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胡洪波,研究员,二级教授,博士生导师。主要从事T细胞发育、衰老和功能的分子调节机制研究。解析了人T细胞、天然淋巴细胞起源和胸腺发育、衰老关键事件等。入选国家特聘专家青年计划,承担国家自然科学基金委“青A”、重大研究计划、重点等项目。已经在*Nature*、*Immunity*、*Nat Cell Biol*、*Nat Aging*、*Nat Chem Biol*、*J Exp Med*、*PNAS*、*Cell Research*等发表论文70余篇。担任中国免疫学会常务理事、青年工作委员会主任委员,中国生理学会血液生理专委会委员,以及*JITC*杂志基础与转化部副主编、*Cellular&Molecular Immunology*编委。

胸腺衰退和T细胞衰老的机制与干预策略

刘 艳[1,2],乔晓娜[2,3],张惠媛[2,3*],胡洪波[2,3,4*]

(1 四川大学生命科学学院,成都 610064;2 四川大学华西医院免疫与血液研究院,成都 610041;3 四川大学生物治疗全国重点实验室,成都 610041;4 天府锦城实验室(前沿医学中心),成都 611130)

摘 要:随着全球人口老龄化的加剧,免疫衰老已成为严重影响老年人健康的关键因素,而胸腺衰退是免疫衰老的核心事件。胸腺作为T细胞发育和成熟的核心器官,随年龄增长出现进行性萎缩,表现为胸腺上皮细胞减少、脂肪浸润及纤维化等结构改变,导致胸腺输出功能显著下降。胸腺结构和功能的衰退直接破坏了T细胞发育所依赖的微环境,引起胸腺定植祖细胞数量减少及阳性、阴性选择过程受损,继而导致外周初始T细胞数量锐减、T细胞受体多样性降低以及免疫耐受功能减弱,显著增加发生感染、肿瘤及自身免疫性疾病的风险。本文系统综述胸腺衰退的细胞与分子机制及其对外周T细胞库稳态的深远影响,并探讨多种促进胸腺与T细胞再生的干预策略,以期为延缓免疫衰老、促进健康老龄化提供新的理论依据与思路。

关键词:胸腺衰退;免疫衰老;T细胞老化;胸腺再生
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Mechanisms and intervention strategies for thymic involution and T cell senescence

LIU Yan[1], QIAO Xiao-Na[2, 3], ZHANG Hui-Yuan[2, 3*], HU Hong-Bo[2, 3, 4*]

(1 College of Life Sciences, Sichuan University, Chengdu 610064, China; 2 Center for Immunology and Hematology, West China Hospital, Sichuan University, Chengdu 610041, China; 3 State Key Laboratory of Biotherapy, Sichuan University, Chengdu 610041, China; 4 Tianfu Jincheng Laboratory (Frontier Medical Center), Chengdu 611130, China)

Abstract: In the context of rapid global population aging, immunosenescence has emerged as a major determinant of morbidity and mortality in older adults. Age-associated thymic involution is recognized as a central driver of this process. This review summarizes current understanding of the cellular and molecular mechanisms underlying thymic involution, and its consequences for T-cell homeostasis, and discusses the emerging strategies to restore thymic function with the goal of delaying immune aging and promoting healthier longevity. The thymus, essential for T-cell development and the establishment of central tolerance, undergoes progressive structural and functional decline with age. This deterioration is characterized by thymic epithelial cell

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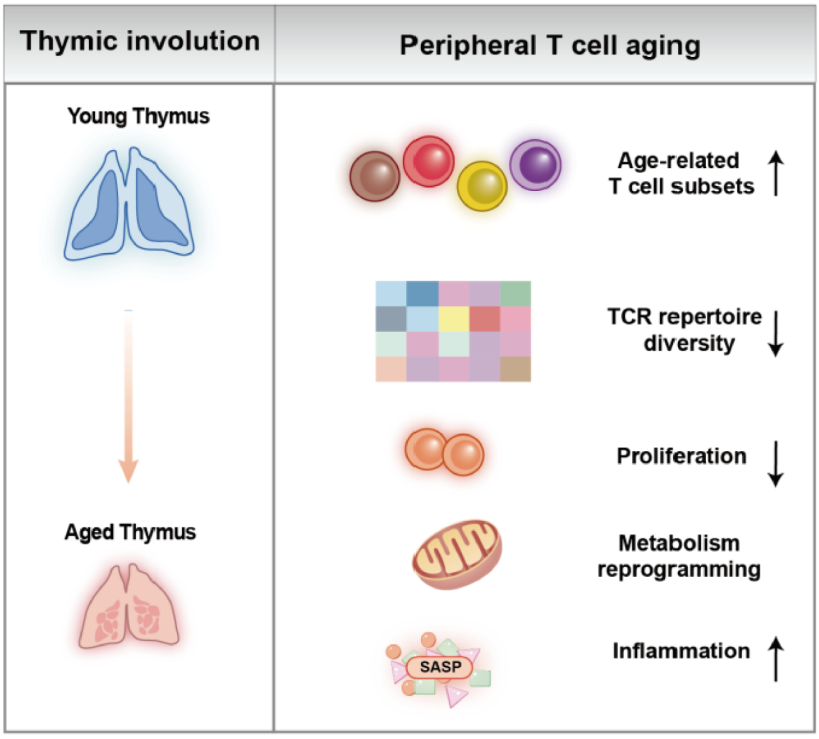
***通信作者**:张惠媛,E-mail:hyzhang@scu.edu.cn;胡洪波,E-mail:hongbohu@scu.edu.cn

(TEC) loss, cortical–medullary disorganization, adipose infiltration, and fibrosis. These changes reflect coordinated remodeling of all stromal compartments. The aged TECs display impaired cytokine production and antigen presentation capacity, fibroblasts promote extracellular matrix accumulation and fibrosis, and adipocytes displace functional parenchyma while releasing immunomodulatory adipokines. Together, these alterations disrupt the thymic microenvironment required for efficient thymopoiesis. As a consequence, early thymic progenitors (ETPs) recruitment to thymus is impaired, together with their reduced T-lineage commitment and TCR gene rearrangement efficiency. More importantly, both positive and negative selection are impaired due to stromal dysfunction, highlighting the potential of autoimmunity. Thymic involution has great impact on peripheral T-cell aging. With age, thymic output of naïve T-cells diminishes remarkably, leading to contraction of TCR repertoire diversity and reduced capacity to respond to novel antigens. This diminished thymic replenishment accelerates the accumulation of senescent and terminally differentiated T-cell subsets, including TEMRA cells, $CD8^+CD28^-$ T cells, $GZMK^+CD8^+$ T cells, virtual memory T cells, and cytotoxic $CD4^+$ T-cells. These subsets display reduced proliferative capacity, metabolic reprogramming, telomere erosion, and a pro-inflammatory senescence-associated secretory phenotype (SASP). They contribute to chronic low-grade inflammation (inflammaging) and increased susceptibility to infections, malignancies, and autoimmunity. Persistent viral infections, such as cytomegalovirus (CMV), further drive oligoclonal T-cell expansion and repertoire skewing. Based on these mechanistic insights, the review discusses therapeutic strategies targeting thymic regeneration and T-cell rejuvenation, including cytokine-based approaches (e.g., IL-7 fusion proteins, thymosin α1), TEC-directed interventions (e.g., FOXN1 gene delivery, FGF21 signaling), and metabolic modulation through caloric restriction or inhibition of mTOR and AMPK pathways. Advances in stem cell-derived thymic organoids provide powerful platforms for modeling human thymopoiesis and hold promise for future regenerative therapies. Integration of multi-omics profiling with machine learning–based immune-age prediction is expected to enable personalized immune monitoring and guide targeted interventions. Future research should focus on deciphering dynamic cell-cell and metabolic regulation within the aging thymic niche to achieve durable restoration of immune competence in elderly individuals.



Key words: thymic involution; immunosenescence; T-cell senescence; thymic regeneration

1　胸腺功能和发育简述

胸腺是存在于人和有颌脊椎动物的一级淋巴器官，位于胸骨下方、心脏上方，呈现出双叶扁平状。胸腺是T细胞发育和成熟的场所[1]；T细胞发育的过程从外周迁入胸腺的胸腺定植祖细胞(thymus seeding progenitors，TSPs)在胸腺定植开始。这些TSP进入胸腺后被称为ETP(early thymic progenitor)，在微环境中完成T细胞谱系定向，再经历

阳性选择和阴性选择的过程，获得MHC限制性和自身耐受，发育为成熟的$CD4^+$和$CD8^+$ T细胞，离开胸腺经血液循环至外周器官，识别并清除病原体和肿瘤细胞[2]。同时，胸腺细胞还通过与胸腺上皮细胞(thymic epithelial cells，TECs)的双向信号交互，主动参与并驱动胸腺皮质和髓质的分区和发育[3,4]。胸腺基质细胞除了提供Notch信号、表达和递呈自身抗原之外，其产生的细胞因子和胸腺肽也具有调节T细胞发育的功能[3]。人胸腺在胚胎期完成发育和成熟，儿童期胸腺体积较大，随年龄增长胸腺发生萎缩，在青春期后加剧，胸腺的体积和重量均会减少。成年期胸腺相对于幼年时期明显缩小，胸腺结构发生退化。正常胸腺具有分界明确的皮质和髓质区，但随着胸腺衰退，胸腺小叶中的皮质、髓质结构变得模糊不清，皮质变薄，髓质区域缩小或紊乱，皮髓质区分界不清。在胸腺衰退过程中，胸腺细胞和TECs明显减少[5,6]，胸腺功能受损；并导致外周血中胸腺最近迁出T细胞(recent thymic emigrant，RTE)和初始T细胞(naïve T cell)的数量减少、衰老相关的记忆T细胞增加[7,8]。TECs在衰老过程中会逐渐失去功能，表现为抗原呈递能力下降，并发生上皮间质转化(epithelial-to-mesenchymal transition，EMT)。衰老TECs不容易再生，进一步影响胸腺功能。此外，胸腺衰退常伴随有脂肪组织的积累并填充胸腺空间[9]，特别是在胸腺的髓质部分，这种脂肪浸润会逐渐取代原有的淋巴细胞富集区，同时胸腺内的胶原纤维和其他细胞外基质组分增生，导致纤维化，共同影响胸腺的结构和功能[5,9,10]。

2 胸腺衰退过程中的细胞学变化

由胸腺基质细胞，包括胸腺上皮细胞和成纤维细胞等构成的微环境是T细胞发育的“摇篮”[1]，胸腺发生衰老相关萎缩的重要特征是这些基质细胞在数量、结构、功能和组成上发生剧烈变化，导致胸腺支持T细胞发育的能力下降以及阴/阳性选择能力不足(图1)。

2.1 胸腺上皮细胞在胸腺衰退中的变化

TECs通过其突起相互连接形成的网状结构构成胸腺微环境的核心，不仅支持胸腺的组织形态，还通过分泌细胞因子等机制，支持T细胞分化过程、诱导免疫耐受，确保T细胞的正常发育[3]。胸腺衰退对TECs的影响尤为严重，主要表现在以下方面。(1)数量锐减：随着胸腺衰退和脂肪浸润，TECs增殖能力逐渐减弱，并伴随着大量细胞死亡，造成TECs细胞总体数量显著下降[5,10-12]。(2)结构和组织紊乱：衰老导致TECs构成的网络结构坍塌、断裂，皮质和髓质的界限模糊不清，从而无法为不同发育阶段的胸腺细胞提供精确的定位和信号，同时TECs的衰退伴随着胸腺脂肪化的现象，该过程显著削弱了胸腺的免疫功能[5,10,13,14]。(3)功能受损：衰老会导致TECs的分泌能力(如分泌CCL25、CXCL12等趋化因子、IL-7等细胞因子)显著下降，对T细胞的发育造成影响[5]。此外，研究表明衰老TECs呈递自身抗原的能力会下降，表现为在中枢免疫耐受和阴性选择过程中的作用减弱，可能导致自身反应性T细胞逃逸的风险升高[15]。

2.2 其他胸腺基质细胞随衰老的改变

胸腺基质细胞还包括成纤维细胞、脂肪细胞、血管内皮细胞等，它们在胸腺的结构和功能中扮演重要角色[1]。伴随衰老，这些基质细胞的变化不仅影响胸腺的结构完整性，还会显著影响T细胞发育、免疫耐受的建立等胸腺功能。

成纤维细胞是胸腺基质的重要组成部分之一，其通过合成和分泌胶原蛋白、弹性蛋白等细胞外基质，参与维持胸腺的三维结构和微环境稳定，并在一定程度上配合TECs调控胸腺发育、免疫耐受的建立及组织修复[16,17]。随着胸腺衰退，胸腺上皮细胞减少、成纤维细胞的比例增加[10]，成纤维细胞的表型及分泌功能发生改变，导致细胞外基质构成和分布重塑[5]，引起胸腺组织不同程度的纤维化和结构紊乱[9]，从而破坏T细胞发育所需的微环境，进而影响T细胞的发育和功能[18-20]。

随着机体衰老的进展，胸腺中的脂肪细胞逐渐增多，脂肪组织不断侵占并取代胸腺原有的功能性实质区域，破坏胸腺上皮细胞网络及皮质-髓质结构，导致T细胞发育和筛选的效率降低[21]。与此同时，脂肪细胞还可能通过分泌多种脂肪因子(如leptin、adiponectin等)改变胸腺局部炎症及代谢状态，进一步影响T细胞的发育[22-24]。

血管内皮细胞在胸腺中构建了致密的血管网络，负责胸腺组织的血液供应，并通过表达趋化因子(如CCL19、CCL21)参与调控TSP向胸腺内定植和成熟T细胞向胸腺外迁移[25]。在衰老过程中，胸腺血管内皮细胞的增殖能力下降，微血管网络发生重

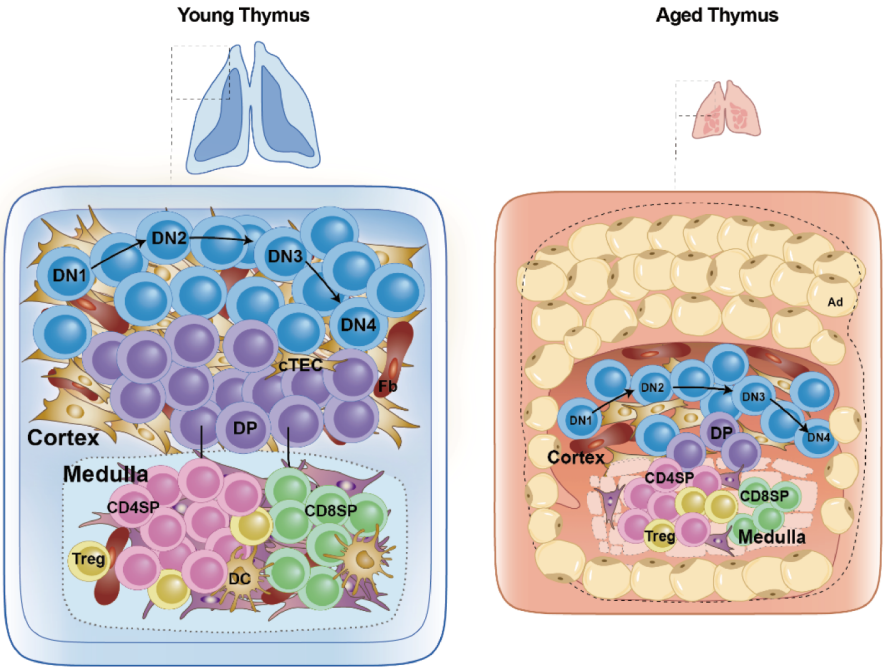


图1　胸腺衰退

随年龄增长，胸腺细胞数量逐渐减少，并伴随组织结构紊乱、初始T细胞生成减少以及外周TCR受体库多样性下降。DN，$CD4^-CD8^-$双阴性细胞；DP，$CD4^+CD8^+$双阳性细胞；Treg，调节性T细胞；DC，树突状细胞；cTEC，胸腺皮质上皮细胞；mTEC，胸腺髓质上皮细胞；Fb，成纤维细胞；Ad，脂肪细胞。

Figure 1　Thymus involution

With age, thymic cellularity gradually declines, along with disruption of tissue architecture, reduced production of naïve T cells, and reduction in the peripheral TCR repertoire. DN, $CD4^-CD8^-$ double-negative thymocyte; DP, $CD4^+CD8^+$ double-positive thymocyte; Treg, regulatory T cell; DC, dendritic cell; cTEC, cortical thymic epithelial cell; mTEC, medullary thymic epithelial cell; Fb, fibroblast; Ad, adipocyte.

塑，不仅影响胸腺的血液供应，还限制了氧气和营养物质的供给，进一步加剧胸腺衰退和功能减弱。同时，血管内皮屏障功能和通透性可能发生改变，对免疫细胞在胸腺中的进出和迁移过程造成干扰，影响T细胞发育所需的微环境[26]。

2.3　衰老过程中的T细胞发育

T细胞发育是一个复杂、高度有序的多阶段过程，在胸腺内从ETP开始，依次经历$CD4^-CD8^-$双阴性（double negative，DN）各亚阶段和$CD4^+CD8^+$双阳性（double positive，DP）阶段，最终发育为$CD4^+$或$CD8^+$单阳性（single positive，SP）T细胞，成为具有完整功能的成熟T细胞[27-30]。随着年龄增长，胸腺结构衰退和微环境改变在多个层面干扰这一发育程序，导致新生成的T细胞数量减少、T细胞受体（T cell receptor，TCR）库多样性下降及免疫耐受受损[6,31,32]。研究表明，16~24周龄的小鼠胸腺细胞总量比4~7周龄的胸腺细胞总量峰值减少约50%[5,32]；在人类胸腺中，RTE的数量在青春期后（约20~25岁）会骤降至仅为青少年早期水平的3.16%~10%，相当于损失了90%~96.8%。成年后胸腺输出T细胞的数量以每年约6.7%的速度持续缓慢减少[33,34]。

2.3.1　衰老过程中ETP谱系潜能的改变

衰老首先影响进入胸腺的祖细胞。随着年龄增长，骨髓造血功能下降及趋化因子、黏附分子表达谱改变，使进入胸腺的TSP数量减少，其增殖和分化潜能亦有所减弱[35,36]。相应地，DN1~DN4各亚群的细胞数目在老年个体中普遍呈下降趋势[37]。有研究表明，老年小鼠DN阶段TCR基因重排相关基因表达下调[38]，重排过程的效率和质量下降，导致生成的功能性T细胞多样性下降。这些改变共同导致进入DP阶段的胸腺细胞基数降低，使后续各发育阶段的细胞数量减少[39]。研究发现，衰老导致ETP发生了根本转变，即其向T细胞分化的潜能显著降低，而向固有淋巴细胞（innate lymphoid cells，ILCs）分化

的潜能增强[38]。

2.3.2 衰老导致DP细胞的阳性选择过程受损

在正常情况下，DN细胞进入DP阶段后，通过与胸腺皮质上皮细胞(cortical TEC，cTEC)相互作用完成阳性选择，从中筛选出能够识别自身MHC/肽复合物且信号强度适中的克隆[29,40]。随着胸腺衰退，cTEC数量减少[5]，导致DP细胞所能获得的存活与分化信号减弱。有研究表明，在人类胸腺中，衰老个体中DP细胞的比例相比年轻个体降低约20%，据此可推测阳性选择的效率和质量可能受到影响，从而导致通过阳性选择进入SP阶段的T细胞数量减少[38,41]。

2.3.3 衰老胸腺的成熟SP细胞表现出炎症特征

SP阶段既是$CD4^+$和$CD8^+$ T细胞谱系最终确定的阶段，也是中枢免疫耐受建立的关键环节。该过程主要在胸腺髓质区完成，依赖胸腺髓质上皮细胞(medullary TEC，mTEC)及树突状细胞(dendritic cells，DCs)等抗原提呈细胞呈递多样化的组织限制性自身抗原库，从而介导阴性选择，并诱导调节性T细胞(regulatory T cells，Treg)生成[40]。在衰老过程中，mTEC数量显著下降，多种组织限制性抗原的表达下调，髓质结构紊乱也降低了胸腺细胞与抗原提呈细胞之间的有效接触机会，从而削弱了阴性选择与Treg生成的效率，导致中枢免疫耐受受损。有研究表明，SOX4低表达的SP细胞在老年胸腺中比例显著增加，这类SP细胞还具有促炎特性和记忆/效应细胞的转录特征。此外，胸腺产生新T细胞的能力显著下降，这些变化共同削弱了免疫监视功能，并增加了感染、癌症及自身免疫病的风险[38]。

2.4 胸腺内其他细胞随衰老的变化

除了胸腺细胞之外，胸腺内还存在多种类型的免疫细胞，如ILCs、B细胞、DCs、巨噬细胞(macrophages)以及粒细胞等。这些细胞通过抗原呈递、细胞因子分泌和清除凋亡细胞等方式参与维持胸腺微环境稳态，调控T细胞发育和中枢免疫耐受。衰老相关的胸腺衰退在影响TECs和基质细胞的同时，也伴随着免疫细胞组成及功能的异常改变，两者共同加剧了胸腺功能的进行性下降。

ILCs是一类广泛分布于多种组织的先天免疫细胞，在黏膜屏障、病原体防御和组织稳态调控中发挥重要作用[42]。胸腺内ILC亚群主要通过分泌多种细胞因子参与调节局部免疫微环境和组织修复。目前关于胸腺中ILCs的年龄相关变化的研究仍然有限，ILCs的数量比例及其细胞因子分泌谱可能受到衰老相关的胸腺结构重塑和细胞因子环境改变的影响。有研究表明，衰老会导致人类胸腺中ILCs的积累和发育潜能增强，这可能反映了胸腺功能衰退及其伴随的免疫系统重塑的过程[38]。

胸腺内的B细胞数量相对有限，其高表达MHC II和共刺激分子，能够摄取并呈递自身抗原，参与对自我反应性T细胞的负选择，维持中枢免疫耐受[43]；部分胸腺B细胞还可表达AIRE(autoimmune regulator)及相关组织限制性抗原，为自身抗原库的广度作出贡献[44]。AIRE蛋白是一种主要在mTEC表达的转录调控因子，其核心功能是广泛诱导大量组织限制性自身抗原在胸腺髓质区异位表达，这些抗原被提呈给发育中的T细胞，导致自身反应性T细胞克隆通过阴性选择被清除，从而建立起对自身组织的中枢免疫耐受。有研究揭示，胸腺B细胞在被CD40信号激活后，能表达并呈递自身抗原AQP4，从而有效清除自身反应性T细胞，是建立对AQP4免疫耐受的核心，且该机制不依赖AIRE[43]。有研究发现，$CD19^+$ B细胞约占年轻小鼠胸腺总细胞数的0.2%，但老年小鼠胸腺中B细胞占比为1.2%，增加了约5倍。尽管频率显著增加，但由于胸腺整体大小随年龄急剧萎缩，胸腺内B细胞的总数变化不大[45]。随着胸腺结构衰退和微环境改变，在人类和小鼠胸腺中，胸腺B细胞中AIRE及其下游自身抗原基因的表达随衰老而下降，提示其功能受损，从而可能削弱其在中枢耐受建立过程中的作用[45]。

DCs和巨噬细胞是胸腺中重要的免疫细胞，分别负责抗原呈递和凋亡细胞清除[46]。DCs与mTEC共同呈递自身抗原，参与阴性选择和Treg细胞生成；巨噬细胞则清除凋亡胸腺细胞，维持免疫微环境稳态[47]。在衰老过程中，这些细胞的功能可能受损，包括抗原呈递能力下降和共刺激分子表达减弱。虽然它们的数量变化不大，但功能和分布的改变会削弱胸腺的耐受功能，可能会导致中枢免疫耐受建立不完善，进而增加慢性炎症和自身免疫风险[48]。

嗜酸性粒细胞在多种组织中常作为组织驻留细胞存在，参与寄生虫感染防御、过敏反应调控以及组织稳态和修复[49]。胸腺内的嗜酸性粒细胞在维持胸腺稳态、损伤后的组织修复以及与II型免疫相关的调控中发挥一定作用。其分布和功能可能因年龄

及炎症、过敏状态而发生改变，但具体规律仍不完全清楚[50]。

3 外周T细胞老化

T细胞从胸腺中发育成熟并进入外周，参与免疫监视和免疫应答[51,52]。胸腺衰退导致其T细胞生成能力下降，从而影响外周T细胞的分化与功能。主要体现在以下方面：(1)外周T细胞生成减少：胸腺衰退导致胸腺内的T细胞发育库缩小，新生T细胞数量减少，这一变化直接造成外周T细胞的数量减少，且多样性显著下降，显著降低了个体对新病原的免疫应答能力，导致免疫反应的减弱[6,31]。(2)外周T细胞的功能下降：衰老过程中外周T细胞功能下降是免疫系统衰老的重要标志之一，特别是在T细胞增殖、细胞因子分泌和免疫记忆形成方面的能力逐渐减弱[53]。衰老T细胞的细胞因子分泌能力显著下降，影响T细胞抗感染和抗肿瘤免疫功能[54]。在衰老个体中多个衰老相关T细胞亚群富集，如$CD8^+CD28^-$ T细胞、$GZMK^+CD8^+$ T细胞等，这些细胞表现出显著的细胞毒性和促炎分子特征[55]。此外，衰老使得T细胞的免疫记忆功能减弱，无法保持对病原的长期记忆，导致反复感染和免疫反应迟钝[18,56](图2)。

3.1 T细胞老化的特征和定义

T细胞老化(T-cell senescence)是指随着个体年龄增长，T细胞在长期的免疫刺激和增殖过程中，其增殖能力、细胞因子分泌能力、免疫反应能力和记忆能力等发生功能性衰退，逐渐失去正常功能的过程[57]。

T细胞老化的主要特征如下：(1)发生不可逆的细胞分裂停滞，关键细胞周期抑制因子p16和p21的表达上调，导致细胞周期阻滞[58,59]；(2)增殖能力显著下降[60]；(3)衰老相关分泌表型(senescence-associated secretory phenotype，SASP)发生改变，衰老T细胞会分泌大量的抑制性和促炎性细胞因子，如TNF-α、IL-8、IL-6、IL-2、IFN-γ以及TGF-β和IL-10，构成独特的SASP[61]；(4)表面标志物的表达发生显著变化，T细胞老化过程中CD57、KLRG1等表面标志物的表达升高，而共刺激分子CD28和CD27的表达显著降低[62]；(5)端粒改变与DNA损伤，随着细胞反复分裂，染色体末端的端粒逐渐缩短，当缩短到一定程度时会触发衰老程序。同时，端粒的功能障碍会激活DNA损伤反应，形成端粒相关的DNA损伤灶[63,64]；(6)代谢水平发生改变，如糖酵解增强、脂质代谢改变和线粒体功能受损[65,66]。

3.2 衰老相关的T细胞亚群

在衰老过程中，外周血中出现了多个独特的T细胞亚群，可作为个体T细胞老化的标志。与衰老相关的T细胞亚群在外周血中的比例随着衰老有所增加，反映了免疫系统在应对感染等刺激时发生的适应性变化，这些亚群通常还伴随着对原始抗原的记忆功能减弱，表明机体的免疫系统在衰老过程中对抗原应答能力也发生了改变[8]。

终末分化效应记忆T细胞(terminally differentiated effector memory T cells re-expressing CD45RA，TEMRA)具有高度的终末分化表型，是T细胞分化途径的终点，具有极低的增殖能力和较高的凋亡率[67]，主要表型为：$CD45RA^+CD45RO^-CD62L^-CCR7^-CD57^+KLRG\text{-}1^+CD28^-$[68]。它们主要响应慢性抗原(如巨细胞病毒CMV)的刺激，其过度克隆扩增占据了初始和中央记忆T细胞的免疫库，导致T细胞免疫多样性下降[69,70]。TEMRA细胞具有强大的瞬时细胞毒性，能够迅速杀伤靶细胞，无需事先分化，并分泌大量促炎因子(如IFN-γ和TNF-α)，参与全身慢性和低度炎症反应，加速免疫衰退[67,71]。

$CD8^+CD28^-$T细胞是指细胞表面缺乏共刺激分子CD28表达的$CD8^+$T细胞亚群，CD28表达的丧失已被广泛认为是T细胞衰老的显著标志之一。新生儿的大多数$CD8^+$ T细胞表达CD28，但到80岁后，$CD28^-$细胞的比例显著增加[72,73]。$CD8^+CD28^-$ T细胞通常表现为较低的增殖能力和较高的凋亡率，其积累可能与年龄的增长、慢性炎症刺激、长期抗原暴露以及免疫耐受的增强有关[74-76]，在人类和非人灵长类中尤其典型，但在小鼠中不常见[77]。$CD8^+CD28^-$ T有显著不同的代谢特征，表现为糖酵解能力增强，这与SIRT1缺失导致的FoxO1降解相关[78,79]。$CD8^+CD28^-$ T细胞还通过调节逃逸、分泌大量促炎因子、发挥细胞毒性以及靶向归巢至病变组织等方式，直接参与并加剧了自身免疫病理损伤[80-82]。

$GZMK^+CD8^+$ T细胞是指表达颗粒酶K(granzyme K，GZMK)的$CD8^+$ T细胞，这类细胞通常与免疫反应中的细胞毒性功能和炎症反应密切相关[83]。GZMK主要通过靶向细胞的线粒体和内质

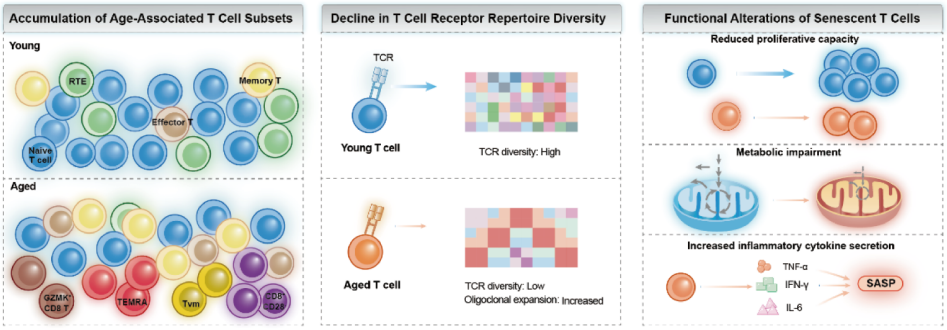


图2 外周T细胞衰老相关的变化

该图描述随年龄增长外周T细胞类型、TCR受体库及功能的变化。(左)伴随衰老,衰老相关T细胞亚群在外周逐渐积累。不同颜色代表不同T细胞亚群:蓝色,初始T细胞;绿色,最近胸腺迁出T细胞(RTE);棕色,效应T细胞;浅黄色,记忆T细胞;深棕色,$GZMK^{+}CD8^{+}$ T细胞;红色,终末分化效应记忆T细胞(TEMRA);深黄色,虚拟记忆T细胞;紫色,$CD8^{+}CD28^{-}$ T细胞。(中)在老年个体中,T细胞受体(TCR)受体库多样性逐渐降低,由年轻时T细胞高度多样的TCR受体库转变为受限的TCR受体库。(右)衰老外周T细胞表现出增殖能力下降、代谢功能受损及炎性细胞因子分泌增加,形成衰老相关分泌表型(SASP)。

Figure 2 Age-related changes in the peripheral T cell

Schematic overview of types, repertoire, and function of peripheral T cells with aging. (Left panel) During aging, age-related T cell subsets accumulate in the peripheral compartment. Different colors denote distinct T cell subsets. Blue indicates naïve T cell; green, recent thymic emigrant (RTE); brown, effector T cell; light yellow, memory T cell; dark brown, $GZMK^{+}CD8^{+}$ T cell; red, terminally differentiated effector memory T cell re-expressing CD45RA (TEMRA); dark yellow, virtual memory T cell; purple, $CD8^{+}CD28^{-}$ T cell. (Middle panel) In aged individuals, the T cell receptor (TCR) repertoire becomes progressively less diverse, as illustrated by the transition from a highly diverse TCR pattern in young T cell to a restricted repertoire in aged T cell. (Right panel) Aged peripheral T cells display reduced proliferative capacity, metabolic impairment, and increased secretion of inflammatory cytokines, giving rise to a senescence–associated secretory phenotype (SASP).

网,触发细胞程序性死亡来发挥免疫效应[84]。人的$GZMK^{+}CD8^{+}$ T细胞表达与IL-6、TNF-α和IL-8水平升高呈正相关,这些细胞因子又与炎性衰老相关。在衰老过程中,$GZMK^{+}CD8^{+}$ T细胞的比例通常会增加[83],尤其是在慢性病毒感染(如巨细胞病毒CMV)或炎症状态下更为明显[38,85]。因此,$GZMK^{+}CD8^{+}$ T细胞被认为是衰老免疫系统中的一个重要标志,反映了免疫反应的失衡。

虚拟记忆T细胞(virtual memory T cells,Tvm)是一类随年龄增长而积累的独特T细胞亚群,在人类和小鼠体内均存在[86,87],其表型特征为$CD44^{hi}CD49d^{low}$,因其处于未接触过实质性抗原的“虚拟记忆”状态而区别于其他记忆T细胞亚群[88,89]。现有证据表明,Tvm细胞可能主要起源于自身反应性T细胞群,在外周I型干扰素、IL-4和IL-15等细胞因子信号的刺激下扩增,因此高表达稳态细胞因子受体(如IL-7R和IL-15R)[90]。功能上,Tvm细胞展现出显著的年龄依赖性双重角色。有研究表明,Tvm细胞在年轻个体中对TCR刺激反应强烈,在感染早期可发挥保护作用[91,92],而在老年个体中则呈现增殖与细胞毒性功能下降的趋势,但在老年个体免疫代谢疾病中的具体作用机制目前尚未明确[93]。

$CD4^{+}$细胞毒性T淋巴细胞($CD4^{+}$ cytotoxic T lymphocytes,$CD4^{+}$ CTL)是$CD4^{+}$细胞中的一类特殊亚群,与辅助性$CD4^{+}$ T细胞不同,该细胞具备细胞毒性功能,能够通过细胞直接接触并释放穿孔素和颗粒酶杀伤靶细胞(如病毒感染细胞和肿瘤细胞)[94,95],同时也可以分泌IFN-γ等细胞因子执行免疫反应[96,97],其表面标志为$CD4^{+}CD28^{-}CD27^{-}CD57^{+}$[97]。随着衰老进展,$CD4^{+}$ CTL细胞的功能会逐渐减弱,表现为细胞因子分泌减少、细胞毒性下降[98]。它们在免疫衰老中发挥重要作用,影响抗病毒与抗肿瘤的免疫反应。在抗病毒免疫中,$CD4^{+}$ CTL通过MHC II限制性杀伤病毒感染细胞[96,99],尤其在$CD8^{+}$ CTL功能受损时发挥关键作用[100],在抗肿瘤中可清除$MHCII^{+}$肿瘤细胞[101,102],但在自身免疫病(如结肠炎、多发性硬化)中,会攻击自身组织,加剧炎症损伤[103-105]。

3.3 衰老过程中TCR库多样性下降和T细胞库维持

TCR库的多样性源自TCR基因的V(D)J重排、连接多样性(N/P核苷酸插入)以及αβ链随机配对等机制,构成T细胞特异性免疫识别的分子基础,同时

也是衡量机体识别广谱抗原能力的关键指标，TCR多样性是适应性免疫的核心[106]。在免疫稳态下，胸腺是初始T细胞的主要生成场所：胸腺内胸腺细胞经历V(D)J重排与正/负选择后，持续输出具有独特TCR序列的新生克隆，以维持外周T细胞库的组成平衡与多样性[38]。

随着年龄相关的T细胞老化，TCR多样性下降，主要由以下机制驱动：一是胸腺衰退，导致输出的初始T细胞数量减少，初始T细胞发育受损使外周T细胞库的更新能力受限，从而引发TCR谱的收缩和多样性下降[107,108]。这一输出减少与初始T细胞扩增共存，可短期延缓多样性的下降[109]，但长此以往，难以扭转此失衡现象[32,109,110]。二是记忆T细胞库的收缩和寡克隆扩增。克隆扩增主要涉及$CD8^+$ T细胞[111]，但也可见于$CD4^+$ T细胞[112,113]。常见的巨细胞病毒CMV感染会频繁地重新激活并挑战免疫系统[114]，从而维持高频率的抗原特异性T细胞。CMV特异性克隆扩增会导致针对其他病毒的抗原特异性T细胞库发生变化[115-117]，因此可能会影响记忆T细胞库中其他抗原特异性T细胞克隆的维持。上述机制最终导致老化T细胞的TCR多样性降低，削弱了机体对新发或变异抗原的识别与应答能力。

人类与小鼠的外周RTE和初始T细胞的比例随着衰老均下降，但维持初始T细胞库的机制存在差异：在2岁小鼠中仍可检测到RTE，表明胸腺在维持初始T细胞库的长期稳定性和功能性方面发挥着重要作用[118]。而人类的胸腺衰退更为显著，在胸腺输出减少的情况下，初始T细胞库的维持主要依赖于已有克隆的稳态增殖，而非新克隆的生成[32,119]。此外，$CD8^+$初始T细胞的稳态增殖能力低于$CD4^+$初始T细胞[119]。除细胞内在因素外，衰老还可能削弱T细胞向二级淋巴器官迁移并定植的能力，改变细胞因子(如IL-7)分泌谱，进一步影响初始T细胞的稳态增殖[120,121]。

3.4 T细胞功能的变化

衰老相关的T细胞功能衰退体现在多个方面，包括增殖能力、杀伤效应和细胞因子分泌谱的改变。在增殖和信号转导方面，衰老T细胞的受体信号转导效率下降，以及共刺激信号减弱，这些因素共同导致其在TCR刺激下的增殖能力受损[122]。此外，老化T细胞的增殖相关因子(如STAT、YY1、TCF1和NRF1)转录活性降低[123,124]，以及线粒体功能障碍引起的能量代谢变化，共同导致其稳态增殖功能障碍。在细胞因子分泌以及炎症环境方面，老化T细胞持续产生IFN-γ和TNF-α，直接导致炎症衰老，并能激活邻近和远端细胞的衰老程序[85]。反过来，SASP会加剧炎症反应，促进Th17和Th1细胞分化[125]，从而形成反馈回路，最终导致组织损伤。在效应细胞的分化方面，随着T细胞衰老，T细胞从静息状态逐渐转向终末分化状态，导致其谱系向特定效应亚群(如TH9)偏移，使分化可塑性和谱系范围受限，从而削弱免疫系统对新抗原挑战的应答能力[126]。多项单细胞转录组学的研究表明，衰老小鼠的$CD4^+$ T细胞群体中积累了耗竭型、细胞毒型和活化型Treg，具有不同的炎症调节特性[62]；$CD8^+$ T细胞群体则表现为寡克隆扩增和衰竭的T细胞群体的积累[83]。

3.5 基于T细胞的免疫年龄评估

免疫年龄可作为衡量免疫系统功能衰老程度的新指标。由于个体的“免疫年龄”与自然年龄并不完全吻合，这一差异性推动了基于免疫细胞的年龄评估方法的发展。近年来，单细胞RNA测序、TCR和BCR测序及质谱流式细胞术等多种前沿技术的发展，促使了免疫年龄的预测模型不断涌现。

T细胞作为免疫系统的核心组分，被广泛用于免疫年龄的预测。研究主要是利用来自不同年龄段个体的T细胞的多组学数据，提取与年龄高度相关的特征集合，结合机器学习算法生成免疫年龄预测模型。近年来，免疫年龄预测模型的研究取得了显著进展，多种基于T细胞及相关亚群的模型相继被报道。

Harries实验室[127]构建了基于免疫细胞中的TCR和IgH免疫球蛋白框架区基因重排多样性进行免疫年龄评估的模型(IMMAX)，该模型基于多种T细胞亚群及衰老标志物的流式细胞学特征，能够较为灵敏地量化老年人的免疫生物学年龄并反映其免疫衰老程度。但该模型与真实感染或疫苗应答场景的临床关联度和外推性仍显不足，亟需在更大规模、多中心人群队列中进行重建和前瞻性验证。有研究者联合T细胞和NK细胞亚群及状态建立免疫年龄预测模型[128]，该模型基于36项免疫变量，对4万余名健康个体组成的超大队列中的T细胞与NK细胞进行全面评估，为不同年龄段人群提供了客观量化的免疫评估工具。但是此模型70岁以上的个体样本比例偏低，导致高龄人群代表性有限，且此模型主要

依赖表型数据，缺乏功能学和临床验证。此外，卜军团队[129]基于人外周血多种免疫细胞亚群(包括T细胞、B细胞、NK细胞、单核细胞等)的单细胞转录组等数据构建免疫年龄评估模型(siAge)。该单细胞免疫年龄(siAge)模型通过整合25个细胞亚群数据，在健康人群中能较准确量化免疫年龄并刻画免疫状态、区分健康与免疫受损个体，但在免疫功能受损者中与实际年龄的相关性下降，反映免疫稳态紊乱的同时也提示其普适性和稳定性仍需在更大人群中进一步验证。

初始T细胞的状态可作为机体整体免疫状态的体现[57]。Naïve T IMmune Evulation(n-TIME)模型[38]基于初始T细胞谱构建，在训练集和测试集中均表现出稳定可靠的预测性能，能够较为准确地评估个体的免疫年龄。通过该模型，不仅可以识别出所谓的“健康衰老”个体，例如许多百岁老人的免疫年龄往往显著低于其实际年龄，还能检测到病毒感染或自身免疫疾病患者普遍存在的免疫年龄偏高现象，从而更真实地反映宿主在衰老过程中的免疫状态，未来仍需更大规模人群队列验证。综上所述，这些模型的建立标志着免疫年龄的预测逐步量化和精准化。

4 胸腺衰退干预和胸腺再生

鉴于胸腺功能对于个体免疫的重要作用，研究者从多个方面探讨了延缓胸腺衰退、恢复胸腺功能的策略。

4.1 靶向T细胞的策略

细胞因子IL-7在胸腺生成过程中发挥着重要作用，因此成为胸腺衰退干预的研究重点。靶向老年人的胸腺也可能有助于恢复老年人T细胞的发育。与此相符，有报道称IL-7融合蛋白(即IL-7与CCR9 N端胞外结构域结合)能够恢复老年人的胸腺结构，表明靶向细胞因子疗法具有广阔的应用前景。但是其局限性在于IL-7分子量较小，半衰期较短，传统IL-7疗法往往需要较高剂量并重复给药。IL-7可作用于多种类型的细胞，其多效性会引发骨质疏松、淋巴瘤、T细胞过度增殖等毒副作用，这给靶向胸腺治疗带来了挑战[130,131]。

胸腺素α1由TECs生成[132]，能够促进淋巴细胞成熟、增强T细胞功能并促进免疫损伤后的恢复。胸腺素α1的受体表达于发育中的胸腺细胞，能够调控其存活和增殖。体外研究表明，胸腺素α1能够拮抗地塞米松诱导的DP胸腺细胞凋亡，以及氢化可的松诱导的胸腺和脾脏质量下降[133,134]。此外，胸腺素α1还能促进TECs产生IL-7[135]。目前已启动多项胸腺素的临床试验，一项I/II期临床研究(NCT00580450)评估了胸腺素α1在造血细胞移植(hematopoietic cell transplantation，HCT)受者中的安全性和有效性。胸腺素α1治疗可增加T细胞数量[136]，并导致针对巨细胞病毒和曲霉菌等的病原体特异性T细胞的免疫反应提前出现。重要的是，胸腺素α1不会加重急性或慢性移植物抗宿主病(GVHD)，并且与吞噬作用和DCs功能的显著改善相关[136]。近年来，胸腺素α1也被用于治疗伴有严重淋巴细胞减少症的COVID-19患者[137]，以增强其免疫力。目前关于胸腺激素恢复胸腺功能的研究以相关性证据为主，能够支持其直接恢复胸腺功能或者显著延缓胸腺退化的临床与实验数据仍明显不足[138]。

4.2 靶向TEC细胞的策略

TECs 在胸腺微环境的组成中发挥着重要作用，而TECs数量的减少和功能丧失与胸腺衰退密切相关[10,139]。有研究将出生1天小鼠的TECs注射到9~12月龄的小鼠胸腺中，发现移植的TECs不仅可以在胸腺内增殖，而且可以促进胸腺的生长并增加T细胞的输出[140]。此外，将携带FOXN1-cDNA的质粒载体注射到老年小鼠的胸腺中，可以部分恢复胸腺的大小和胸腺细胞的数量[141]。因此，靶向FOXN1基因治疗也可能为恢复衰老胸腺的结构和功能带来巨大希望。先天性淋巴细胞产生的IL-22可以促进TECs的增殖和存活[142]，参与驱动放射损伤后的胸腺再生过程。此外，全身照射引起胸腺衰退后，TECs的增殖和分化还依赖于成纤维细胞生长因子7(FGF7)的产生[143,144]。近来的研究也相继报道了由mTEC分泌的FGF21具有维持胸腺结构和大小、促进T细胞发育的功能，而且安全性较高，为衰老过程中维持胸腺功能提供了新的潜在干预靶点[145,146]。

4.3 代谢调控在免疫治疗中的作用

代谢调控与胸腺稳态及T细胞的功能密切相关，因此，了解并靶向胸腺衰退和T细胞老化的代谢通路对于恢复基于T细胞的免疫功能至关重要。现有临床研究证明，为期2年的热量限制能有效减缓胸腺衰退，提示代谢干预对维持胸腺结构与功能具

有积极作用[147]。老化T细胞的代谢变化主要表现为糖酵解增强、脂质代谢改变和线粒体功能受损[148]。靶向老化T细胞的代谢途径主要涉及以下两个方面[149]：mTOR是细胞对氨基酸、能量和生长因子等营养信号的整合核心，靶向mTOR信号通路可通过调节细胞代谢，缓解胸腺上皮细胞功能减退及胸腺衰退，是缓解T细胞老化的可行方法[150]。在临床试验中，mTOR抑制剂依维莫司已在老年个体中显示出对免疫系统的促进作用，提示其可用于治疗衰老相关疾病。另一方面，AMPK作为细胞能量感知的关键调节因子，在维持T细胞的代谢平衡和功能中扮演着重要角色[151]。AMPK通过调节脂肪酸氧化和糖酵解，增强细胞对代谢压力的适应能力，它不仅感知代谢状态，还与mTOR和p38MAPK通路相互作用[151,152]。有研究显示，在衰老的$CD4^+$ T细胞中，AMPK可通过TAB1 scaffold触发p38MAPK的激活，从而抑制这些衰老$CD4^+$ T细胞的端粒酶活性及细胞增殖，驱动并维持了衰老表型，因而精准靶向AMPK也是一个可行的干预策略。尽管代谢干预为延缓胸腺衰退带来新思路，但目前多数研究仍处于临床前或早期临床阶段。由于脱靶效应以及副作用的存在[153,154]，仍需开展更多研究，以确保调节这些通路不会导致意外的免疫抑制或功能障碍，从而实现针对胸腺代谢微环境的精准调控。

4.4 胸腺类器官的构建与应用

在胸腺类器官研究方面，近些年取得了多项进展。Ramos等[155]构建了由人类多能干细胞诱导生成的功能性胸腺类器官，表达了一系列关键的TECs标志物，可支持T细胞发育，具有重要的临床应用潜力。Zeleniak等[156]报道了由诱导多能干细胞分化成人类胸腺类器官的方法，可以支持不同的功能性人类T细胞群体的从头生成。iPSC-thymus移植能使造血人源化小鼠产生T细胞，介导细胞和体液免疫应答，表现出较强的抗肿瘤免疫反应，促进有效的Ig类别转换。iPSC-thymus移植的造血人源化小鼠，不仅可以作为新的动物模型研究人类T细胞介导的免疫，也为该方法的临床应用提供了前期安全性和有效性的关键证据。此外，利用胸腺体内异位移植、胸腺组织芯片以及组织工程再生技术等[157,158]，也能够实现人胸腺衰退的干预，但仍需足够研究推动其在临床上的广泛应用。

5 展望

本文系统阐述了胸腺随年龄增长发生的结构性萎缩与功能衰退，及其对T细胞发育、功能和老化的深远影响。胸腺不仅是T细胞成熟的“摇篮”，其衰退更直接导致初始T细胞减少、TCR多样性下降及外周免疫应答能力减弱，进而增加感染、肿瘤及自身免疫性疾病的风险。未来的研究应集中于深入了解胸腺衰退和T细胞老化背后的细胞和分子机制，进一步解析胸腺微环境中上皮细胞、基质细胞与免疫细胞间的动态交互，以及代谢重编程等分子机制在胸腺衰退中的作用，并探索恢复胸腺结构和功能的方法。随着类器官、单细胞测序与基因编辑等技术的发展，构建人源化胸腺模型、开发靶向胸腺再生及T细胞功能重建的干预策略将成为重要方向。同时通过整合多组学数据与人工智能评估“免疫年龄”的手段，有望实现个体化免疫监测与免疫衰老干预，从而延缓免疫系统衰退，为有效应对老龄化提供新思路与新策略。

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