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# Thymic Senescence

*Krisztian Kvell*

## Abstract

Thymic senescence develops in every person, although at different pace. Thymic senescence significantly lowers the production of naive T cells, leading to increased incidence of infections, cancer and autoimmune diseases. Certain external factors can accelerate thymic senescence. These include chemicals (copper-chelators), hormones (androgens), infections (viruses, fungi, protozoa). Others may slow the aging process of the thymus including perturbations to the hormonal (sex-steroid) system, genetic alterations (PPARgamma deficiency) or chemical compounds (PPARgamma antagonists). Thymic senescence research may provide insight to underlying molecular events and potentially appoint novel therapeutic targets for senescence intervention strategies. These hold promise to postpone thymus senescence and enhance T cell production. That would result in a decreased incidence of infections, cancer and autoimmune diseases, currently affecting the elderly. The attributed drop in health-care costs and gain in quality of life share tremendous economic and social interest.

**Keywords:** thymus, senescence, adipose tissue

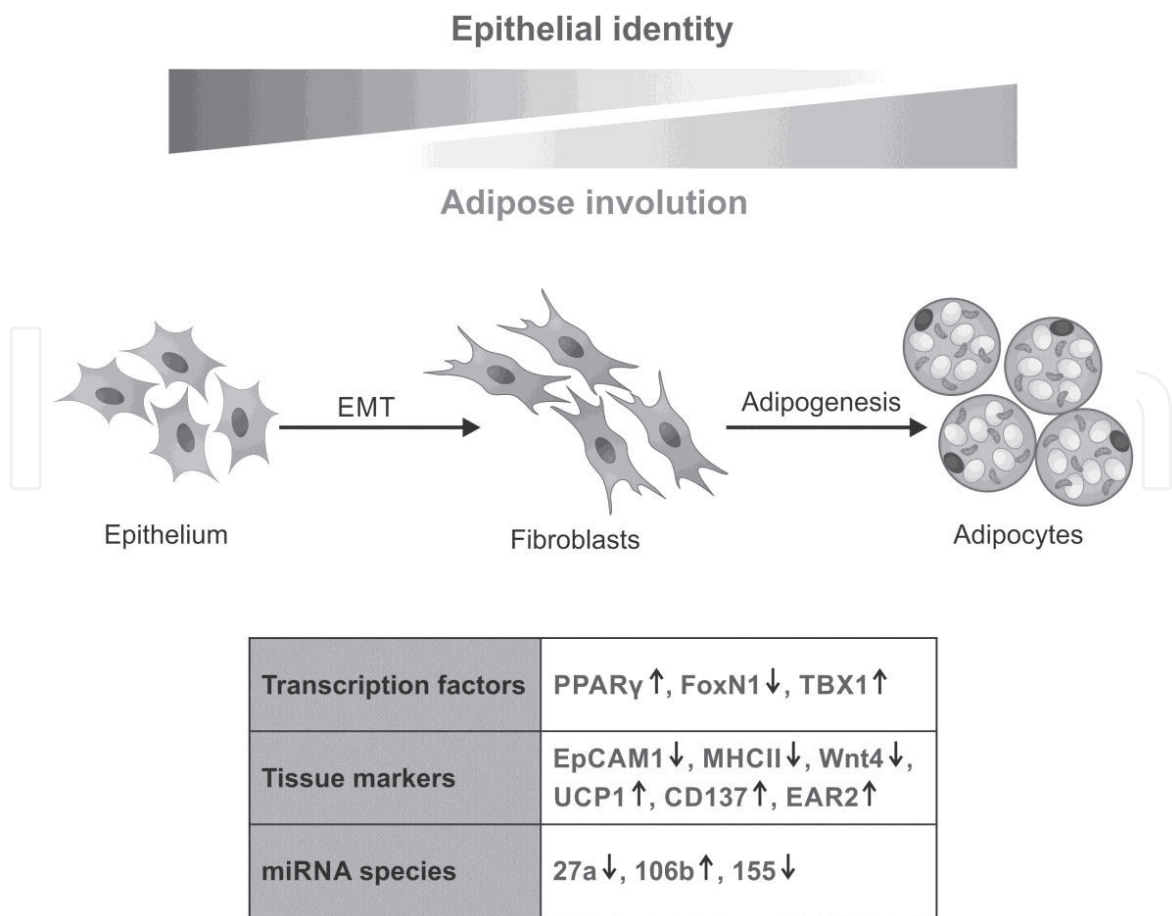
## 1. The aging thymus

Transcription factor TBX-1 is a mastermind in the formation of the third pharyngeal pouch involved in thymus organogenesis during embryonic development [1]. Patients with 22q11.2DS that impairs TBX-1 often present thymus hypoplasia. Similarly, *Tbx-1*<sup>null</sup> mice develop hypoplasia of the thymus [2, 3]. In both cases, defective thymus organogenesis leads to impaired thymocyte development [4]. However, as reported recently, the role of TBX-1 in thymus organogenesis is not straightforward. Ectopic forced expression of TBX-1 can inhibit transcription factor FoxN1, the mastermind of thymic epithelial identity thus indirectly impair thymus identity via sustained presence [5]. The thymus contains developing T cells (aka thymocytes) along with the non-lymphoid thymic stromal elements comprising the microenvironment that promotes thymocyte differentiation. Stromal elements include thymic epithelial cells (aka TECs), mesenchymal cells, endothelial cells as well as non-lymphoid hematopoietic cells (e.g., dendritic cells or macrophages). TECs constitute the main functional stromal cell type necessary to promote thymocyte differentiation [6, 7]. Soon after birth the thymus expands to increase the output of naive T cells, in order to colonize available niches in the periphery [8–10]. Cortical TECs (aka cTECs) are required for T lineage commitment, along with thymocyte expansion and differentiation, and positive selection. Medullary TECs (mTECs) are necessary for the induction of central tolerance and subsequent stages of thymocyte maturation before leaving the thymus. Of note, in order to maintain the well organized cortical and medullary compartments active (reverse) intercellular signaling is also required from developing thymocytes towards TECs

(aka cross-talk) [11, 12]. At a vaguely defined time point, the thymus begins to show involution, resulting in adipose degeneration of the organ; hence the process termed adipose involution. This senescent process is accompanied by the stepwise disorganization of thymic compartments, also shifting TEC subset ratios and reducing naive T cell production. Although the detailed mechanisms triggering these processes remain to be fully elucidated, they finally deteriorate thymus structure and function, severely impairing the output of fresh naive T cells. Decline of fresh naive T cells results in the inverse increase of memory T cell representation due to aging [13–15]. The observed bias in cTEC:mTEC ratio, and the fading of the most differentiated MHC class II-expressing TEC subsets leads to the development of a less complex medullary architecture along with the blurring of the cortico-medullary junction. This is followed by the focal disappearance of epithelial cells, gradually being replaced by adipose tissue in the perivascular spaces [16–20]. There is mounting evidence that adipose cells may have an thymic origin. Thymic adipose cells also produce an array of cytokines and signaling molecules that directly affect (impair) thymopoiesis [21–25]. As a result, although the appearance of thymic adipocytes may not trigger involution, their increasing presence with senescence can indirectly facilitate or perhaps even directly deteriorate thymus function. Thymus involution likely develops as a sum of failure of thymocyte progenitors and the inappropriate function of TEC compartments. It has been reported that the number of early T lineage precursors (aka ETPs) shows a gradual decline with senescence [26]. Reconstitution experiments of senescent thymi with bone marrow precursors from young donors cannot restore thymic compartments nor rescue impaired thymopoiesis. The opposite, however, reconstitution of young recipients using senescent bone marrow cells does not impair thymopoiesis [27, 28]. The genetic inactivation of cell cycle inhibitor p27 (aka Cdkn1b) also leads to the development of an enlarged thymus and enhances fresh naive T cell output along with normal stromal organization [29–33]. Recent thymic emigrants (aka RTEs) show a decrease upon enhanced expression of LIF, SCF, IL-6, and M-CSF [34, 35].

## 2. Characterization of thymic adipose tissue

There are significant differences between adipose tissue subtypes. At least three subtypes are distinguished: white adipose tissue (WAT), brown adipose tissue (BAT) and the recently described beige adipose tissue. White adipose tissue stores energy, brown adipose tissue generates heat (via NST or non-shivering thermogenesis), while beige adipocytes act as intermediates. It has currently been described that thymic adipose involution yields beige adipose tissue based on its gene expression, miRNA, histology and metabolic profile [36]. In terms of gene expression and histology characteristic epithelial markers show down-regulation (FoxN1, EPCAM1, MHCII, Wnt4) (see **Figure 1**). Considering the miRNA profile beige-adipose tissue-associated miRNA species show supportive changes (miR27a, miR106b, miR155) (see **Figure 1**). While PPARgamma is the mastermind of all adipose tissue subtypes, TBX-1 has been acknowledged as a key and specific marker of beige adipose tissue development [17–20]. Beige adipocytes respond to adrenergic stimuli by thermogenesis via mitochondrial uncoupling of biochemical degradation and energy production [21]. Along with TBX-1 other beige-indicative markers have also been reported. These include mitochondrial uncoupling proteins (mostly UCP-1), EAR2 (also known as Nr2f6) and CD137 (also known as Tnfrsf9) [22]. The above-mentioned adipose and beige markers show up-regulation along (see **Figure 1**). The adult thymus expresses PPARgamma, TBX-1 and UCP-1 in the epithelial compartment, and latter two have been reported to initiate beige adipose



**Figure 1.**  
*Key molecular events of thymic senescence.*

tissue development. Thymic adipose tissue may also be classified based on cellular analysis from an adipocyte perspective [23–26]. Thymus tissue appears to be unique expressing TBX-1 during embryonic development and also during senescence embedded in different contexts. It is appreciable that TBX-1 plays a role in thymus organogenesis (immune peak) and thymic adipose involution (metabolic peak). This suggests an intersection of immunity and metabolism, and a dual role of TBX-1 showing bimodal expression [36].

### 3. Natural resistance to senescence

A medical condition termed persistent thymus has been known for long [37]. In the affected population the thymus is rescued from involution. These individuals, however, have severe defects in their hormonal system, affecting the level of sex steroids. It is the lack of androgen-effect that prevents thymus involution on one hand, but hampers the endocrine system on the other hand. Recently another medical condition termed FPLD3 (familial partial lipodystrophy type 3) has also been associated with the lack of thymus involution [38]. FPLD3 also derails the hormonal system by affecting PPARgamma activity. As for all adipose tissue subtypes, PPARgamma plays a crucial role during thymus adipose involution as well [39]. It has been suggested by others previously based on direct fate-mapping experiments that with senescence thymic adipose tissue develops from the thymic stromal or epithelial compartment [22]. In further support, epithelial to adipose trans-differentiation has been reported to occur as indicated by the presence by EpCAM-1/PPARgamma double-positive cells at a given time point during thymus senescence. Such cells express cell



surface markers as memories of their fading thymic epithelial identity (EpCAM-1), yet already show signs of their novel adipocyte differentiation program in their nuclei (PPARgamma). Further experiments showed that the medullary compartment is rescued from age-related shrinking in case of PPARgamma deficiency. Prolonged survival of thymus stromal niche provides permissive environment for sustained fresh naïve T cell production as indicated by increased mTrec values. Thymocyte subpopulations were equally supported by PPARgamma deficiency and fresh naïve T cells outnumbered memory T cells despite age. The sustained support of fresh naïve T cells provides functional advantages even at elevated ages. Oral consumption of foreign T-dependent antigen initiates immune tolerance to block potential immune response, even along with parallel immunization. Unfortunately, this tolerance is impaired at old age [40–42]. Loss of oral tolerance is a potential link to increasing food intolerance prevalence [43–46]. However, tolerance is rescued by PPARgamma deficiency at senior age [38]. In senior individuals protection from seasonal flu strains declines despite annual vaccination [47–49]. The cause: low levels of neutralizing antibody titers due to lacking naïve T-cells required for T-B cooperation. This, however, is also rescued by PPARgamma deficiency [38].

#### **4. Induced rejuvenation**

It has been reported early on that the thymus may be regenerated by a variety of interventions (aka thymic rebound) [50]. FoxN1 (a forkhead class transcription factor) is the mastermind of TEC differentiation [51–55]. FoxN1 has also been shown to promote proliferation [56]. Reducing (but not fully diminishing) FoxN1 expression early on triggers premature thymus involution (aka thymus progeria). The opposite, however, over-expression of FoxN1 efficiently postpones thymus involution [57]. Among secreted factors, Wnt4 and keratinocyte growth factor (aka KGF) have also verified as key factors of both thymic senescence and rebound [58–61]. The onset of adolescence presents a frequently proposed physiological cause for thymic degeneration. In accordance, both chemical and surgical castration that result in sex-steroid ablation (SSA) yield thymic rebound [62, 63]. SSA-triggered thymic rebound correlates with both increased thymus size and thymocyte number leading to increased fresh naïve T cell production. At the histological level this is suggested by the recovery of the cortico-medullary junction [64]. Accordingly, systemic hormonal changes associated with senescence partly explain changes observed during thymic senescence. In harmony, deletion of the androgen receptor results in an enlarged thymus and resistance to androgen induced thymus atrophy [65]. This is also in line with reports showing that the thymus reaches peak size and productivity early after birth, and not later at puberty [66–68]. Unfortunately, castration-induced rebound is only a transient phenomenon, and the thymus re-involutates within a couple of weeks. Apparently, although SSA may trigger the expansion of the thymus, yet does not rejuvenate it [69]. In the case of the thymus, in comparison with other organs, little is known about the molecular and cellular mechanisms that control its development and maintenance. FoxN1 certainly is a mastermind linking development and maintenance of the thymic microenvironment throughout life, yet some TEC differentiation also occurs independent from Foxn1 [70].

#### **5. Novel trends of rejuvenation**

Transcription factor FoxN1 - the mastermind of thymus organogenesis and identity - is a known as the molecular target of the glycolipoprotein Wnt4 [71, 72].

For this reason Wnt4 plays a crucial role in thymus development and maintenance [73–77]. With senescence thymic epithelial cells secrete less Wnt4, however, their Frizzled receptors (Fz4 and Fz6) become up-regulated as compensatory mechanism [78]. It is his loss of Wnt4 expression that allows for thymic adipose involution to develop due to PPARgamma-effect [79, 80]. The Wnt/b-catenin pathway and PPARgamma act as inhibitors of each other hence exogenous Wnt4 can reinforce thymic epithelial identity [79–84]. Wnt4 loses activity when purified, because the Wnt molecules travel in extracellular vesicles (EVs, or exosomes in this case) or on their surfaces [85, 86]. It has been reported that miR27b also specifically inhibits PPARgamma activity [87, 88]. The miRNA species are known travel in EVs and in exosomes as well [89, 90]. The thymus is a rich source of exosomes with immunological relevance in e.g. thymocyte selection [91–94]. As a combination of the above, artificially produced (transgenic) exosomes containing Wnt4 and miR27b in excess can block PPARgamma-effect in thymic epithelial cells thus efficiently counteracting senescence observed as thymic adipose involution [95].

World population is approaching 7.7 billion as of 2019 [96]. Global population increases due to increasing life expectancy, rather than increasing birth rate. However, increasing lifespan is not proportionally attributed with increasing health-span. As a result social expenses rise and novel solutions are urged. Central immune (thymus) senescence research based novel solutions can potentially improve senior immune fitness through decreasing the incidence of infections, malignant and autoimmune disorders. These could also thus alleviate the current burden on healthcare systems and increase quality of life in the elderly. An ultimate goal is to prolong immune fitness and realign it with constantly increasing lifespan.

With aging the thymus shows adipose involution. During this process thymic epithelial cells trans-differentiate into beige adipocytes through an intermediate fibroblast stage. Key molecular events are summarized at the level of transcription factors, tissue markers and miRNA species.

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## Author details

Krisztian Kvell  
Department of Pharmaceutical Biotechnology, Faculty of Pharmacy,  
University of Pecs, Pecs, Hungary

\*Address all correspondence to: [kvell.krisztian@pte.hu](mailto:kvell.krisztian@pte.hu)

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