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Obesity-induced thymic involution and cancer risk

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ABSTRACT

Declining thymic functions associated either with old age (i.e., age-related thymic involution), or with acute involution as a result of stress, infectious disease, or cytoreductive therapies (e.g., chemotherapy/radiotherapy), have been associated with cancer development. A key mechanism underlying such increased cancer risk is the thymus-dependent debilitation of adaptive immunity, which is responsible for orchestrating immunoediting mechanisms and tumor immune surveillance. In the past few years, a blooming set of evidence has intriguingly linked obesity with cancer development and progression. The majority of such studies has focused on obesity-driven chronic inflammation, steroid/sex hormone and adipokine production, and hyperinsulinemia, as principal factors affecting the tumor microenvironment and driving the development of primary malignancy. However, experimental observations about the negative impact of obesity on T cell development and maturation have existed for more than half a century. Here, we critically discuss the molecular and cellular mechanisms of obesity-driven thymic involution as a previously underrepresented intermediary pathology leading to cancer development and progression. This knowledge could be especially relevant in the context of childhood obesity, because impaired thymic function in young individuals leads to immune system abnormalities, and predisposes to various pediatric cancers. A thorough understanding behind the molecular and cellular circuitries governing obesity-induced thymic involution could therefore help towards the rationalized development of targeted thymic regeneration strategies for obese individuals at high risk of cancer development.

1. Introduction

The thymus is a primary lymphoid organ of T cell maturation and education, and is essential for cellular immunity. The thymus sits encapsulated above the heart in the mediastinum and has two lobes, which divide into lobules that are further compartmentalized into distinct zones, the cortex and the medulla. These thymic compartments represent functional niches that provide essential spatiotemporal signals regulating key processes of thymocyte development, such as the homing, survival, and expansion in the thymus, as well as T cell receptor chain rearrangement, positive selection, and establishment of central tolerance. In both embryonic and adult thymi, the above processes are regulated by organotypic microenvironmental signaling, orchestrated by a thymic epithelial network of cortical and medullary thymic epithelial cells, abbreviated cTEC and mTEC, respectively, along with supportive non-epithelial stromal cells (e.g., mesenchymal cells, macrophages, and dendritic cells), which all reside in and specialize their functions within distinct thymic compartments [1–18].

The maturation of diverse cTEC and mTEC populations is highly complex and is phenotypically defined by the concomitant upregulation of several genes. The mature cTEC exhibit a specialized repertoire of molecules, critical for the initial stages of the T cell development [19]. In brief, these include: (a) Homing factors for the early thymocyte progenitors, such as C-X-C-chemokine ligand 12 (CXCL12) and C-C chemokine ligand 25 (CCL25) [20–22]; (b) T cell lineage commitment factors, such as delta-like ligand 4 (DLL4) [23,24]; (c) Growth factors that promote thymocyte survival, proliferation, and expansion, such as interleukin-7 (IL7) [25]; (d) Various components of the antigen-processing/presentation machinery, such as major histocompatibility complex-1 (MHC-I) and – 2 (MHC-II), along with specific proteasomal subunits (e.g., thymoproteasome β5t subunit), and proteases (e.g., cathepsin-L1), which together facilitate exposure of

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developing thymocytes to self-antigens [26–30].

The mature mTEC have a larger phenotypic and functional heterogeneity than cTEC, to support the diverse medullary functions. In principle, mTEC are distinguished into mTEC^{lo} and mTEC^{hi} on the basis of autoimmune regulator (AIRE) expression [1]. The AIRE^{-} mTEC^{lo} subset exerts a high expression of CCL21 [31–33], a key chemoattractant for homing of positively-selected thymocytes into the medulla. The AIRE^{+} mTEC^{hi} subset on the other side, is characterized by the concomitant upregulation of several genes participating in negative selection, such as MHC-II, CD80, and the tissue-restricted antigens (TRAs) [18]. To establish self-tolerance, mature mTEC^{hi} cells express and present developing thymocytes with a complete array of self-proteins and -peptides that might be encountered once naive T cells are released into the periphery. A strong interaction of the T cell receptor with any of the generated MHC-TRA complexes would indicate a highly self-reactive T cell, and hence, a target for deletion. A failure of the mTEC^{hi} subset to express even a single TRA, or the escape of a self-reactive T cell via another means could result in devastating autoimmunity [34–37]. Although it has remained a biological mystery for a long time, and although it is not the focus of the current review, it is suffice to say that the phenomenon of *promiscuous gene expression* of hundreds of TRAs at the population level is an intrinsic ability of AIRE^{+} mTEC^{hi} cells, allowing them to express up to 90% of the coding genome [38–40]. Interestingly, lineage tracing experiments have revealed that AIRE^{+} mTEC^{hi} cells may continue to differentiate, thus giving rise to terminally differentiated mTEC subsets, which in turn, exert supportive roles to the described medullary functions. Examples of such "post-AIRE" mTEC are the neuroendocrine thymic tuft cells and the corneocyte-like mTEC (also known as Hassall corpuscles), among others [41–47].

When compared with other lymphoid and non-lymphoid organs, the size and cellular composition of the thymus is remarkably dynamic, as can be showcased by enhanced growth and naïve T cell output in infants/children, followed by the progressive loss of cTEC/mTEC populations and T cell output with increasing age [48–52]. These physiological changes, collectively known as "age-dependent thymic involution", have been linked with hindered T cell-mediated anticancer immunity, and associated with increased occurrence of cancer in old age [53–59]. In addition, the thymus is the most sensitive lymphoid organ to either acute or chronic toxic stimulants and stress, leading to its rapid involution, a phenomenon also known as "acute thymic involution" [4, 60–62]. Among the plethora of toxic stimulants, which include cytoablative therapies, various infections, and even pregnancy, there is now cumulative literature that obesity may also represent a significant factor contributing to premature thymic involution [63].

The obsolete viewing of adipose tissue as just a fat storage depot has been completely replaced nowadays by its classification as an endocrine organ producing key hormones that affect metabolism and physiology. Obesity, which is characterized by excess body fat accrual in an individual, is a growing public health concern, and its exploding prevalence will likely contribute to an epidemiological burst of cardiovascular disease, diabetes, and cancer, in the next few decades [64]. Although epidemiologic evidence is abundant [65–67], mechanistic insights linking obesity with increased cancer risk have just begun to emerge. Overall, the defective secretory products of the dysfunctional obese adipose tissue are known to promote low-grade chronic inflammation, insulin resistance, and hormonal imbalances, which together lead to the emergence of preneoplastic lesions, and eventually cancer development with associated morbidity and mortality [68–71].

Despite the majority of studies that have linked obesity with the development of malignancy focused on the direct impact of high adiposity on the primary tumor interface [69,71], this review article will critically explore available evidence that causatively links obesity and cancer from the viewpoint of obesity-induced thymic involution as an intermediary pathology (Fig. 1). This fresh insight will lay groundwork for viewing obesity as a systemic condition affecting multiple organs simultaneously, especially the systemic anticancer immunity, rather than as a predisposing factor that locally conditions preneoplastic lesions.

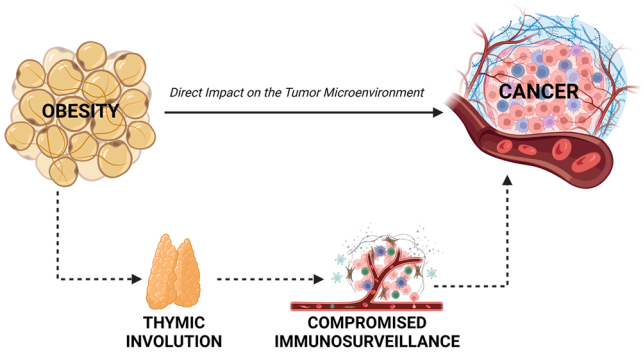

Fig. 1. The Causative Relationship Between Obesity and Cancer Development. Obesity is causatively linked to cancer development in the periphery through direct impact of obesity-driven mediators (e.g., proinflammatory molecules) on the tumor microenvironment. However, obesity may also promote premature thymic involution, thus compromising immune surveillance mechanisms that prevent tumor development via cancer immunoediting. As such, obesity may simultaneously target multiple cancer hallmarks, which together conspire in the cancer development and progression. Illustration created with BioRender.

2. Thymic involution and cancer risk

The causative link between age-associated decline of thymic functions and cancer risk has long been recognized [59]. Mechanistically, the overarching paradigm proposes that reduced peripheral immune surveillance and anticancer immunity following thymic involution favors development of preneoplastic lesions, and immune evasion maneuvering by newly transformed tumor cells. Although most studies focus on age-dependent thymic involution, it has been proposed that toxic stimulants may also lead to premature thymic involution with equal consequences in peripheral immune surveillance [62]. In this section, we will briefly explore the cellular and molecular interplay, via which thymic involution hinders immune surveillance and anticancer immunity (Fig. 2).

2.1. Age-induced thymic involution

The strongest association between thymic involution and cancer development is evidenced by the declined T cell-mediated immune surveillance of tumors following thymic involution/atrophy. Specifically, thymic involution associated with old age results in significantly reduced T cell output, leading to increased oligoclonal expansion of peripheral memory T cells and concurrent restriction of TCR repertoire diversity [58,72–78]. Together, these immunological alterations may impair the ability of the peripheral T cell pool to recognize tumor neoantigens resulting either from somatic mutations in proto-oncogenes and tumor suppressor genes [a.k.a., tumor-specific antigens (TSAs)], and/or from non-specific tumor antigens, such as embryonic proteins that are overexpressed in tumor cells [a.k.a., tumor-associated antigens (TAAs)] [79–84]. In general, the molecular basis of anticancer immunity and effective immune surveillance against tumor cells is evidenced by the ability of T effector cells to recognize a plethora of TSAs and TAAs in peripheral tissues [85–89]. As such, under conditions of age-dependent thymic involution/atrophy, TSAs and TAAs might be neglected or overlooked by the peripheral T cells due to restricted TCR repertoire diversity, thus eventually leading to the survival and expansion of tumor cells [54,56,59,62,90].

Besides reducing thymic output, age-dependent thymic involution may also affect the quality of thymopoiesis, in particular by promoting the development of a peripheral T cell pool with a senescent phenotype.

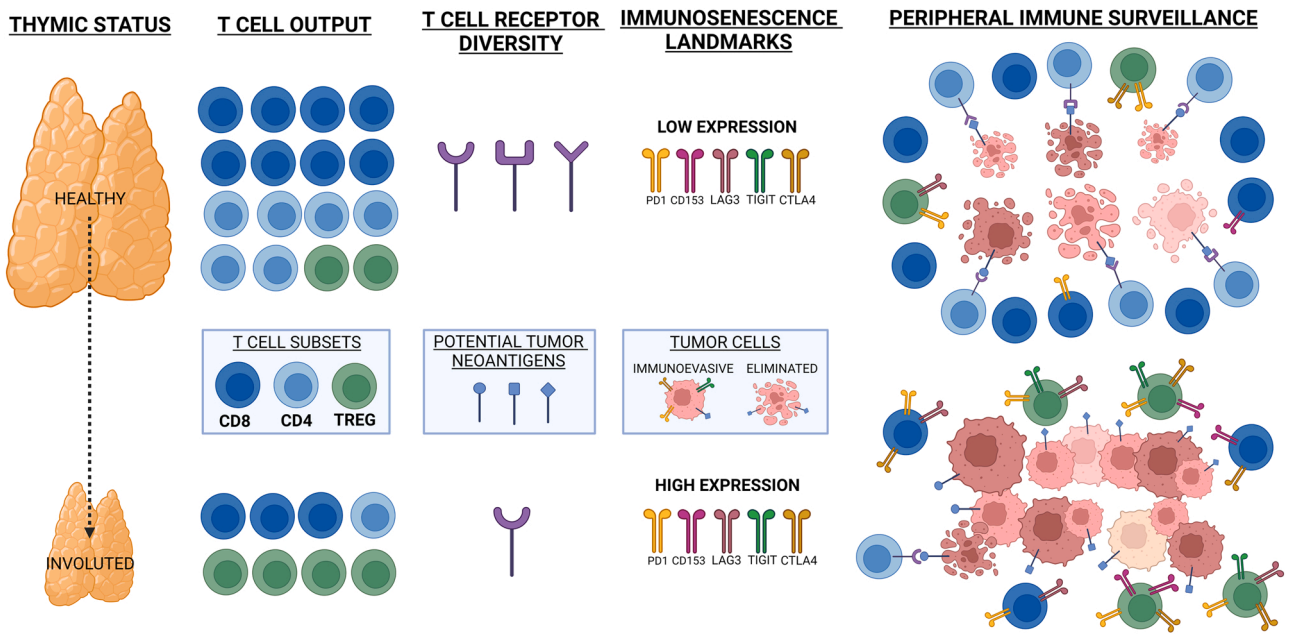

Fig. 2. Mechanistic Links Between Thymic Involution and Cancer Development. Thymic involution, either age-dependent or premature due to acute cytotoxic stress, can lead to impaired anticancer immune surveillance in peripheral tissues and organs, leading to earlier escape from the equilibrium phase and the establishment of neoplastic tissue. There are at least three distinct phenotypic characteristics of an involuted thymus that may lead to increased cancer risk through compromised anticancer immunity. First, the involuted thymus exerts reduced thymic output, as can be viewed by an overall decrease of naïve mature $CD4^+$ and $CD8^+$ T cells, and a concurrent increase of the T regulatory (Treg) cell population responsible for increased peripheral immunosuppression. As such, fewer immunocompetent T cells can survey peripheral tissues for new tumor formation. Second, the involuted thymus produces a relatively restricted T cell receptor diversity repertoire, which minimizes the chance that specific T cell clones will be able to identify tumor neoantigens. As such, most tumor cells will present neoantigens via MHC-II molecules that will be neglected by T cells in the periphery. Third, the involuted thymus produces mature T cells with increased expression of immunosenescence markers such as PD1, CD153, LAF3, TIGIT and CTLA4. As such, when $CD8^+$ T cells in the periphery encounter neoplastic cells, the immune checkpoint inhibitory signaling will not produce an immunostimulatory effect for the successful elimination of the cancer population, leading to $CD8^+$ T cell exhaustion and cancer cell survival. Illustration created with BioRender.

T cell immunosenescence is defined as a relatively permanent phenotype exerting a significant reduction of co-stimulatory molecules, such as CD28, and concurrent increase of the inhibitory checkpoint receptors, such as PD1 and CD153 [91–100]. Immunosenescent T cells tend to lose responsiveness to co-stimulation, and are more prone to become "exhausted" in an environment that is enriched in checkpoint receptor ligands, such as PDL1 [101–103]. Furthermore, immunosenescent T cells are involved in chronic inflammation, often serving as a preneoplastic condition for many types of cancer [104–107]. Indeed, many external (e.g., chemotherapies) or internal stressors (e.g., obesity) promote the bias towards the development of immunosenescent T cell phenotypes, which is more likely to provide peripheral T cells that are prone to exhaustion. For instance, PD1 is significantly increased in T cells and contributes to proinflammatory lesions and colon cancer development in the AZO/DSS mouse model of chemical carcinogenesis [108]. In the case of hemophagocytic histiolymphomatosis, a non-neoplastic hyperinflammatory syndrome that is characterized by persistent inflammation, it has been shown that PD1, TIM3, and other immune checkpoint markers of T cell senescence are significantly overexpressed in $CD8^+$ T cells, causing T cell exhaustion characterized by reduced cytokine production and compromised degranulation [109]. Immunosenescent $CD4^+$ T cells also produce proinflammatory cytokines and osteopontin in response to stimuli, and have reduced capacity to proliferate and expand in peripheral tissues [110]. Tumor cells typically express high levels of the PD1 ligand, PDL1 [111], a critical cancer immunoediting mechanism that leads to increased probability of PD1/PDL1 interactions in the periphery, and eventually to T cell exhaustion and failure of tumor immune surveillance mechanisms [112–114].

In addition to reducing the naïve T cell output and promoting T cell immunosenescence through the upregulation of immune checkpoint inhibitors, age-dependent thymic involution is also associated with extrinsic pathways of immunosuppression, i.e., an increased ratio of T regulatory (Treg) cells versus T effector (Teff) cells [115,116]. The involuted thymus has been shown to skew differentiation of $CD4^+$ single positive T cells to $CD4^+FoxP3^+$ Treg cells through intermediate TCR signaling strength interaction with MHC-II/self-peptide complexes [117–119]. Because age-dependent thymic involution results in the functional decline of the medullary thymic epithelial cell (mTEC) compartment, coinciding with reduction of MHC-II/self-peptide complexes [115], several self-reactive T cells that would have otherwise been negatively selected, are instead promoted to Treg cells, due to intermediate TCR signaling strength [120]. Although Treg cells sustain peripheral tolerance through suppressing excessive Teff-dependent immune responses, they are capable of orchestrating an immunosuppressive environment that hampers anticancer immunity and immune surveillance of tumors [121–127]. Indeed, the targeted inhibition and clearance of Treg cells is a promising strategy for enhancing antitumor immunity [127]. Among strategies of Treg inhibition/depletion, employment of inhibitors targeting immune checkpoint inhibitors, such as CTLA4, TIGIT, and LAG3, with the exception of PD1, have also been demonstrated to inhibit Treg immunosuppressive activity and frequency within tumors, despite the fact that off-target effects towards other T cell subsets partially counterbalanced these effects creating marginal outcomes in certain cases [128–133]. Other attractive strategies of Treg cell depletion that have shown preclinical promise, include the use of co-stimulatory molecule antibodies for members of the tumor necrosis factor receptor superfamily, such as GITR, OX40, and CD27, which can also serve as key targets of Treg cell exhaustion, and Teff cell activation [134–136]. Importantly, Treg depletion-based immunotherapies have also passed from preclinical stages into cancer patients [137–139].

Recent investigations have determined that Treg cells in adults are

relatively short-lived and that their peripheral numbers are maintained by rapid cell division and continuous replenishment from the thymus, in an autoimmune regulator (AIRE)-dependent manner [140–143]. Therefore, the relative increase of Treg cells due to age-dependent thymic involution could represent a key mechanism leading to an impairment of anticancer immunity and failure of tumor immune surveillance mechanisms [59,122]. It should be mentioned however that besides the thymically-derived Foxp3$^+$ Treg cells (tTregs), the Treg program can also be turned on in conventional T cells as a consequence of antigen exposure in peripheral tissues [144]. The induction of such "peripheral" Treg cells (pTregs) could be the result of certain inflammatory and non-inflammatory conditions [145–147], some of which could well be associated with increasing age. In view of key distinctions in the gene/protein expression profile and T cell receptor repertoire between pTreg and tTreg cells [148–151], it is currently debatable if either or both populations have a causative role in regulating cancer immune surveillance and/or anti-cancer immunity [152]. In addition, the extent via which the documented increase of Treg cells in ageing is dependent on either tTreg-based or pTreg-based developmental pathways is still unanswered. In the future, comprehensive knowledge of these pathways will be critical to promote pharmacological modalities that alleviate tTreg- and/or pTreg-dependent immune suppression and cancer risk.

2.2. Acute (age-independent) thymic involution

The thymus is particularly susceptible to a wide array of cytotoxic stressors, which may induce premature thymic involution, also known as "acute thymic involution". External stressors, such as chemotherapy, radiotherapy, and infections, typically destroy the thymic epithelium. For instance, function and morphological studies have demonstrated the vacuolization and apoptosis of cTEC following severe cytoablative/cytotoxic treatments [153–159]. On the other side, intrinsic stressors such as pregnancy, could induce milder thymic involution without extensive annihilation of thymic infrastructure, probably through the immunosuppressive functions of progesterone [53,160–163]. As opposed to the age-dependent lesions described above, acute thymic involution is a reversible condition, in which the thymus has the endogenous capacity to self-regenerate [4,60–62,164]. Despite being reversible to a certain extent, premature thymic decline as a result of cytotoxic stress could exert similar consequences as those of age-dependent thymic involution. For example, pediatric cancer survivors tend to develop late adverse immunological effects, such as second primary malignancies, persistent/mortal infections, and autoimmune diseases, most of which could be indirectly linked to thymic involution at the time they received chemotherapy/radiotherapy for their childhood tumors [165–171]. Indeed, acute thymic involution is accompanied by poor naïve T cell output, limited T cell receptor repertoire diversity, and increased expression of immunosenescence markers, suggesting hindered cancer immune surveillance mechanisms and anti-cancer immunity [62]. These data suggest that despite transient, acute thymic involution could provide an ample time-window, during which defective thymopoiesis leading to inadequate immunosurveillance, could be exploited by newly transformed (neoplastic) cells.

Although a huge diversity of extrinsic and intrinsic factors may cause acute thymic involution as described above (with obesity potentially one of them), it should not be conjectured that they could all lead to late adverse health manifestations, such as cancer, to an equal degree. For instance, pregnancy-induced acute thymic involution, whose physiological purpose is to minimize maternal-fetus conflict leading to embryo rejection, is a desired effect for successful gestation [161,163,172,173]. Although therapeutic interventions to improve thymic function would thus not be appropriate in this scenario, pregnancy has been found to have profound impact on the risk associated with certain types of cancer, such as breast cancer [174]. Therefore, elucidating the key molecular and cellular pathways leading to thymic regeneration following termination of the stressor (regardless of its nature, e.g., cytotoxic chemotherapy, pregnancy, obesity, or other), is critical to support long-term systemic and anti-cancer immunity in patients affected by thymic involution.

3. Obesity as a cause of premature thymic involution: a historical perspective

The earliest observations about possible compromising effects of obesity on thymic functions were made (in the late 60 s) in the Obese Strain (OS) chicken, in which the development of spontaneous autoimmune thyroiditis was noted [175,176]. Initially, the presence of circulating autoantibodies in OS chickens implied the sole involvement of the bursa for the development of autoimmune thyroiditis [177,178]. However, conflicting data from parabiosis between OS and normal strain chicken embryos failed to demonstrate evidence of autoimmune thyroiditis in the latter [179]. Subsequent in-depth investigations in OS chicken concurrently developing autoimmune thyroiditis and allergic encephalitis revealed a complex etiopathology by confirming involvement of lymphoid cells both from the bursa and from the thymus [180–182]. More definitive experiments conducted over the next decade clearly demonstrated that neonatal thymectomy coupled with anti-thymocyte serum could significantly alleviate autoimmune thyroiditis in OS chickens [183]. Moreover, the adoptive transfer of OS chicken thymocytes into T cell-depleted histocompatible normal strain chickens was able to induce autoimmune thyroiditis [184], eventually confirming that obesity-induced autoimmunity was, at least in part, dependent on the thymus in this animal model.

Around the same time, experimental observations in genetically obese mice following deletion of the leptin gene (also known as *ob/ob mouse*), confirmed a similar phenotype (i.e., thymus and spleen weight reduction) to that of OS chicken, suggesting reduced immunocompetence in those mice [185–187]. Mechanistic experiments conducted over the next decade revealed that leptin administration could partially restore thymic involution in *ob/ob* mice and could even protect thymocytes from dexamethasone-induced apoptosis [188]. Perhaps the most definitive experiments revealing a causative link between obesity and thymic atrophy, resulted from transplantation experiments of wild-type (WT) adipose tissue in *ob/ob* mice. In these experiments transplantation of WT adipose tissue was capable of completely normalizing all the metabolic, immune, and inflammatory alterations observed in *ob/ob* mice, such as thymic cellularity, thymocyte subpopulations and thymocyte apoptosis rates [189]. However, certain studies supported that leptin could only augment thymopoiesis in a certain context, for instance during leptin deficiency and/or lipopolysaccharide-induced thymic atrophy [190]. Later studies performed in genetically obese Zucker (*fa/fa*) rats were in concordance with those performed in *ob/ob* mice, revealing profound T lymphopenia in the peripheral blood, spleen and thymus of obese (fa/fa) rats at 8 weeks of age, compared to non-obese (*fa/-*) littermates [191]. Interestingly, both CD4$^+$ and CD8$^+$ T cell subsets were equally reduced in the thymus, spleen and peripheral blood of the obese individuals [191].

In ensuing years, it has been progressively accepted that obesity increases the risk of multiple comorbidities that adversely affect health and life expectancy. The causative association between excess calorie intake and impaired immunity, including intrathymic T cell, has been strengthened, and even extended into primates [192–194]. In a definitive and seminal study by Yang et al. (2009) [63], it was demonstrated that dietary obesity in mice induced premature thymic involution, characterized by reduced thymocyte counts, increased T cell apoptosis, accelerated decrease of T cell receptor excision circles (TREC)-bearing circulating lymphocytes (an index of thymopoiesis), and compromised T cell receptor (TCR) repertoire diversity, as showcased by TCR spectratyping. The authors further demonstrated that all of the above were accompanied by reduced lymphoid-primed multipotent progenitors (Lin$^-$Sca1$^+$Kit$^+$Flt3$^+$), as well as common lymphoid progenitors

($Lin^{-}Sca1^{+}CD117^{lo}CD127^{+}$), suggesting obesity-induced decrease of thymic input, as well [63]. In this study, progressive adiposity also revealed compromised thymic output in humans, confirming clinical relevance of obesity-induced thymic involution [63]. In aggregate, a causative link between obesity and thymic involution has been established for more than ~40–50 years in both humans and a variety of animal models, most of which are widely used even today for studies of obesity. Even more importantly, historical observations presented in this section have instigated scientific curiosity on the impact of obesity on lymphocyte development, thus triggering detailed studies to dissect the underlying mechanisms (as will be reviewed in the ensuing sections).

4. Mechanistic underpinnings of obesity-induced thymic involution

In this section, we will explore if established factors known to

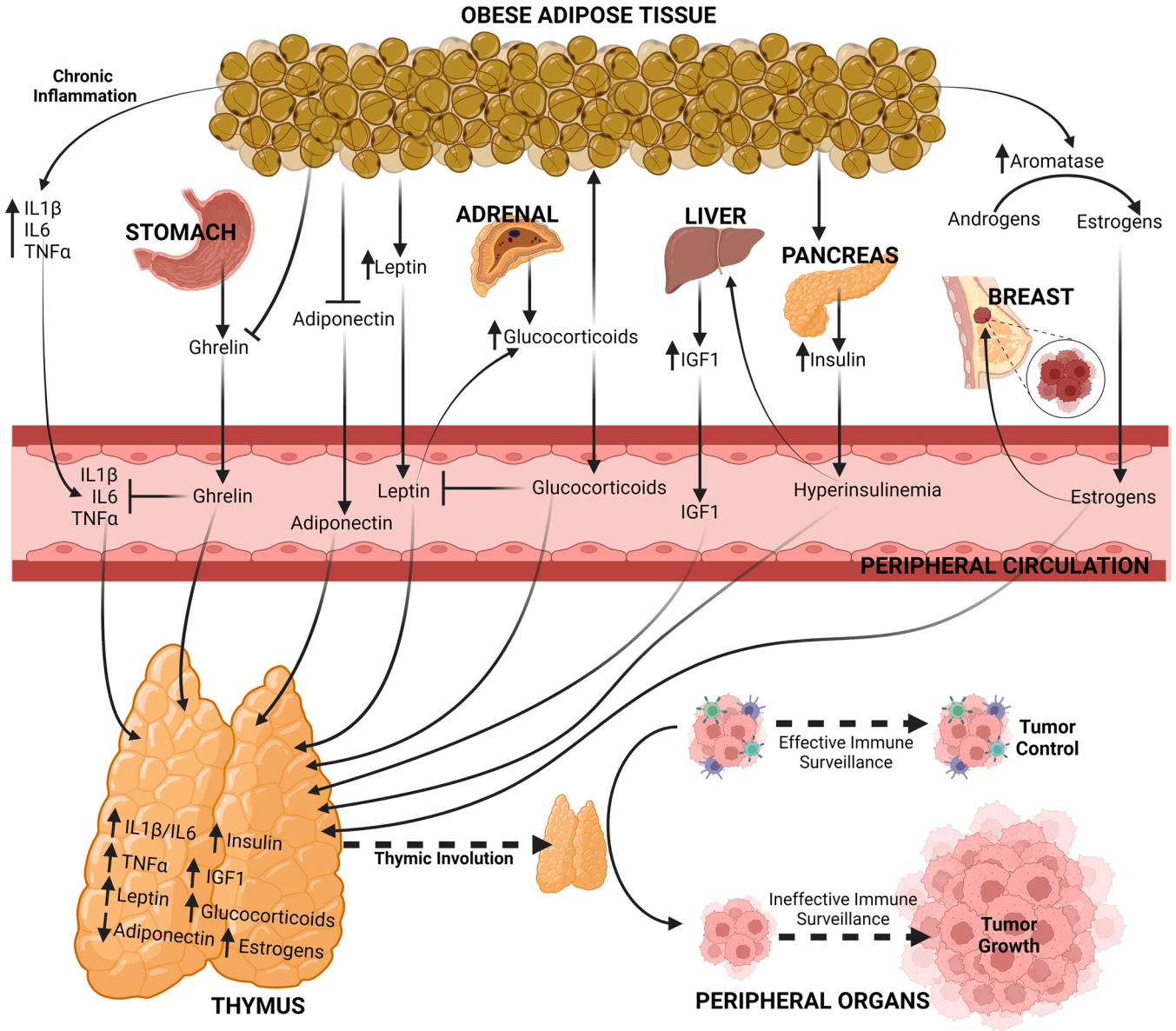

Fig. 3. Systemic Regulation of Thymic Mass and Function by Obese Adipose Tissue. Obesity can systemically regulate thymic mass and function through a variety of adipose tissue-mediated factors, the most notable of which are proinflammatory mediators (e.g., IL1β, IL6, TNF) and adipokines (e.g., leptin). Because obesity is a systemic condition, an interference with other organs/tissues can also indirectly affect thymic tissue. For instance, it is well-known that stomach-secreted ghrelin, a hormone which naturally suppresses all the aforementioned proinflammatory mediators, is significantly suppressed by the dysfunctional obese adipose tissue, thus augmenting the proinflammatory cascades promoting thymic involution. In the case of leptin on the other side, which primarily exerts protective effects on thymic function, it has been found that counter-regulatory mechanisms, such as glucocorticoid secretion by adrenal glands, may obfuscate/reverse leptin's positive impact on thymopoiesis. In a similar manner, other thymus-protective factors that are amplified through obesity, such as the insulin/IGF1 axis for instance, may be counteracted by a plethora of systemic defects because obese individuals typically suffer from a (pre)diabetic condition. Finally, the high aromatase activity in obese dysfunctional adipose tissue, can convert androgens to estrogens, which in turn leads to increased estrogen-dependent thymic toxicity. The overall impact of obesity on thymic cellularity/function is therefore determined by the balance of thymus-supportive versus thymus-inhibitory factors, all triggered in obese individuals. Although the presence of thymus-protective factors, such as leptin and IGF1, could potentially offer a relatively optimistic perspective, there is sufficient preclinical and clinical evidence suggesting that obesity shifts the balance towards thymic involution, thus not favoring normal or increased thymic cellularity. As such, premature thymic involution has a direct negative impact on peripheral immune surveillance mechanisms, which significantly increase the risk for the development of clinically overt tumors. Illustration created with BioRender.

mechanistically connect obesity and cancer, also serve as key determinants of premature thymic involution. The discussed pathways entail obesity-driven chronic inflammation, adipocyte-derived cytokines (i.e., adipokines), steroid-sex hormones, and the insulin/insulin-like growth factor 1 (IGF1) signaling axis (Fig. 3).

4.1. Chronic inflammation

The most well-known intermediary pathology via which obesity promotes cancer development, is chronic inflammation, which is characterized by elevated circulating levels of interleukin-6 (IL6) and tumor necrosis factor-alpha (TNF) [195–197]. In certain mouse strains, high-fat diet alone can increase the incidence of spontaneous hepatocellular carcinoma (HCC), even in the absence of other genetic modifications [198]. In a mouse model of chemical liver carcinogenesis via challenge with diethylnitrosamine, it was shown that mice that are predisposed to obesity either via high-fat diet or leptin gene deletion (e.g., *ob/ob* genotype), may develop a higher HCC burden compared to lean controls, following the diethylnitrosamine challenge [199]. Interestingly, pharmacological inhibition of the IL6-STAT3 axis suppresses diethylnitrosamine-induced HCC in obese mice [200]. Besides HCC, various animal models of dietary and genetic obesity have demonstrated increased incidence of colorectal cancer (CRC) [197,201–203]. Interestingly, the disruption of obesity-induced chronic inflammation, either genetically (e.g., IL6-KO mice), or pharmacologically (e.g., via TNF neutralizing antibodies), has documented in both instances a reduced incidence and burden of CRC in obese mice compared to lean individuals [204–206]. These preclinical observations collectively suggest that obesity-induced proinflammatory responses can trigger the development of certain cancer types, such as HCC and CRC.

Despite the abundance of preclinical observations, the precise molecular/cellular pathways linking obesity-induced inflammation to neoplastic transformation are not clearly understood. In current years, chronic inflammation manifesting locally in peripheral tissues is viewed as a preneoplastic state for solid carcinomas [105,106,207–210]. Chronic inflammation could be the result of infections, such as *Helicobacter* species-dependent gastric inflammation and cancer development [211], a combination of genetic and environmental factors, for example inflammatory bowel disease leading to colorectal cancer development [212,213], as well as obesity [214], and old age among others. Regardless of the exact origins of chronic inflammation, it seems that the molecular paths leading to inflammation-linked cancers are commonly associated to the local induction of IL6 and TNF, as key orchestrators of neoplasia. For instance, TNF is highly increased in the colon of mice receiving a high-fat diet [215]. Accordingly, IL6 expression is also increased during high adiposity, possibly through various signaling pathways including from adipose tissue macrophages (e.g., toll-like receptor 4 signaling), or adipose cells themselves [216]. Indeed, phenotypic changes of white fat cells during fat mass increase (e.g., fatty acids, ATP, cholesterol etc.), may lead to both the accumulation and prominent molecular changes in a variety of immune and stromal cells, including macrophages, neutrophils, mast cells, endothelial cells, and fibroblasts, among others [71,217–219]. These cells may in turn produce TNF, IL6, IFNγ, and IL1β, among other cytokines and growth factors, which together remodel the immune cell landscape and favor cancer cell growth [71,220–223]. It is thus undeniable that obesity-induced chronic inflammation exerts a direct and local impact on tumor development.

On the other side, the extent to which chronic inflammation could systemically (and not only locally) influence the immune cell landscape, and by doing so, exert an indirect impact on cancer growth, is not well-understood. Regardless, a causative link between chronic inflammation and thymic involution exists, albeit not specifically in the context of obesity-related inflammation. For instance, the administration of dextran sulfate sodium (DSS) in mice, a well-established model of inflammatory bowel disease, induces colitis with concurrent reduction of mature $CD4^+$ and $CD8^+$ single positive thymocytes, thus indicating that thymic involution is intimately connected to the intestinal inflammatory response [224]. In general, evidence suggests that age-dependent thymic involution results from chronic inflammation associated with age-related disease [55,57,225]. However, a definitive link between obesity-induced inflammation and thymic functions emerges from the ability of certain metabolic hormones to co-regulate inflammatory responses and lymphocyte development. Ghrelin for example, an endogenous ligand for growth hormone secretagogue receptor, is a circulating hormone regulating food uptake, energy expenditure, and adiposity [226–228]. Available evidence suggests that ghrelin infusion in old mice promotes various determinants of thymopoiesis, including T cell receptor excision circles in peripheral T cells and T cell repertoire diversity [229]. Interestingly, another study demonstrated that ghrelin infusion into old mice leads to significant reduction of the proinflammatory cytokines IL6, IL1β, and TNF [230], thus suggesting that ghrelin-enhanced thymopoiesis occurs due to anti-inflammatory response. Under conditions of obesity, the neuroendocrine pathway controlling expression of ghrelin and its receptor in immune and other cells is significantly suppressed [231–233], thus leading to compromised control of chronic inflammation and, as such, thymocyte development.

The exact impact of proinflammatory cytokines, such as IL6 and TNF, on the development of thymocytes has not been well studied. Early studies on thymocyte development demonstrated that IL2 and IL6 could act together in *in vitro* thymocyte suspensions as "cytotoxic differentiation factors", promoting the differentiation of immature thymocytes into mature polyclonal $CD8^+CD4^-$ T lymphocytes [234,235]. Subsequent studies revealed that expression of IL1α, IL1β, and IL6 by cTEC and mTEC was under the transcriptional control of epidermal growth factor (EGF) and transforming growth factor alpha (TGFα) [236,237]. In an ensuing study, it was shown that different proinflammatory cytokines followed a spatiotemporal expression pattern in the fetal murine thymus [238], characterized by an initial IL4/IL6/TNF wave (days 13–14), followed by a subsequent IL1β/IL4/IL6 wave (days 16–17), and concluding with an IL1β/IL5/IL6/IFNγ/TNF wave before birth (day 19). Additional studies suggested that cytokines could cooperate with or antagonize one another, to dictate the developmental fate of distinct thymocyte lineages [239–242]. Although these observations paradoxically suggest that proinflammatory cytokines are necessary for T cell development, they also indicate that their expression is strictly regulated at the steady-state and tightly controlled at a contextual and spatiotemporal level. Such finely-tuned homeostatic mechanisms are disturbed in chronic inflammation, driven either by obesity or other conditions, leading to unrestrained expression of proinflammatory cytokines, thus promoting thymocyte apoptosis and impairing thymopoiesis [243]. As proof-of-principle, the *in vivo* administration of IL6 in mice disrupts the homeostatic steady-state IL6 cytokine levels, and induces thymic atrophy with loss of $CD4^+$ and $CD8^+$ cortical thymocytes [244]. In a lipopolysaccharide-induced acute thymic involution rat model, it was determined that increased levels of IL1β, IL6 and TNF were the primary contributors of thymic function impairment [245]. Although there is no direct evidence linking obesity-induced IL6/TNF and thymic involution to our knowledge, the aforementioned data collectively suggest that a cytokine turmoil within the thymic environment obfuscates the developmental pathways of lymphocytes and promotes lymphocyte apoptosis.

4.2. Adipokines

Certain cytokines secreted by adipose cells, also known as adipokines, exert endocrine effects in multiple tissues and organs of the body, besides the well-established brain functions. Two major adipokines investigated in homeostasis and a range of metabolic diseases/syndromes, leptin and adiponectin, have relatively opposing functions and are profoundly perturbed in states of obesity, with leptin levels typically rising and adiponectin levels decreasing in obese individuals [69]. There

is strong epidemiological evidence that increased circulatory leptin levels exist in patients with colorectal adenomas [246] and breast carcinomas [247], while in reverse, decreasing plasma levels of adiponectin have been associated with increased risk of colon [248] and breast cancer [249] development. Because both normal and transformed cells express leptin/adiponectin receptors, the role of adipokines in cancer development has been mostly investigated as paracrine effect of the dysfunctional obese adipose tissue on cancer cells [250–254]. In certain cancer types such as in breast, tumor cells directly invade the adipose stromal compartment haloing the neoplastic tissue, and as such, adipocytes can remodel the tumor microenvironment and directly regulate the hallmark capabilities via adipokine signaling [68]. However, emerging evidence demonstrates that obesity-induced adipokine perturbations may also be reflected systemically and exert grave endocrine effects on organs that are distant to the primary tumor sites.

Earlier investigations demonstrated that exogenous administration of leptin could protect from starvation-induced lymphoid atrophy in *ob/ob* mice [188], and could selectively augment thymopoiesis during lipopolysaccharide-induced thymic involution [190]. Generally, rodent models of leptin signaling deficiency, such as the *ob/ob* mouse model that produces no leptin, as well as the *db/db* mouse and Zucker rat models that produce truncated non-functional forms of leptin receptor, present with aberrant thymic dysfunction, characterized by reduced thymic cellularity, increased number of Hassall's corpuscles, vacuolization of thymic epithelial cells, and reduction of TEC-secreted hormones such as thymulin, all of which indicate a state of thymic involution [255–258]. In addition, leptin can exert an apoptosis-inhibiting effect on thymocytes, via JAK2-STAT3 activation following leptin-leptin receptor binding interaction [259]. Given that high adiposity often leads to systemic increase of leptin levels, it is thus evident that high leptin levels cannot reverse, or at least partially counteract, obesity-driven thymic atrophy. The most attractive explanation behind this phenotypic paradox would be the acquisition of leptin resistance, a phenomenon which is observed in obese individuals [260–266]. Leptin resistance occurs as a result of a large constellation of both central (i.e., hypothalamic) and non-central (e.g., metabolic disease) mechanisms, but thorough analysis of such mechanisms is beyond the scope of the current review. One, however, could envision that hypothalamic resistance/insensitivity to leptin may trigger a cascade of molecular events leading to insulin resistance, diabetic and other metabolic abnormalities, and a chronic inflammatory state, which may together hinder thymic functions.

Besides resistance, another intriguing possibility on why high leptin levels observed in obesity might fail to restore thymic cellularity and functionality, is the counter-inhibition by glucocorticoids. In general, glucocorticoids exert immunosuppressive signaling on the immune system. The thymus in particular is under the constitutive suppressive control of endogenous glucocorticoids that are systemically derived from the adrenal glands, although local production of glucocorticoids by the thymic microenvironment has also been documented [267–278]. Administration of exogenous glucocorticoids in rodents, such as dexamethasone and cortisone, causes severe thymocyte and mTEC apoptosis, leading to thymic hypoplasia and involution [155,157,271,277]. Interestingly, locally-produced glucocorticoids have been reported in the thymus with increasing age, albeit not specifically linked to obesity as the responsible pathology [279]. As in the case of systemically produced glucocorticoids, an increase of locally-produced glucocorticoids in the thymus, has also been linked to involution [280]. In general, glucocorticoid metabolism is dysregulated in obesity, presenting as a decrease of glucocorticoids in the liver, but an increase of tissue glucocorticoids in the adipose tissue [281–283]. Besides the established evidence that glucocorticoid signaling can induce thymocyte apoptosis via canonical signaling, a prior speculation that glucocorticoids function as counter-regulatory hormones of leptin has been proposed [284]. These studies revealed that leptin administration presented stronger effects on body weight and food intake in adrenalectomized compared to wild-type mice [284]. Although exogenous glucocorticoid administration promotes obesity and leptin overexpression, it has been demonstrated that leptin exerts suboptimal activity in elevated glucocorticoid levels [285]. Therefore, glucocorticoid-dependent leptin "incompetence" could represent an alternative mechanism of leptin resistance and thymic involution in obese patients.

Besides leptin, the role of other adipokines such as adiponectin and apelin, has not been widely demonstrated in thymic homeostasis and function. It has been shown that such adipokines play distinct roles in cancer development and progression. For example, adiponectin seems to exert both tumor-suppressive effects by suppressing tumor cell proliferation and tumor-promoting effects by exerting proangiogenic properties [286–288]. Apelin on the other side has been documented to support tumor development and progression by enhancing angiogenesis, proliferation, metastasis and drug resistance [289]. However, the available evidence mostly pertains to the paracrine effects of such adipokines in the local tumor microenvironment, without any indication that thymic function could be involved whatsoever. It should be mentioned that expression of the apelin receptor has been documented in the thymus [289], and adiponectin has been found in T regulatory cells within thymic nurse complexes [290]. As such, a more robust role of these adipokines in controlling thymic cellularity is yet to be established.

4.3. Steroid sex hormones

Sexual steroid metabolism, especially involving estrogens, is disturbed in obesity. In particular, high adiposity has been linked to the production of proinflammatory factors and adipokines, which together promote the expression and secretion of aromatase, a member of the cytochrome P450 superfamily, capable of synthesizing estrogens via the aromatization of testosterone and androstenedione [291–294]. Although estrogen synthesis occurs primarily in the ovarian follicles and corpus luteum of premenopausal women, it has been shown to exclusively occur in extragonadal tissues (e.g., white adipose tissue) of postmenopausal women and men [291–295]. Given the high total mass of adipose tissue generally, and of obese individuals specifically, its relative contribution to total estrogen levels becomes rather significant [296–298]. As such, aromatase and estrogen production are both increased in dysfunctional obese adipose tissue, equally exerting local and systemic repercussions. The contribution of locally produced aromatase/estrogens to cancer risk has been widely explored [299–305]. However, here we exclusively discuss the systemic effects of obesity-induced aromatase/estrogens on thymic functions, as a possible etiology for the increased risk of cancer development.

Although estrogens generally wield supportive functions in peripheral T cells [306], they mostly exert immunosuppressive functions via directly affecting intrathymic pathways of T cell development [53,160,307]. The latter has been demonstrated in preclinical animal models subjected to either oophorectomy or estrogen blockade, both of which result in thymic hyperplasia/hypertrophy, while supplementation with estrogens exerts opposite effects, i.e., thymic atrophy/involution [308–311]. Estrogens signal through the nuclear receptors ERα, and ERβ, as well as the G-protein coupled receptor, GPER1 [160]. However, thymic cellularity is primarily regulated by ERα, and to a smaller extent by GPER1, but not by ERβ, as evidenced through experiments in which exogenous estrogens are administered in genetically-engineered mouse models with specific deletion in each one of the three estrogen receptors [160,311–313]. Currently, it is established that estrogen-mediated signaling suppresses cortical thymopoiesis through multiple mechanisms, involving different estrogen receptors. First, ERa, but not GPER1, can suppress NF-κB signaling in DN thymocytes, which is known to promote survival and proliferation of β-selected thymocytes, thus promoting developmental arrest at this early stage [312,314]. Second, exogenous estrogen administration can promote apoptosis of double negative (DN) thymocytes that have not undergone β-selection in an

GPER1-, but not ERα-, dependent manner [312]. Interestingly, 17β-estradiol can inhibit proliferation and promote apoptosis of TECs in mice [315], indicating that estrogens may not only exert immunosuppressive functions to thymocytes, but also to the thymic epithelium.

Besides reducing thymic cellularity, emerging evidence now suggests that estrogen signaling also contributes to defective thymic output, by affecting the quality of thymopoiesis and the ability of the thymus to establish self-tolerance. Dragin et al. (2017) demonstrated that MHC class II expression is not altered in ERα-knockout and ERβ-knockout mice, but is significantly increased in Aromatase-knockout mice, suggesting that estrogens induce an ER-independent transduction pathway to control MHC-II expression in the thymus [316]. In the same study, it was also reported that estrogen signaling disturbs the intrathymic chemokine network, such as CXCL13 [316], which suggests that estrogens may disturb homeostatic mechanisms of lymphocyte trafficking during T cell development. Because obesity is associated with increased expression/secretion of aromatase in adipose cells [317], and aromatase is known to convert androgens to estrogens [294], an aromatase-dependent hypothesis of MHC-II downregulation is extremely relevant in the context of obesity-induced thymic impairment. Besides MHC-II downregulation, estrogen treatment has been additionally demonstrated to induce methylation of the *AIRE* promoter, resulting in the downregulation of AIRE and AIRE-dependent tissue restricted antigens (TRAs) in the $mTEC^{hi}$ subset [318]. Because the expression of peripheral TRAs in $mTEC^{hi}$ is implicated in the establishment of central tolerance and future prevention of autoimmunity [319–321], these observations collectively suggest that enhanced estrogen signaling (possibly due to obesity or to other factors) may overall hijack the ability of $mTEC^{hi}$ to present antigens to positively selected thymocytes.

Besides estrogens, obesity is also associated with significant alterations in androgen secretion, transport, metabolism, and function in the body. Although androgens are produced by the testes and mainly stimulate male characteristics, it has been documented that androgen precursors may also be produced by the adrenal glands, and hence produced in females, too. Increased adiposity in males has been characterized by progressive decrease of testosterone levels, while in females, a functional hyperandrogenism tends to develop instead [322], thus partially explaining prior documented sex-related differences in thymus homeostasis and function. Although thymic involution has not yet been established as an intermediate pathology, the causative relationship between androgens and cancer, e.g., prostate cancer, has existed for long time [323]. It is therefore critical to ascertain whether obesity-driven androgen perturbations could systemically impact thymic functions, and as a result, lead to an increased cancer risk in both males and females.

In the thymus, exogenous androgen administration leads to thymic atrophy, whereas castration or pharmacological suppression of androgen synthesis both lead to increased thymic size in an androgen receptor- (AR-) dependent fashion [324–327]. *In vitro*, it has been shown that androgen administration in thymocytes can induce TNF production and apoptosis [328]. However, the latter seems to be either an *in vitro* bias, or just a secondary mechanism of androgen-dependent thymic atrophy, because an effect on thymic cellularity *in vivo* is observed only when AR is conditionally knocked out from the TEC compartment, and not from thymocytes [325]. Subsequent studies revealed that androgens can suppress key cTEC functions via suppressing the expression of essential microenvironmental prerequisites for thymocyte development, including CCL25 (thymocyte homing chemokine), DLL4 (T lineage commitment factor), IL7 (thymocyte survival and proliferation/expansion factor), and their ability to orchestrate positive selection [52,329,330]. Besides affecting cTEC function, there is no indication that androgens can directly impact cTEC growth and proliferation. Instead, there is evidence that $mTEC^{hi}$ growth can be obfuscated by AR signaling, and hence, castration alleviates the suppressive effect of androgens on $mTEC^{hi}$ growth [52]. In conflicting studies, AR-mediated signaling was found to upregulate the expression of AIRE and AIRE-dependent TRAs [318,331], thus offering an attractive explanation for the lower propensity of males, when compared to females, in developing autoimmunity. Therefore, obesity-driven androgen perturbations could potentially promote both damaging and protective effects on different thymic compartments, thus affecting distinct physiological processes. Although the androgen impact on thymic involution has been extensively investigated, most studies are limited to unraveling an effect under non-obese conditions, using pharmacological and or surgical manipulations, as described above. Hence, the precise impact of obesity-mediated androgen dysregulation in thymic function and cancer risk remains an open field of study.

4.4. Hyperinsulinemia and insulin-like growth factor 1 (IGF1) signaling

Among the well-documented signaling pathways via which obesity confers increased risk for cancer development is the insulin/IGF1 signaling axis [332–334]. Insulin is exclusively produced by the β cells of the pancreatic Islets of Langerhans and can positively trigger the expression and release of IGF1 from hepatocytes [335–337]. Overweight/obese individuals usually present with hyperinsulinemia coupled to elevated circulating levels of IGF1, while concurrently demonstrating low circulating levels of the insulin-like growth factor-binding protein 1 (IGFBP1), the latter functioning as endogenous IGF1 inhibitor capable of reducing IGF1 bioavailability after binding [338–340]. The current paradigm of how increased levels of IGF1 may contribute to neoplasia is mainly via its mitogenic activity. In particular, the binding of IGF1 to its cognate receptor (IGF1R) initiates mitogen-activated protein kinases (MAPKs) and the PI3K-AKT signaling pathway, both of which are known to promote tumor growth and proliferation among other cancer hallmarks [70,341–344]. Moreover, insulin and IGF1 cross-react with each other's receptors, thus forming stable insulin receptor/IGF1R heterodimers, which also potentiate the aforementioned oncogenic MAPK and PI3K/AKT signaling cascades [345,346].

Although the causative link between IGF1/IGF1R and cancer development has been studied and verified experimentally in transgenic mice [347–351], its direct effect in thymic functions has been particularly controversial. Early studies in a rat model of cyclosporine-induced thymic involution revealed that administration of recombinant human growth hormone (GH) and IGF1 accelerated thymic regeneration post-cyclosporine treatment [352]. Along these lines, a progressive decline in the plasma concentration of both GH and IGF1 has been associated with age-dependent thymic involution, and as such, the therapeutic delivery of GH, IGF1, and/or GH secretagogues, has been shown to partially reverse age-dependent thymic involution in both rodents and humans [353–356]. Although IGF1/IGF1R have been found to be expressed by the thymic epithelium, and in particular by Hassall's corpuscles [357], all the aforementioned studies collectively determined that GH/IGF1 primarily functions to restore the lymphocyte progenitor pool in the bone marrow, by suppressing lymphocyte apoptosis in a PI3K/Bcl2-dependent manner [353–356]. As such, GH/IGF1 may indirectly exert protective thymic functions by preventing failure of lymphocyte progenitor homing into the thymus [353–356].

Interestingly, the aforementioned studies are assessing the effects of GH and IGF1 in parallel, and as such, the individual contributions of these two hormones on thymic function, homeostasis and involution, are not as clear. This is especially relevant in view of the well-established regulatory interplay between GH and IGF1. For instance, it is long-known that IGF1 is under transcriptional regulation of the GH [358–361], and that GH secretion from the pituitary gland is decreased in obesity [362–365]. Despite this positive feedback loop, a high IGF1 expression along with insulin can in turn inhibit GH secretion in a negative-feedback loop [366], in part explaining why GH levels are low in conditions of high adiposity. Although these intricate hormonal regulatory mechanisms complicate our understanding on the individual

impact of the IGF1/Insulin axis on obesity-induced thymic involution, they sufficiently manage to highlight their importance in regulating thymic functions and homeostasis as a collective endocrine network.

Among the mechanistic principles (as dissected throughout Section 4), via which obesity promotes systemic perturbations leading to premature thymic involution, defective immune surveillance, and high cancer risk, the insulin/IGF1 axis seems to paradoxically and counter-intuitively elicit protective thymic functions. *Would it thus be erroneous to assume that obesity exerts at least one immuno-protective effect by amplifying the insulin/IGF1 axis?* To gain an insight into this question, one should consider that it is unlikely that obesity-induced hyperinsulinemia/IGF1 is the only metabolic perturbation of obese patients. Indeed, hyperinsulinemia is only one manifestation that typically precedes and then persists after the onset of type 2 diabetes; however, a large number of metabolic perturbations, including GH reduction, as explained above, characterizes type 2 diabetes [335,367–369], suggesting a complex regulatory cascade that could exert a damaging impact on thymic functions. Although literature suggests an overall positive impact of insulin/IGF1 on thymocyte development, one should therefore weigh benefit versus detriment (e.g., chronic inflammation, damaging adipokines, steroid hormones, etc.), when assessing the effects of high adiposity on immune cell development, function, and associated cancer risk.

5. Adipogenic transformation of the thymus – impact of aging and obesity

In the previous section, we explored mechanisms via which high adiposity promotes premature thymic involution, by exerting a systemic-endocrine effect on the thymus. However, it is now well-established that the thymus undergoes adipogenic transformation starting at middle-age, and in an exaggerated fashion it has been shown that by the age of 50, approximately 80% of the thymic mass becomes dysfunctional and composed of white adipose cells [370]. A similar phenomenon, in which hematopoietic niches are progressively occupied by adipose tissue, is also prevalent in the bone marrow with increasing age [371]. Because loss of thymocytes during age-dependent thymic involution precedes the emergence of white fat cells occupying intrathymic niches, the old dogma behind this puzzling phenomenon postulated that adipocytes are “passive” cells that simply cover for the loss of space during aging. This hypothesis has been repeatedly rejected however, because lymphopenic mice (e.g., SCID mice, RAG knockouts, IL-2 receptor chain knockouts), do not present with any intrathymic adipogenicity at all, despite the partial or complete absence of thymocytes [14,370,372]. Instead, several studies now support the alternative hypothesis that specific adipogenic mechanisms dominate over the differentiation program of thymic stromal cells, which eventually lead to the compromise of intrathymic niches [373,374].

Besides the better-established age-related factors, there is indirect evidence that obesity might be directly related to a premature imprinting of the adipogenic program in the thymic parenchyma. For example, dietary caloric restriction can specifically target the adipogenic program by reducing expression of PPARγ, a key transcription factor and master regulator of lipid uptake and adipogenesis in fat cells [375], on PDGFRα^{+} thymic mesenchymal cells [193]. Contextually, platelet-derived growth factor receptor-alpha (PDGFRα) expression in the thymus defines fibroblasts that are present in connective tissue capsule and trabeculae (i.e., capsular/trabecular fibroblasts), as well as peri-endothelial pericytes and adventitial cells that spatially demarcate the thymic perivascular space (PVS) in the medulla [376]. Interestingly, PDGFRα^{+} mesenchymal cells have high adipogenic potential and may give rise to ectopic adipocytes in many tissues under certain conditions [377]. Accordingly, intrathymic adipocytes observed in age-dependent thymic involution are not randomly distributed within the thymic parenchyma. Instead, they are spatially correlated with regions occupied by pre-existing PDGFRα^{+} mesenchymal cells [370]. Despite the above, we were unable to identify any studies, where similar observations were made more directly, for example whether increased calorie *intake* induces PPARγ-driven adipogenesis in the thymus.

As mentioned above, under conditions of defective high adiposity, ghrelin expression along with its beneficial anti-inflammatory and thymopoietic effects, is abolished [232]. Moreover, the experimental deletion of ghrelin in non-obese mice not only accelerates thymic involution but also increases intrathymic adipogenicity [374]. Although obesity-driven ghrelin suppression could potentially exert a similar phenotype, i.e., high intrathymic adipogenicity, this hypothesis has not been formally tested. Literature suggests that thymic adipogenicity may also occur under ghrelin-independent mechanisms [378]. Together, these data provide substantial, yet indirect, evidence that both obesity and obesity-driven metabolic disturbances could promote an intrathymic adipogenic program. Using scanning electron microscopy, Cavallotti et al. (2008) demonstrated in a definitive way that intrathymic adipocytes and thymocytes are in close proximity and can physically interact with each other [379]. Overall, despite these data being highly indicative of the existence of a paracrine loop between adipocytes and thymic parenchyma, the extent to which such network is sufficient and/or necessary to severely compromise intrathymic functions and hence, to promote premature thymic involution, remains to be resolved.

6. Clinical repercussions of obesity-induced thymic involution and cancer risk

Obesity is nowadays viewed as a rapidly growing public health problem reaching epidemic proportions worldwide [380–383]. Various epidemiological models and studies estimate that more than 25% of the global population will be obese (excluding overweight individuals) by 2025, raising a concern in health care burden and expenditure [380, 384–386]. It is likely that increased prevalence of obesity in both developed and developing countries will lead to increased prevalence of cardiovascular disease, diabetes, and cancer [380–383,387–389]. Many studies have evaluated the contribution of obesity as comorbidity to the aforementioned diseases, as they belong to the most burdensome illnesses for the patient and the healthcare system. However, less is known about how obesity affects the immune system in general. Here, we examined possible repercussions of obesity on thymic functions, which are otherwise known to naturally decline with increasing age [56]. Hence, a deeper understanding behind the mechanisms via which obesity compromises thymus health and homeostasis to promote emergence of new cancers, will help us gain a more holistic overview of the obesity-cancer relationship, and also help develop novel therapeutic and/or preventive interventions to support thymic health in obese patients at high risk of developing neoplastic disease.

As an exaggerated example delineating the importance of the pediatric thymus in establishing a lifelong T cell repertoire in adulthood, a prominent study has revealed that surgical resection of the thymus in pediatric patients leads to significant naïve T cell loss, and that the peripheral T cell repertoire of thymectomized young adults (i.e., at 22-years of age) is reminiscent of an old individual’s [390]. As such, obesity-induced thymic involution could be particularly relevant in obese children, as this condition can become a key molecular determinant of premature thymic involution with lifelong impairments on systemic immunity, with the potential of leading to early cancer onset. The prevalence of childhood obesity is alarmingly high with an estimated number of 42 million obese/overweight children under the age of five living globally on 2010 [381].

It is generally accepted that obesity results from imbalance between energy intake and expenditure. Although generally, dietary intake, physical activity (e.g., sedentary behavior), and genetic predisposition have been among the most established risk factors of obesity, it has been proposed that several other factors could be equally impactful in the context of childhood obesity. Examples of those, are family characteristics, parenting style/habits, the lifestyle of parents, as well as

environmental factors, such as school culture, and neighborhood characteristics among others [391–397]. Such epidemiologic evidence advocates that the emerging concept of obesity-induced thymic involution in children should not only be examined from the traditional molecular/cellular perspective, but also from a socio-economic standpoint.

7. Conclusions

Despite depicting an early phenotypic observation, the mechanistic links between high adiposity and hindered thymic functions have only recently begun to emerge. Although the dysfunctional obese adipose tissue promotes the perturbation of a variety of systemic factors impacting thymic functions, including but not limited to: proinflammatory cytokines, adipokines, as well as sex and metabolic hormones, one should consider that each of these factors may individually exert either supportive or suppressive effects on thymopoiesis. Thus, experimental and clinical observations that obesity may promote premature thymic involution surmises that the thymus-suppressive factors can cumulatively outweigh the thymus supportive ones, when viewed under a common model of systemic regulation of thymopoiesis (**Fig. 3**). To our knowledge, there are currently not many studies that mechanistically investigate the adverse late effects of childhood obesity on premature thymic involution leading to impaired immune surveillance and increased cancer risk. In the future, it will be the duty of the basic and clinical scientists working together under one auspice, to elucidate the precise mechanistic underpinnings underlying this newly documented phenotype, and propose therapeutic interventions to promote thymus health in overweight/obese children.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Data availability

No data was used for the research described in the article.

Authorship

MKL and GSK conceived the idea, drafted the figures, wrote the manuscript and agreed to the submitted version of the manuscript.

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