, the tissue is sliced and cultured for 13–20 days. Donor T lymphocytes are eliminated before transplantation, while the thymic stroma is preserved. The tissue, which has not lost its integrity, has a living stroma, and is negative for infectious agents, is transplanted to the quadriceps muscle. The recipient's hematopoietic precursor cells migrate to the thymic implant after transplantation, where they mature and can go to the periphery (33-35).

Six months after thymic transplantation, there is an increase in circulating naive T cells, peaking in the first 1-2 years. A normal proliferative response to mitogens is obtained 9–12 months later. B-cell functions normalize 1-2 years after transplantation (34).

Comorbidities such as congenital heart defects should be treated before transplantation. Preparation with immunosuppressive drugs such as Cyclosporin A (CSA) and anti-thymocyte globulin (ATG) + Methylprednisolone is necessary for atypical cases. CSA is continued after transplantation until the thymic output is obtained (34).

The most common complications after thymic transplantation include recurrent infections and autoimmune and inflammatory complications until immunological reconstitution occurs. Hemolytic anemia and renal disease may be seen in the early stages before immunological reconstitution, while cytopenias and autoimmune diseases related to the thyroid may emerge later. Partial HLA compatibility reduces the risk of autoimmunity to some extent (34).

The number of centers performing CTTI is quite limited. Currently, it is performed only by two centers in the world: Duke University Hospital in the United States and Great Ormond Street Hospital in the United Kingdom. In a study evaluating the data of 105 patients who underwent thymic transplantation, a 22q11.2 deletion was detected in 38% of the patients, a CHD7 mutation in 11%, a FOXN1 homozygous mutation in 3%, a TBX1 mutation in one patient, and a TBX2 mutation in another. No mutation was detected in 39% of the patients. Of the 41 patients with thymic aplasia who underwent thymic transplantation, 29 were babies of diabetic mothers. The survival rate after thymic transplantation was found to be 72% (76 out of 105 patients). Of the 29 deaths, 23 occurred within the first year after thymic transplantation. Thirteen of these deaths, mostly occurring pre-engraftment, were due to infections (36).

Currently, research is being conducted on the production of ex-vivo thymic organoids as an alternative to thymic transplantation.

Funding

The study did not receive funding.

Conflict of Interest

The authors declare no conflict of interest.

Authorship Contributions

Concept: **Saliha Esenboga,** Design: **Saliha Esenboga,** Data collection or processing: **Saliha Esenboga,** Analysis or Interpretation: **Saliha Esenboga,** Literature search: **Saliha Esenboga,** Writing: **Saliha Esenboga,** Approval: **Saliha Esenboga.**

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