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Decoding T cell senescence in cancer: Is revisiting required?

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ABSTRACT

Senescence is an inherent cellular mechanism triggered as a response to stressful insults. It associates with several aspects of cancer progression and therapy. Senescent cells constitute a highly heterogeneous cellular population and their identification can be very challenging. In fact, the term "senescence" has been often misused. This is also true in the case of immune cells. While several studies indicate the presence of senescent-like features (mainly in T cells), senescent immune cells are poorly described. Under this prism, we herein review the current literature on what has been characterized as T cell senescence and provide insights on how to accurately discriminate senescent cells against exhausted or anergic ones. We also summarize the major metabolic and epigenetic modifications associated with T cell senescence and underline the role of senescent T cells in the tumor microenvironment (TME). Moreover, we discuss how these cells associate with standard clinical therapeutic interventions and how they impact their efficacy. Finally, we underline the importance of precise identification and thorough characterization of "truly" senescent T cells in order to design successful therapeutic manipulations that would delay cancer incidence and maximize efficacy of immunotherapy.

Abbreviations: RS, Replicative Senescence; SIPS, Stress-Induced Premature Senescence; DNA DDR, Damage Response; SASP, Senescence-Associated Secretory Phenotype; NK, Natural Killer; OIS, Oncogene-Induced Senescence; ROS, Reactive Oxygen Species; TIS, Therapy-Induced Senescence; HIV, Human Immunodeficiency Virus; CMV, Cytomegalovirus; SARS-CoV-2, Severe Acute Respiratory Syndrome CoronaVirus 2; KLRG1, Killer cell lectin-like receptor subfamily G member 1; RIPK1, Receptor Interacting Protein Kinase 1; SA-b-Gal, Senescence Associated beta Galactosidase; SOD, Superoxide Dismutase Type, TNF-a, Tumor Necrosis Factor-alpha; IL-6, Interleukin-6; AMPK, Adenosine Monophosphate-activated Protein Kinase; P38MAPK, p38 Mitogen Activated Protein Kinase; DC, Dendritic Cell; PD-L1, Programmed cell Death Ligand-1; ADCC, Antibody-Dependent Cellular Cytotoxicity; TME, Tumor Microenvironment; TILs, Tumor-Infiltrating Lymphocytes; IL-2, Interleukin-2; CTLA-4, Cytotoxic T Lymphocyte Associated protein-4; Tim-3, T cell immunoglobulin and mucin-domain containing-3; LAG-3, Lymphocyte-Activation Gene 3; BTLA, B and T-lymphocyte attenuator; TIGIT, T-cell Immunoreceptor with Ig and ITIM domains; ICI, Immune Checkpoint Inhibitor; IL-8, Interleukin-8; IL-2, Interleukin-2.; IFN-γ, Interferon-gamma; TGF-β, Transforming Growth Factor-beta; GzmB, Granzyme B; TCR, T Cell Receptor; ZAP70, Z chain Associated Protein kinase 70; Lck, Lymphocyte specific protein tyrosine kinase; Lat, Linker for activation of T cells; DLG1, Disks Large homolog 1; SLP-76, SH2 domain containing Leukocyte Protein of 76 kD; Treg, T regulatory; ATM, Ataxia Telangiectasia Mutated; CAMP, cyclic Adenosine Mono-Phosphate; PKA, Protein Kinase A; GPR84, G-protein-coupled receptor 84; CPLA2, group IVA phospholipase A2; MAPK, Mitogen-Activated Protein Kinase; STAT1/3, Signal Transducer and Activator of Transcription 1/3; H3K27me3, Histone H3 lysine 27 trimethylation; KLF2, Kruppel like factor 2; FOXO1, Forkhead box protein O1; Tcf7, transcription factor 7; LEF-1, Lymphoid Enhancer-binding Factor-1; MDSCs, Myeloid Derived Suppressor Cells; Foxp3, Forkhead box P3; NSCLC, Non Small Cell Lung Cancer; IrAE, immune-related Adverse Events; NRF-2, Nuclear factor erythroid 2-related factor 2; BHLHE40, Class E basic helix-loop-helix protein 40.

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1. Cellular senescence in the context of cancer

Senescence is an inherent homeostatic cellular mechanism triggered upon stress insults [1]. It was initially reported in cell culture in the form of Replicative Senescence (RS) that senescence depends on telomere shortening and/or dysfunction [2]. However, it soon became evident that various stress signals can induce an independent of telomere length senescence type, termed Stress-Induced Premature Senescence (SIPS) [2]. Irrespective of the type or stress inducer in the majority of cases, senescence is the outcome of a sustained DNA damage response (DDR) [1,2]. Nowadays, it is recognized that senescent cells comprise a very heterogeneous cellular population characterized by a highly variable transcriptome profile and a temporal/dynamic phenotype [3]. RNA-seq analyses have shown that senescent cells of different cell types present different characteristics [3]. However, even in the same cell type, the senescence phenotype can largely vary, depending on the hallmarks of the stressor or the senescence phase (early or late) [4–6].

This dynamic nature of senescent cells renders their characterization a quite elaborate and challenging task. Despite this multi-faceted phenotype, they share four interconnected hallmarks: a) cell cycle withdrawal, b) de-regulated metabolism, c) macro-molecular damage and d) a proinflammatory secretory activity, termed SASP [1,7] (Fig. 1). Overall, senescent cells do not divide, remain viable and metabolically active but have developed mechanisms to tolerate cell death while harboring damage, features that led to their characterization as "zombie" cells. Interactions between non immune senescent cells and the immune system are dynamic. As a homeostatic mechanism, transient senescence contributes to the removal of dysfunctional cells by the immune system, during physiological processes. Senescent cells trigger their elimination by recruitment of immune cells (mainly Natural Killers, (NKs) [8]) or initiate immune surveillance [9,10]. They may also directly initiate T-cell responses by expressing antigen presenting MHCI [11] or MHCII [12] molecules. However, when not timely removed senescent cells accumulate in tissues, favoring aging and the pathogenesis of many age-related disorders such as cancer.

Indeed, during carcinogenesis, senescence plays a pivotal role. In the early stages of cancer and in line with the oncogene-induced DNA damage model for cancer development, cellular senescence acts as an anti-tumor barrier, restricting the expansion of developing cancer cells [13,14]. However, cells undergoing OIS, being in a "dormant state", can exert tumor promoting properties in later stages, either via their SASP or by "escaping" from OIS [2,8,15–18]. Regarding SASP, depending on its composition, although it may initially play a beneficial role supporting tumor immune surveillance [19] and facilitating tumor stalling [20], on a long term basis it becomes detrimental. Particularly, SASP can interact with the tumor microenvironment (TME) mediating a variety of processes [21]. These include stemness and invasiveness of tumor cells [22], as well as resistance to ferroptosis [23], tumor-associated angiogenesis or vessel hyperpermeability [24] and immune evasion and suppression [20,25,26]. As far as senescence "escape" is concerned, replication stress induced genomic instability fuels further alteration of the genomic landscape and can drive breach of the tumor-suppressing barriers of apoptosis and senescence and cell cycle re-entry accompanied by malignant transformation, eventually favoring cancer progression [2,15–18].

In the course of anti-cancer therapy, senescence may be also triggered in both malignant and non- malignant cells (including immune populations), given that conventional clinical manipulations

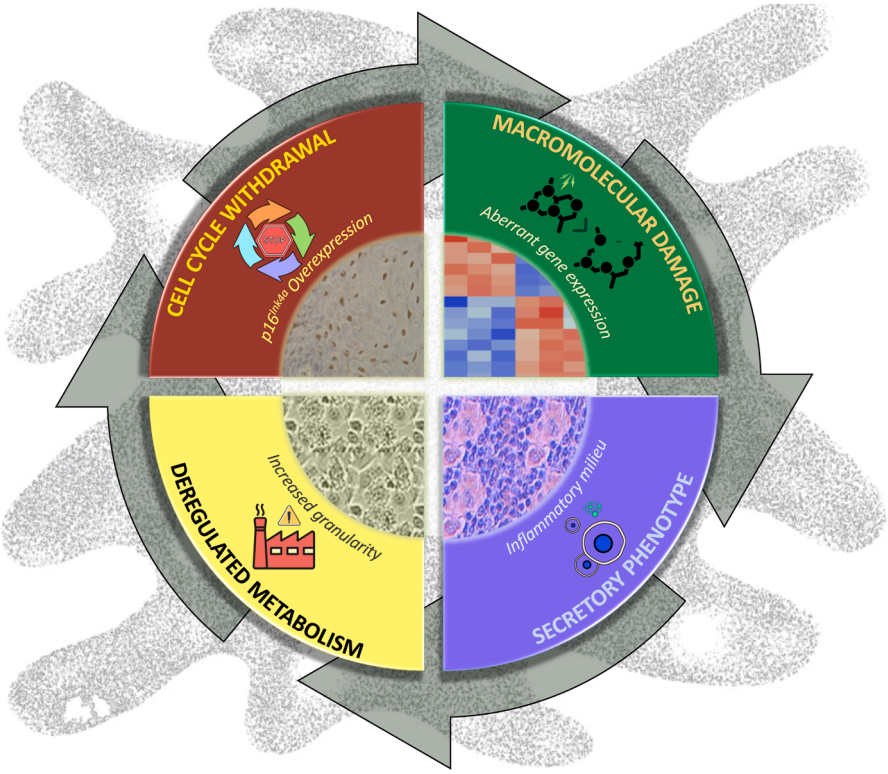


Fig. 1. Major hallmarks of senescent cells. Senescent cells exhibit four inter-dependent (curved arrows) hallmarks: 1) cell cycle withdrawal, 2) Senescence Associated Secretory Phenotype (SASP), 3) macromolecular damage and 4) altered gene expression, as depicted in the outer circle. The inner cycle includes distinct morphological and functional features that mirror these hallmarks. Cell cycle withdrawal is represented by $p16^{Ink4a}$ overexpression (*brown nuclear signal-upper left image*) while the inflammatory milieu is associated with SASP. Lipofouscin accumulation assessed with GL13 (SenTraGor) staining (*brown cytoplasmic staining- lower right image*) reflects macromolecular damage and deregulated metabolism. Altered "gene expression" is associated with transcriptional "noise" boosting macromolecular damage [205] and translation deficiency may additionally favor lipofuscin assembly [122], while increased cytoplasmic granularity (*lower left image*) due to the accumulation of defective lysosomes and dysfunctional mitochondria mirrors deregulated metabolism.

(chemotherapy, radiotherapy, targeted therapies) target proliferating cells conferring DNA damage and ROS production [27–30]. Again, although the so-called TIS initially associates with beneficial events halting proliferation of tumor cells, accumulating evidence suggests that senescence may eventually contribute to reduced patient resilience to cancer therapies and via "escape" from TIS to disease recurrence [31–34]. Taken together, cellular senescence is a heterogeneous, multi-faceted and dynamic phenomenon, exerting a bimodal mode of action during carcinogenesis and following traditional anti-cancer therapies that is time and context dependent, similar to autophagy [35], rendering its manipulation for tumor handling a very challenging task.

2. Immune senescence: "Uncharted waters"

Despite its established contribution to several aspects of tumor initiation, progression and therapy, senescence has been almost exclusively studied in the non-immune compartment. In fact, the incremental use of the term 'immunosenescence' in recent literature mostly refers to the organismal age-related deterioration of immune functions and responses that are associated with inflammaging, decreased new T-cell generation by the thymus, hematopoietic stem cell dysfunctions, decreased naïve and increased memory lymphocyte numbers and compromised efficacy of regulatory cells [36,37]. It has also been described as an adaptive mechanism that prevents from T-cell inflation and maintains memory cell function [38].

However, although interconnected and highly associated, immune senescence cannot be exclusively attributed to aging, as this stress-response mechanism may occur throughout human lifespan, even during embryonic development [1,39]. In line with this notion, senescence has been reported irrespective of age in various contexts encompassing involvement of the immune system including autoimmune diseases [40–42], viral infections (HIV, CMV, SARS-CoV-2) [43–45] and anti-cancer therapies [46–50].

At the cellular level, the term 'immunosenescence' mainly refers to a lymphocyte population that undergoes replicative senescence, exerting SASP and is mostly intertwined with inadequate expansion of T cell receptors [51] and broad compromised immune activation [51,52]. So far, the presence of KLRG1, CD57 and γ-H2AX or loss of CD28 and CD27 have been attributed to senescent T cells [37]. However, to the best of our knowledge, until now there has been no specific marker to accurately identify immune cell senescence. The majority of the investigations dealing with this matter and presented herein refer to senescence based on markers that can be shared with other dysfunctional cell states. Thus, the term "senescence" has been often misused in the literature and misleading conclusions have been drawn. This motivated the senescence community to propose a multi-marker algorithmic approach for precise senescence identification [1,7,53]. As an example, RIPK1 deficient CD4 T cells were characterized as senescent ones, based on the upregulation of SASP-related genes, while commonly applied senescence markers were lacking and proliferation markers, well-known to be downregulated in senescence, such as Ki67 were markedly elevated [54]. Taken together, we present a critical overview of the current literature on what has been previously described as T cell senescence and provide grounds supporting the need for revisiting the field.

Being the most prominent weapon in the immune armamentarium in vertebrates, T cells will be the focal point of this review. Nevertheless, we believe that it is also important to briefly summarize the available studies reporting "senescence" in other immune cell types that are also implicated in tumor-mediated responses such as Natural Killers or Neutrophils, or interact with T cells such as Dendritic cells or Macrophages.

2.1. Natural killer cells (NKs)

Regarding NKs, several studies document the reduced efficacy of NKs in aged humans or mice [55–57]. Senescent NK cells defined by concurrent SA-b-Gal and CD57 positivity have been detected in murine breast cancer and melanoma tumors, exhibiting impaired functions, active glucose and lipid metabolism [58]. Of note, unlike T cells, high CD57 positivity is observed among terminally differentiated NK cells, that are highly cytotoxic and preserve their capacity to proliferate [59]. A senescent cell phenotype has been described upon CD158 activation in NKs mediating proliferation arrest, alterations in shape, as well as angiogenic properties through SASP [60].

2.2. Macrophages

Intriguingly, mature macrophages share common features with nonimmune senescent cells, such as cell cycle arrest, a secretory phenotype and increased lysosomal load [61]. Senescent-like $p16^{Ink4a+}$/SA-b-Gal^{+} macrophages have been reported in mice [62–64] and have been associated with the immunosuppressive M2 phenotype [62]. Age-related decrease in macrophage efficiency has also been extensively reported [65–68], however, it has not been linked to cellular senescence. Noteworthy, $p16^{Ink4a}$ expression and SA-β-Gal activity have been detected in non-senescent macrophages and therefore senescence may be difficult to be validated in this cell population [62], rendering the need for new senescence markers imperative.

2.3. Microglia

Microglia is part of the neuronal support tissue and refers to a population of resident immune cells within the central nervous system (CNS) responsible for surveillance [69]. Senescent Microglia cells have been identified in the brain of aged mice and isolated from transgenic rats (bearing the SOD^{1G93A} mutation that is linked to amyotrophic lateral sclerosis. Although they have been shown to drive aging of the brain and its disorders, they present distinct features compared to aged brain microglia cells [70–73].

2.4. B cells

In the case of B cells, a double negative IgD/CD27 peripheral population has been characterized as senescent/exhausted [74]. These cells exert SASP (produce cytokines such as TNF-a, IL-6 without being stimulated), express $p16^{Ink4a75}$ and are less responsive to antigens [75,76]. In this context, the metabolic sensoring enzyme AMPK and p38MAPK signaling pathways have been shown to be upregulated [75]. Enrichment of a senescent B cell related gene signature in bladder cancer patients was recently found to predict poor response to immunotherapy and unfavourable outcome [77].

2.5. Neutrophils

Senescence has been recently reported in neutrophils of chemotherapy receiving breast cancer patients, favoring chemoresistance [78]. In the case of neutrophils, the term "senescent" is often misused to describe the pro-apoptotic terminally differentiated ones [79–81]. However, a recent study identified a senescent neutrophil subpopulation selectively located within the TME that is more suppressive than its non-senescent counterpart and is highly resistant to apoptosis [82]. A senescent neutrophil signature derived by this study was also associated with a poor prognosis in prostate cancer patients [82]. In line with this notion, senescent neutrophils have been shown to promote chemoresistance in breast cancer [78].

2.6. Dendritic cells (DCs)

DCs are specialized antigen-presenting cells with a crucial role in T-cell mediated anti-tumor immunity [83]. The impact of aging in DC efficacy has been documented [84]. Senescent SA-b-Gal^{+} DCs have been shown to exert tolerogenic activity in breast cancer [85]. Of note, tumor-derived γδ Tregs facilitate senescence induction in DCs via PD-L1 and STAT3 signaling promoting tolerogenic functions in breast cancer [85,86].

Given that all the aforementioned immune subpopulations co-

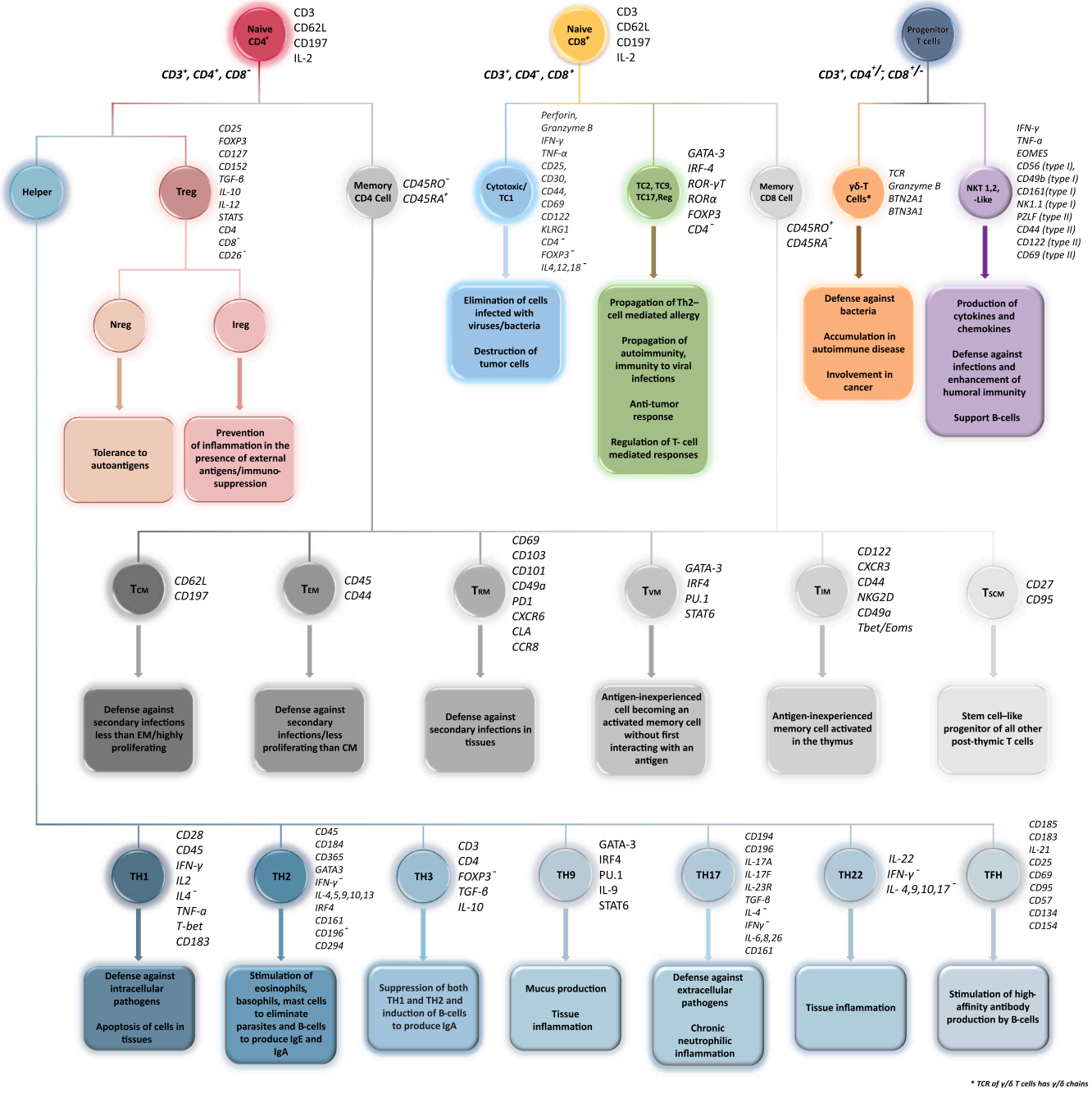


Fig. 2. Major T-cell subtypes: functions and markers. Upon stimulation, naïve T cells may differentiate into CD4^{+} T helper, CD8^{+} T cytotoxic effector cells (Tc1, Tc2, Tc9, Tc22, Tc17) or memory cells. Among CD8^{+} T cells, the most typical cytotoxic T subtype is the Tc1 group, being able to directly kill tumor cells. Among CD4^{+} T helpers we may identify the following groups: Th1 and Th9 are considered the predominant anti-tumor players. On the other hand, Th2 and Th17 cells may exert beneficial or deleterious actions. Th22 are associated with induction of inflammation, Th3 play a regulatory role and T follicular helper (Tfh) cells interact with B cells. Memory T cells may be either CD8 or CD4, mediate the long-lived anti-tumor immunity because they can immediately expand upon reencountering the antigen they experienced. According to their phenotype and function, memory T cells may be subdivide in to the following groups, most common being the central (Tcm), effector (Tem) and tissue-resident memory (Trm) memory. Virtual memory (Tvm) and innate memory (Tim) T cells share a memory-like phenotype without previous exposure to an antigen. Finally, stem-cell like T memory cells (Tscm) are characterized by consistent self-renewing. Among CD4 cells, T regulatory cells (Tregs) are considered the main immunosuppressive population inhibiting the anti-tumor responses and can be subdivided at thymic derived natural (nTregs) or peripherally induced (iTregs). Finally, the rear populations of γδ TCR are characterized by gamma and delta chains in the TCR complex and may have controversial role in tumor progression. Natural Killer T (NKT) cells share common markers of NK and T cells and have a regulatory effect on other immune cell types by amplifying their response.

inhabit the TME with T cells, senescence may affect their interactions leading to immune dysfunctions or aberrant expansion. For instance, a DC senescent phenotype may have a tolerogenic impact either leading to T cell anergy or promoting Treg cell induction. Deficient recognition of antigens by senescent B cells might render them unresponsive to T cell helpers leading to decreased antibody production and impaired ADCC.

3. T-cell senescence, exhaustion and anergy: dysfunctional T cell states that require clear demarcation

T cells constitute a hallmark of immune surveillance in cancer and are of therapeutic and prognostic relevance. Although $CD8^+$ T cells mediated responses are considered to be the most prominent against tumor cells, CD4 T cells comprise an equally important player. The major T cell subsets, their main functions, and characteristic markers are summarized in Fig. 2 [87–94], as their extended description goes beyond the scope of the current work. T-cell functional state in the TME is considered as a critical determinant of effective antitumor immunity and immunotherapy response [95,96]. Several studies have revealed that although T lymphocytes including $CD4^+$ and $CD8^+$ T cells highly infiltrate the TME to eradicate tumor cells, they eventually fail to counteract tumor progression. The latter suggests that the TME converts the functional TILs into dysfunctional hyporesponsive ones that hinder effective antitumor immunity and induce immunotherapy resistance [97–99].

T-cell anergy, exhaustion and senescence are the major dysfunctional T-cell states found in the TME and share common functional defects, such as deficient proliferation, impaired cytotoxicity and cell cycle arrest. However, anergic, exhausted and senescent T cells differ in terms of generation and development as well as in their metabolic and transcriptional profiles in the course of tumor progression [100,101]

Anergy is a T-cell hyporesponsive state characterized by diminished IL-2 secretion and cell cycle arrest in G1/S phase [102,103] found to occur in T cells that infiltrate tumors [104]. Antigen-specific T-cell anergy is commonly developed in the early stages of tumor development due to the immunosuppressive nature of the TME. Defective maturation of DCs seems to account for improper tumor antigens presentation [105], resulting thus in anergic T-cell phenotypes due to the poor co-stimulatory and/or high co-inhibitory signals [106,107]. Unfortunately, the downstream molecular pathways governing the anergic state remain elusive and the lack of surface markers for the definition of anergic T cells makes it even harder to fully decipher this dysfunctional state.

T-cell exhaustion is another dysfunctional state initially described in chronic viral infections, however exhausted T cells have also been identified in cancer patients and are associated with poor prognosis and poor therapeutic outcome [108,109]. The dominant trait of exhausted T cells in the TME is the enhanced expression of several inhibitory receptors, PD-1, CTLA-4, Tim-3, LAG-3, BTLA, TIGIT, the natural killer cell receptor 2B4 (also called CD244), and the glycoprotein CD160 [110,111]. Nevertheless, the elevated expression of inhibitory receptors is not sufficient for the characterization of a T cell as exhausted because T-cell activation generally upregulates the above-mentioned inhibitory molecules. Importantly, current ICIs have been designed to target several of those inhibitory receptors (i.e. PD-1, CTLA-4) to restore the effector functions of exhausted TILs showing promising results in many types of cancer [112,113]. However, their overall response rates remain limited, indicating the presence of other mechanisms of resistance in the TME beyond T-cell exhaustion. Of interest, exhausted T cells have been reported to exhibit increased SA-b-Gal activity and overexpression of potent cell cycle regulators such as $p21^{Waf1/Cip1}$ and $p16^{Ink4a}$, markers commonly also evident in senescent cells [114].

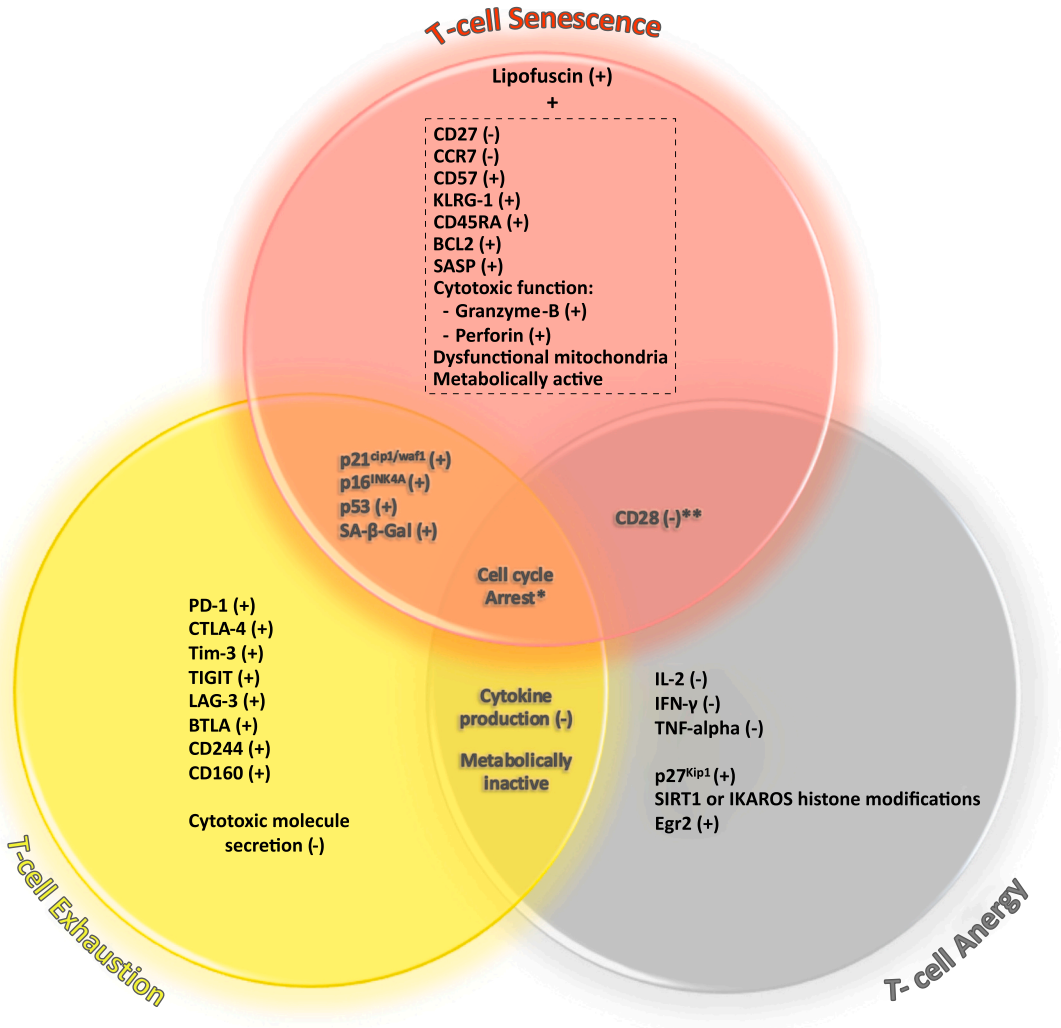
Similar to exhausted, senescent T cells have been reported accumulating in tumor-bearing hosts [115,116]. T cells presenting specific phenotypic changes, telomere shortening, cell cycle arrest and reduced effector functions have been characterized as senescent ones. As aforementioned, among the phenotypic alterations, high expression of SA-β-Gal [117,118], loss of the costimulatory molecules CD27 and CD28 as well as the significantly enhanced expression of CD57, KLRG1, Tim-3 and CD45RA are the most typical phenotypic changes found in these T cells [117,119,120]. However, the increased heterogeneity within the circulating and tissue-resident T-cell compartment along with the lack of a single and specific senescent biomarker renders the characterization of senescent T cells a brain teaser. Towards this notion, the use of a broader multi-marker approach is recommended for more robust detection of senescent T cells *in situ* [1,7,53]. Of note, we have recently generated a new Sudan Black-B (SBB) based fluorophore-conjugated compound termed GLF16 that strongly interacts with lipofuscin [121]. Lipofuscin, the "dark matter" and hallmark of all senescent cells accumulates in their cytoplasm reflecting both macromolecular damage and deregulated metabolism [1,122] (Fig. 1). This reagent complements our previous SBB analogue (GL13) [123] and allows for analysis of senescence by fluorescence microscopy and importantly by flow cytometry, an essential assay in Immunology, overcoming existing drawbacks when studying senescence. As such, it has emerged as a powerful new tool for the identification and live tracking of senescent immune and T cells *in vitro* and *in vivo* [7,121]. In fact, given that widely applied markers to assess cellular senescence such as SA-b-Gal, $p16^{Ink4a}$ and $p21^{Waf/Cip1}$ have been also observed in the context of exhaustion, lipofuscin accumulation seems the only reliable option to distinguish exhaustion from senescence [124] (Fig. 3, Table 1).

Unlike exhausted, T cells described as senescent remain metabolically active and produce high amounts of proinflammatory cytokines, such as IL-6, TNF-a, IL-8, and IFN-γ, as well as the suppressive cytokines IL-10 and TGF-β [125] that potently amplify immunosuppression within the TME. While in non-immune cells the SASP secretome more likely favors cellular senescence, in immune cells that physiologically secrete a variety of cytokines, assessment of senescence relying exclusively on SASP markers can lead to misleading outcomes. Moreover, the large range of cytokines mapped in the T cell SASP-like secretome, may also indicate that senescent T cells could emerge in various flavors.

On the other hand, similar to exhausted T cells, T lymphocytes that are characterized as senescent, exhibit impaired cytotoxicity due to the diminished expression of the effector molecules perforin and GzmB [125]. In addition, they do not respond to TCR triggered proliferation as they have lost the key molecules involved in the TCR signaling, including ZAP70, Lck, Lat, DLG1 and SLP-76 [125]. Cell cycle arrest is mediated by the up-regulation of the cell cycle inhibitors $p16^{Ink4a}$, $p21^{Waf1/Cip1}$ and p53 [92,93,117,125]. Major characteristics and markers that could facilitate the discrimination of senescent T cells against exhausted and anergic ones are summarized in Fig. 3 and Table 1.

4. Metabolic and epigenetic reprogramming of putative senescent T cells in cancer

Metabolic fitness is crucial for the activation and function of T lymphocytes [126]. As a result, T cell metabolism has been thoroughly investigated in recent years, however, the metabolic regulation of reported T cell senescence remains elusive [127]. More specifically, it has been demonstrated that putative senescent $CD8^+$ T cells defined as $KLRG1^+/CD57^+/\gamma\text{-}H2AX^+/Ki67^-$ preferentially employ glycolysis for energy production, as opposed to non-senescent subsets which are considerably more metabolically adaptable and can use either glycolysis or oxidative phosphorylation (OXPHOS), to support their effector functions [128]. Importantly, senescent $CD8^+$ T cells experience mitochondrial dysfunction and ROS accumulation which might explain why they depend on glycolysis for energy production [128]. These mitochondrial defects may derive from the activation of p38 and inhibition of the PI3K/Akt/mTOR axis to regulate autophagy [128]. Another study reported that in $CD4^+/CD27^-/CD28^-$ T cells, p38 is activated by the metabolic sensor AMPK [129] upon detection of intracellular changes including DNA damage and drop of energy levels. In turn, p38 activation



Abbreviations:

PD-1:	Programmed cell death protein -1
CTLA-4:	Cytotoxic T lymphocyte -associated protein 4
Tim-3:	T cell immunoglobulin mucin -3
TIGIT:	T-cell immunoglobulin and immunoreceptor tyrosine -based inhibitory motif (ITIM) domain
LAG-3:	Lymphocyte-activation gene 3
BTLA:	B and T-lymphocyte attenuator
CD244:	Natural killer cell receptor 2B4
CD160:	Natural Killer Cell Receptor BY55
CD28:	Cluster of Differentiation 28
CD27:	T-Cell Activation Antigen CD27
CCR7:	C-Chemokine receptor type 7
CD57:	beta-1,3-glucuronyltransferase 1
KLRG-1:	Killer-cell lectin-like receptor G1
CD45RA:	Long isoform of Protein tyrosine phosphatase, receptor type, C
p21cip1/waf1:	Cyclin-dependent kinase inhibitor 1
$p16^{INK4A}$:	Cyclin-dependent kinase inhibitor 2A
SA-β-Gal:	Senescence associated β-galactosidase
BCL2:	B-cell leukemia/lymphoma 2
SASP:	senescence associated secretory phenotype: IL -2, IL-6, IL-8, TNF-alpha, IFN-γ and the suppressive cytokines IL -10 and TGF-β
SIRT1:	Histone deacetylase Sirtuin 1
IKAROS:	Transcription factor
Egr2:	Early growth response protein 2

* Mediated by $p27^{Kip1}$ in Anergy and by p21 $^{cip1/waf1,}$ $p16^{INK4A}$ and p53 in both Exhaustion and Senescence (See Table for details)
** Inhibition in Anergy, Loss in Exhaustion

Fig. 3. Significance of lipofuscin accumulation in discriminating senescent against exhausted and anergic T cells. Overview of major markers and features accompanying senescent, exhausted and anergic T cells. Lipofuscin accumulation is essential compared to the other markers in characterizing senescent T cells and holds a central role for their distinction from exhausted and anergic ones (see text for details).

prevents T cell proliferation and telomerase activity [129].

Although, many types of cancer cells [119,130,131] can directly induce cellular senescence in TILs, limited information exists on T cell senescence induction upon interaction (direct or indirect) with other cells of the immune system or non-hematopoietic cells (i.e. stromal cell) within the TME. To this end, recent studies have demonstrated that Tregs that highly infiltrate the TME are also capable of inducing effector T cell senescence in different ways. In detail, Treg cells in the tumor mass exhibit increased glucose uptake and elevated glycolysis capacity and as a result, they antagonize with effector T cells for glucose consumption. This competition for glucose uptake initiates an ATM-mediated DNA damage response and induces a senescence-like phenotype in responder T cells characterized by the simultaneous loss of CD27 and CD28 co-stimulatory receptors and the upregulation of SA-β-Gal, $p16^{Ink4a}$, $p21^{Waf1/Cip1}$ and p53 cell cycle inhibitors [132,133]. In addition, reported T-cell senescence may also be regulated by glucose metabolites within the TME. More specifically, cAMP which is highly produced by tumor cells, represents a critical component of the hypoxic TME that could potently inhibit the function of tumor-specific effector T cells [134,135]. It has been shown that effector T cells can directly receive cAMP from tumor cells via gap junctions. The transferred cAMP then activates the PKA-LCK pathway and an ATM-mediated DNA damage

Table 1
Markers discriminating T-cell Senescence from Non-Immune Senescence, T-cell Exhaustion and T-cell Anergy [206–213].

Feature	Markers				
	Non-immune Senescence	T-cell Senescence	T-cell Exhaustion	T-cell Anergy	References
Surface factor	DcR2 (+), DPP4 (CD26) (+), uPAR (+), ICAM-1 (+), DEP1 (+), NOTCH1 (+), B2MG/B2M (+), CD9 (+), CD264 (+), CD36 (+), SCAMP4 (+), NKG2D (+), ULBP2 (+), CD30L (+), CD153 (+)	CD27 (-), CD28 (-), CD57(+), CCR7 (-), KLRG-1 (+), CD45RA (+)	PD-1 (+), CTLA-4 (+), Tim-3 (+), TIGIT (+), LAG-3 (+), BTLA (+), CD244 (+), CD160 (+)	CD28 (-)	1, 7, 37, 53, 118, 121, 179, 198, 208, 209, 210, 211, 212, 213 *206 and 207 **179 ła198 łb15 §124 (and Refs therein) #Depends on cell type and stimulus
SA-β-Gal activity	(+/-*), false positive in non senescent cells*	(+/-)§	(-/+**)	NE	
Lipofuscin accumulation	SenTraGor (+), GLF16 (+)	SenTraGor (+), GLF16 (+)	(-)	(-)	
Cytokine expression	SASP (+)#: IL-6, IL-8 , IL-1a, IL-1b, CXCR2, IGF2, IGFBP3, IGFBP5, IGFBP7, STC1 , GDF15, SERPINs, CCL2 , CXCL1, CXCL2, CXCL10, IL15, VEGFA	IL-2, IL-6, IL-8, TNF-a and IFN-γ, suppressive cytokines IL-10 and TGF-β	(-)	(-)	
Metabolic Alterations	Dysfunctional mitochondria (+), Glycolysis (+), ROS (+), OXPHOS (-), p38 phosphorylation (+)	Dysfunctional mitochondria (+), Glycolysis (+), OXPHOS (+) , ROS (+), cPLA2a (+), p38 phosphorylation (+)	Dysfunctional mitochondria (+), Glycolysis (-), OXPHOS (-), p38 phosphorylation (+)	Metabolically anergic	
Nuclear membrane	Lamin B1 (-)	NE	Lamin B1 (-)**	NE	
Cell Cycle arrest	p53 (+), $p21^{Waf1/Cip1}$ (+), $p16^{Ink4a}$ (+)	p53 (+), $p21^{Waf1/Cip1}$ (+), $p16^{Ink4a}$ (+)	p53 (+), $p21^{Waf1/Cip1}$ (+), $p16^{Ink4a}$ (+)	$p27^{Kip1}$	
Proliferation	Generally absent: Ki67 (-), BrDU (-)/Under circumstances cell cycle re-entrance ła and łb	Generally absent: Ki67 (-). BrDU (-)/ Retain the capacity to proliferate§	In principle absent. Able to proliferate§	Absent	
DNA Damage	p-ATM (+), γ-H2AX (+), 53BP1 (+), DNA-SCARS/TAFs (+)	p-ATM (+), γ-H2AX (+)	p-ATM (+), γ-H2AX (+)	NE	
Apoptosis Resistance	BCL-2 family members (+), Annexin V (-), Caspases (-), TUNNEL (-)	BCL-2 (+)	Susceptible to apoptosis: PD-1 (+)	BCL-2 family members (+)	
Telomere length	Short/dysfunctional	Short/Intact	Intact/Short	NE	
Telomerase activity	(-)	(+/-)	(-)	NE	
Chromatin Modifications	SADs/SAHFs (+), H3K9-methylation (+), PML bodies (+), HP1-γ (+), HIRA (+), macroH2A (+)	FOXO1, KLF2, TCF suppression via DNA methylation (+), H3K27me3 (+), Loss of open chromatin configuration at promoters	TOX and NR4a linked epigenetic changes, DNMT3A mediated increased chromatin accessibility	IKAROS (acetylation), Sirt1 (+)	
Cytotoxic function	(-)	Granzyme-B (+), Perforin (+)	(-)	(-)	

Abbrevations:
CXCR2: Interleukin 8 receptor, beta
IGF2: Insulin-like growth factor 2
IGBP3: Insulin like growth factor binding protein 3
IGBP5: Insulin like growth factor binding protein 5
IGBP7: Insulin like growth factor binding protein 7
CXCL2: MIP2-alpha
CXCL10: IP-10
VEGFA: Vascular endothelial growth factor A
TNF: Tumor Necrosis Factor
OXPHOS: Oxidative Phosphorylation
BrDU: Bromodeoxyuridine
p-ATM: Phospho-ATM
SADs: Senescence-associated distension of satellites
SAHFs: senescence-associated heterochromatin foci
PML bodies: PML nuclear bodies (NBs)
HP1-γ: Heterochromatin protein 1
macroH2A: Macro domain Histone 2 A
FOXO 1: Forkhead box protein O1
KLF2: Krüppel-like Factor 2
NR4A: Nur77 orphan nuclear receptor
DNMT3A: DNA (cytosine-5)-methyltransferase 3 A
(+): Presence
(-): Absence
NE: Not Examined

response that eventually induces T-cell senescence [130] (Fig. 4). Importantly, recent studies have revealed that TLR8 activation in Tregs or tumor cells may rescue effector T-cell senescence by selectively blocking the absorption, transport, and breakdown of glucose in the former or downregulating cAMP production in the latter [117,130,133]. Other suppressive cells, like myeloid-derived suppressor cells (MDSCs), also dominate in the TME and are in direct contact with T cells suppressing their activity. Of note, Liu J et al. recently reported that $GPR84^+$ MDSCs, a subset of MDSCs that strongly inhibit the $CD8^+$ T cells function, can transfer their GPR84 via exosomes to $CD8^+$ T cells to attenuate their cytotoxicity [136]. Mechanistically, they showed that the transferred MDSCs-derived GPR84 to $CD8^+$ effector T cells induces the development of a senescent-like profile via the activation of the p53 signaling pathway [136] (Fig. 4). In addition, it is well recognized that T cells become activated upon recognition of their cognate antigens presented by the antigen-presenting cells (APCs) in the context of the major histocompatibility complexes [137]. These APCs-T cells interactions have been recently correlated with T cell senescence prevention. Specifically, Lanna et al. revealed that APCs can transfer telomeric DNA to $CD4^+$ memory T cells via vesicles, to prevent their telomere shortening and senescence development, promoting T-cell expansion and memory [138]. However, whether it applies in APCs-T cells interactions within

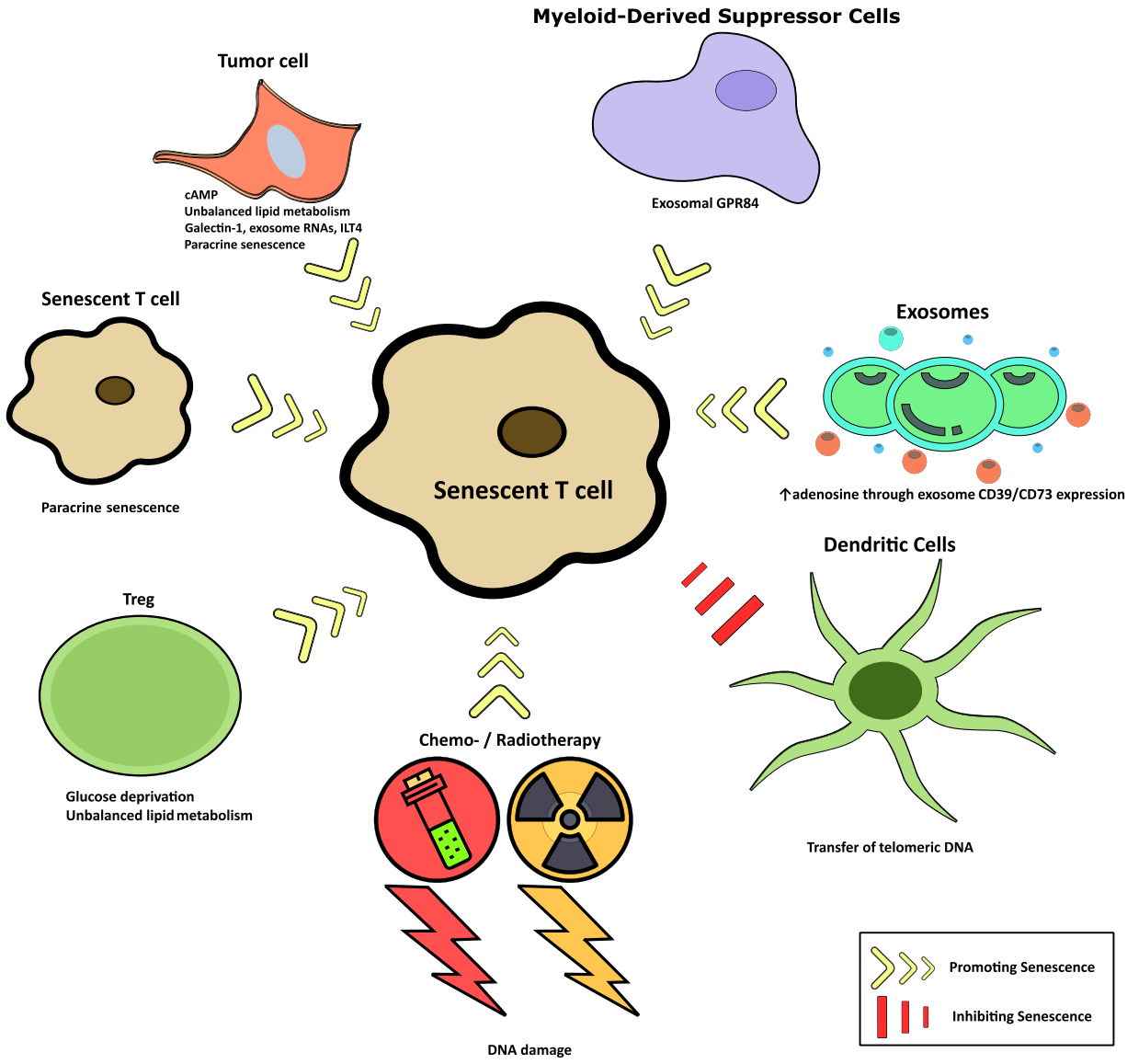


Fig. 4. Cellular and molecular network putatively involved in T-cell senescence. Cancer cells, Treg cells and other cells in the TME such as Myeloid Derived Suppressor Cells (MDSCs) can induce senescence in responder T cells. Particularly, glucose metabolites such as cAMP highly produced by tumor cells can be directly received by effector T cells triggering a DNA damage response mediated senescence. Tregs exhibit increased glucose uptake and elevated glycolysis antagonizing with effector T cells for glucose consumption. This competition initiates an ATM-mediated senescence phenotype in responder T cells. Tumor cells and Tregs alter lipid metabolism (expression of enzymes that regulate cholesterol and fatty acid synthesis as well as fatty acid oxidation) and induce senescence in effector T cells via enhancing cPLA2a expression. Moreover, MDSCs-derived G-protein-coupled receptor 84 (GPR840) transferred via exosomes to T cells results in the acquisition of a senescent-like profile. Increased adenosine in the TME through exosome CD39/CD73 expression as wells as tumor-derived exosomes, Galectin-1, exosome RNAs and Immunoglobulin-like transcript 4 (ILT4) can also induce T cell senescence [143]. Paracrine senescence via SASP comprises another mechanism so far known to be triggered by tumor or neighboring T cells. Of note, T-cell senescence can be reverted as T cells have been shown to acquire telomeric DNA by Dendritic cells (DCs) through vesicles.

the suppressive TME remains to be explored [138]. Finally, T cells (including Tregs) are in close contact with stromal cells, specifically cancer-associated fibroblasts (CAFs) [139]. If the formation of synapsis between those cell subsets instructs T cell senescence is a field of active investigation.

Unbalanced lipid metabolism has been also associated with senescence in T cells [140]. It may be induced by both tumor cells and Tregs and results in changes in the expression of enzymes that regulate cholesterol and fatty acid synthesis as well as fatty acid oxidation, which, in turn, lead to the accumulation of lipid droplets in responder T cells. Tumor cells and Tregs alter lipid metabolism and induce senescence in effector T cells via enhancing their expression of group cPLA2a [140] (Fig. 4). Mechanistically, cPLA2a upregulation is achieved through the engagement of MAPK or STAT1 and STAT3 signaling pathways. Of note, inhibition of cPLA2a can reprogram effector T cell lipid metabolism and rescue their senescent profile enhancing antitumor immunity and immunotherapy efficacy in melanoma and breast cancer-bearing mice [140]. Collectively, all these studies suggest that reprogramming of the metabolism of senescent TILs could reverse their senescent state and defective effector functions indicating that targeting metabolic pathways in senescent T cells might be a new strategy for developing more effective cancer immunotherapies. In recent years, it has become clear that metabolic and epigenetic pathways are functionally related in immune cells. Regarding T cells, changes in metabolite concentrations modulate their epigenetic landscape, thereby affecting T-cell subset specification, memory and function [126].

Importantly, although senescence is tightly regulated by the metabolism-epigenetics axis, the precise epigenetic mechanisms driving T cell senescence remains largely elusive. Similarly, it is still unclear how the TME imprints on the epigenome of TILs and regulates the development of their senescent program. This could be probably be justified by the fact that until recently there was no appropriate methodology for the isolation of "pure" senescent T cells that could enable their further epigenetic and metabolic analysis. Notably, whether metabolic mediators could be incorporated into cancer-related SASP of senescent T cells needs to be determined. Initial ATAC-seq data derived from aged T cell subpopulations demonstrated that repressive signals, including H3K27me3 modifications and increased DNA methylation, are prominent in genes related to stemness, including KLF2, FOXO1, Tcf7 and LEF-1 [141]. Thus, the aberrant activation of transcription factor networks that control the differentiation process after T cell activation and drive the loss of quiescence, is considered the major outcome of the aging process on the epigenome of all T cell subsets [141]. Large differences were observed between aged $CD4^+$ and $CD8^+$ T cells and the latter were more susceptible to harbor the above-mentioned age-associated epigenetic modifications [141]. How senescence imprints on the epigenome of T cell subsets remains largely unknown and more clarification is needed.

5. Functional impact of "senescent" T cells within the TME network

As it was previously mentioned, cancer cells, Treg cells and most likely other cells in the TME may induce senescence in responder T cells hindering their effector functions [130–132,136,140] (Fig. 4). Thus, senescence induction in TILs is considered a potential strategy utilized by malignant cells to evade immunosurveillance. T cells characterized as senescent ones have been related to the maintenance of immunosuppression within the TME, promoting tumor development and progression [86,117,119,130,131,142]. More specifically, these cells, although unable to respond to tumor antigen recognition and to mediate their effector functions, remain metabolically active and can release a SASP-like phenotype that may affect both immune and tumor cells in different ways within the TME. However, we should point out that the above reports [86,117,119,130,131,142] and the ones to follow, need to be evaluated cautiously because T-cell senescence was determined with debatable markers, such as SA-b-Gal (can be positive also in exhausted T cells) or SASP factors (not reliable for senescence in immune cells), as already mentioned.

Recent studies indicate that senescent T cells, secrete large amounts of proinflammatory cytokines such as IL-6, IL-8, TNF-α, and IFN-γ [125, 131] that can induce premature senescence to effector TILs via autocrine or paracrine mechanisms [143]. In this manner they could promote the development and further accumulation of senescent T cells within the TME. Senescent T cells seem also to directly inhibit the function of other immune cells, including Th1, Th17, $CD8^+$ T cells, and dendritic cells[143,] via the enhanced secretion of the suppressive cytokines IL-10 and TGF-β [117,130,143], that amplify tumor immunosuppression. Furthermore, they secrete mediators that can promote the infiltration and expansion of Tregs and MDSCs within the TME and enhance their suppressive potential favoring the vicious cycle of immunosuppresion [143].

In addition to the maintenance of a suppressive TME, senescent T cells can also facilitate cancer development and progression through various means. Senescent T cells are able to disrupt the normal mammary differentiation [144] that could potently lead to malignant transformation [145,146] Furthermore, senescent T cells can enhance the proliferation and metastatic potential of neoplastic epithelial cells, favoring epithelial-mesenchymal transition (EMT) and increasing aggressiveness of metastatic tumors [114,144,145,147,148]. Therefore, a deeper understanding of the implication of senescent T cells in anti-tumor immunity could provide novel strategies to enhance cancer immunotherapies.

Besides effector $CD4^+$ and $CD8^+$ T cells, Tregs also constitute an important and indispensable subset of the T cell compartment. Tregs defined by the expression of the transcription factor Foxp3, are best characterized as master regulators of the immune system. These cells exert a special role in maintaining self-tolerance and preventing autoimmunity by suppressing both innate and adaptive immune cell responses to achieve a state of immune homeostasis [149]. In addition to their protective role against autoimmunity, Tregs also act as powerful inhibitors of anti-tumor immunity. Notably, in the context of cancer, Tregs are abundantly recruited in the TME, where they create a highly immunosuppressive microenvironment that favors tumor growth and promotes tumor immune evasion [150]. Of note, the vast majority of studies about T cell senescence referred to $CD4^+$ and $CD8^+$ effector T cells while Treg cell senescence remains largely elusive. In contrast, several studies suggest that Tregs *per se* can act as senescence inducers for effector T cells during tumor development [117,130,132,133]. However, whether Treg cells develop senescence-related features during cancer progression is still unclear. Importantly, it is known that cellular senescence is a general feature in cancer that is closely associated with the impaired functionality of effector T cells within the TME that fail to counteract tumor development [125]. On the other hand, it is widely accepted that Tregs remain highly functional in the tumor mass and robustly suppress the anti-tumor immune responses, acting as major obstacles to effective anti-tumor defense and immunotherapy response [150]. As a result, several questions need to be addressed. For instance, do Tregs adopt senescence at a different pace compared to T effectors? Are Tregs resistant to senescence? Could Treg cell senescence induction offer a novel therapeutic strategy to battle tumor progression?

6. Anticancer therapies and T-cell senescence: a vicious cycle

6.1. Chemo/radio-therapy

Despite the emergence of several targeted approaches (including immunotherapy) that promise to conquer the future of cancer therapeutics, chemotherapy and/or radiotherapy still remain the first line choice for cancer patients [151]. Chemo/Radio-therapy targets proliferating tumor cells inducing cell death. However, a residual population of senescent tumor cells may emerge (especially when administered in low doses) as the outcome of genotoxic and oxidative stress [152,153]. These senescent tumor cells can "escape", re-entering the cell cycle and acquiring more aggressive features, boosting tumor relapse [16].

Chemotherapeutic agents are administered systemically, thus they are expected to affect both the malignant and the non-malignant compartment (including T cells), rendering these cell types senescent [152]. Immune cells could also adopt senescence in a paracrine manner by SASP-signaling from treated cells undergoing TIS [62,85,86,140]. Furthermore, immunosenescence may exist prior chemotherapy and be further enhanced by the therapeutic intervention. Several studies support the latter [140,152,153,154], while others report the controversial finding that chemotherapy did not affect immunosenescence [155], implying a cancer type dependent relation [154,156]. On another level, whether chemotherapy-induced immunosenescence correlates with better response is a controversial matter and might be cancer type dependent [154,156]. However, all aforementioned findings refer to investigations conducted in blood T cell populations. Although circulating T cell populations reflect to a large extent the phenotypes inhabiting the TME, they are not identical to them (e.g. many exhaustion markers are not detected in the periphery) [157] and immune senescence might be underestimated.

Radiation therapy is also regarded a first-line treatment for cancer patients and it is known to induce senescence mainly by causing DNA damage [18]. A recent *in vitro* study revealed that radiosensitivity varies among CD4 T memory populations, with $CCR6^+$ Th17 being the most vulnerable to irradiation cell type [158]. In Acute Myeloid Leukemia, the number of senescent T cell numbers was elevated in patients with

refractory or relapsed disease (non responders to radiation) and associated with worse clinical outcome [159], while in responders the population of these cells was reduced [160]. Similarly, high numbers of $CD28^-/CD8^+$ T cells were found to predict a worse response to radiation therapy in metastatic NSCLC patients [161] and an unfavorable outcome of breast cancer [162], acute myeloid leukemia [159] and NSCLCs [163]. However, given the limited number of studies and the discrepancy of the senescence-relevant markers applied in the above-mentioned analyses, conclusions should be cautiously drawn.

6.2. Immunotherapies

Immunotherapies, including immune checkpoint inhibitors (ICIs), cancer vaccines, and adoptive T cell therapy, have revolutionized cancer treatment in the last decades and have led to remarkable results for many patients with different types of malignancies. However, their overall success rates remain low and vary among tumor types [113,164] suggesting that further elucidation of the underlying causes leading to failure of immunotherapy is urgently needed. Several strategies of resistance that rely on the interplay between cancer and immune cells have been proposed to date. These include the loss of neoantigen expression by cancer cells, the immunosuppressive nature of the TME, antigen presentation deficiencies and the aberrant activation of oncogenes or loss of tumor suppressor genes [165]. Another key determinant of the therapeutic efficacy of immunotherapies is the functional state of T cells [95,96]. Despite the absence of specific senescence markers and their significant overlap with T cell exhaustion and anergy (Fig. 3, Table 1) the overall evidence is indicative that T cell senescence is a feature of the TME. If future specific mapping of the phenomenon confirms it, targeting the T cell senescent population could emerge as a promising concept for enhancing anti-tumor defense and immunotherapy response [166]. Within this context, recent studies suggest that accumulation of reported senescent T cells in the TME may partially contribute to immune checkpoint blockade treatment failure [167,168] due to the loss of CD28 expression. These findings further emphasize the need to overcome T-cell senescence concurrently with ICIs for cancer elimination.

Despite the unquestionable success of ICI immunotherapy, more than half of treated patients do not derive considerable benefits. A significant proportion of responders often develop autoimmune manifestations, termed immune-related adverse events (irAE) [150]. These may impede the therapeutic process and lead to life-threatening conditions [150]. Although several mechanisms have been postulated to contribute to the evolution of irAEs, including defects in Treg cells [169] and activation of T effector cells, the precise molecular mechanisms underlying their development remain poorly understood. Considering that T cell senescence constitutes a dysfunctional state that could be implicated in immunotherapy reponses [125,131], the one plausible hypothesis may be that senescent T cells secrete proinflammatory cytokines in response to ICI immunotherapy as part of the SASP [117,131] contributing to the development of irAEs. These SASP-derived cytokines may exacerbate inflammation and promote the development or even determine the intensity of irAEs.

IrAEs seem to rely on the destabilization of Tregs. Treg cell fragility (retained Foxp3 expression but lack of suppressive properties) and induction of ex-Tregs (loss of Foxp3 expression and expression of proinflammatory cytokines) are mainly responsible for Tregs instability that may lead to autoimmune manifestations [169,170]. Whether Treg cell senescence could also constitute a cause of Tregs destabilization that contributes to irAEs development is largely unknown. Furthermore, whether ICIs may induce Treg cell senescence remains obscure. Therefore, delineating the characteristics and function of senescent T cells in cancer, particularly in ICI-mediated irAEs evolvement, may lead to the development of targeted effective therapeutic regimens and diminished unwanted autoimmune toxicities.

7. Future perspectives and concluding remarks

7.1. Is revisiting of T cell senescence required?

Given the plasticity of immune cell phenotypes and the heterogeneity and dynamic nature of cellular senescence, identification of immune senescent cells remains a challenging and to a large extent unmet task. Specifically for T cells, the vastly used T cell senescence markers $CD28^-$, $CD57^+$, $KLRG1^+$ are not selective and specific. For instance, although loss of CD28 associates with loss of telomerase activity, $CD28^-/CD27^-$ T cells retain their ability to proliferate but to a lesser extent [171–173]. Loss of CD28 has been also found to be independent of replicative senescence [174,175]. Similarly, expression does not affect telomerase activity while it up-regulates with differentiation [176,177]. Blockage of KLRG1 in differentiated $CD8^+/CD28^-/CD27^-$ senescent T cells, resulted in a significantly enhanced T cell proliferation, questioning whether the reported senescence, is true or not [177]. In line with the latter, $CD28^-$ T cells are more resistant to suppressive signals by Tregs [178]. Apart from the aforementioned markers that are not functionally related to cellular senescence, traditional markers extensively applied in senescent non-immune cells like SA-b-Gal, γ-H2AX and those involved in cell cycle withdrawal, such as $p16^{Ink4a}$ or $p21^{Waf1/Cip1}$, are often up-regulated in non-senescent immune populations such as exhausted T cells or macrophages [62,179,180]. Noteworthy, $p21^{Waf1/Cip1}$ and $p16^{Ink4a}$ may be upregulated in T cells (outside the context of immunosenescence) during beneficial responses that enhance immune tolerance and thus arrest autoimmune reactions [86,181]. Telomeric shortening is not a reliable feature of T cell senescence since telomerase is upregulated upon T cell receptor activation [182] and CD28 loss may lead to downregulation of telomerase [183]. The picture gets even more complicated since T cells have been recently shown to acquire telomeres by APCs through vesicles [138]. Finally, although promising, assessment of SASP markers to identify senescent T cells cannot be easily applied [124], due to impediments related to low quantities of these markers and the heterogeneity of the SASP secretome.

Taking into account all the above, identification of immune senescent cells should be strictly based on the established senescence hallmarks and exploited in senescence detection algorithms: cell cycle arrest, SASP secretion, deregulated metabolism, macromolecular damage and lipofuscin accumulation [1,7]. In this manner we will be able to precisely distinguish them from other dysfunctional populations, achieve their accurate characterization and most importantly, gain deeper insights into their functions. Apart from the main issue of selective identification and isolation of truly senescent T cell populations, many other issues regarding immunosenescence and T-cell senescence, remain uncharted territories. We first need to spatiotemporally characterize the phenomenon and delineate how it associates with immune evasion and suppression. Do peripheral T senescent cells reflect the ones inhabiting the tumor or the metastatic niche? Are the latter different from those infiltrating the primary tumors? What functions does the SASP impose on their profile? Which secreted components characterize the SASP in this context? Next, we need to understand the transcriptional and epigenetic programs driving senescence in order to isolate and exploit the specific targets towards manipulation and/or reversal of T cell senescence.

Given the widely discussed difficulties in senescent cell identification, the senescence community has proposed an algorithmic approach to be followed for accurate and reproducible detection of senescent cells [53] which relies on an initial screening for SA-β-Gal and/or lipofuscin. Lipofuscin accumulation can serve as the most reliable marker for senescent cell identification [122] as it is among the most stable features and functionally related to senescence, being the outcome of deregulated metabolism and macromolecular damage [1,7].

In this context, a novel fluorophore-conjugated SBB-based reagent (GLF16) that robustly interacts with lipofuscin has entered the scene,

complementing previously developed SSB derivatives and covering the imperative need for selective tracking and isolation of senescent cells *in vitro* and *in vivo* [7,121]. Such a unique tool is anticipated to instigate studies aiming to address all the above raised concerns related to immune cell senescence and given that "*you can deal with what you can see*", to further allow the development of tangible strategies to cope with or reverse this harmful cell population.

7.2. Exploring elimination of T cell senescence as a novel therapeutic and preventive strategy

Senescent T cells could be responsible for progressive disease and low response rates to **chemo/radio-therapy** as well as immunotherapy [125]. If so, senescent T-cell elimination may constitute a novel therapeutic strategy for cancer treatment.

Senescent T cells, through their SASP-derived factors, could modulate the TME in favor of tumor growth. Particularly, T cells characterized as senescent ones may indirectly promote tumor angiogenesis and progression by favoring the secretion of proinflammatory cytokines and angiogenic factors by monocytes and macrophages [184]. T cells reported to undergo senescence can also hamper anti-tumor immunity by inhibiting the activation, proliferation and function of non-senescent effector T cell subsets [119,185]. In addition, they may enhance the TME immunosuppression by facilitating the infiltration of immunosuppressive populations including Tregs and MDSCs in the tumor mass as well as by inducing the polarization of monocytes and myeloid cells towards M2 type macrophages and MDSCs that induce effector T cell exhaustion [143]. Therefore, the elimination of senescent T cells in cancer patients may restrict tumor growth and reinforce anti-tumor responses and immunotherapy efficacy.

In B lymphoid hematological malignancies, the reported T cell senescence has been suggested to influence the response to CAR T cell therapy [186]. Responders who achieved complete or partial response had a lower frequency of senescent populations and higher numbers of less differentiated $CD8^+$ T cells on their CAR T cell product compared with non-responders [185]. Therefore, eliminating senescent T cells prior to *ex vivo* T cell expansion during the CAR T cells manufacturing process could maximizes the therapeutic efficacy and long-term persistence of CAR T cell therapy [187].

It is well known that cancer vaccines do not achieve satisfactory clinical efficacy in limiting existing tumor cells or hurdling metastases in aged cancer patients [188]. It has been proposed that weakened cytotoxicity of described senescent $CD8^+$ T cells against tumor-associated antigens could be involved [189]. In relation to this, inhibition of p38 either through blockade of the stress responsive proteins called sestrins [190] or by applying a p38 MAPK inhibitor (losmapimod) [190,191] significantly enhanced the number of antigen-specific T cells following antiviral vaccination in older individuals. The latter suggests that the elimination of senescent T cells may represent a novel promising strategy to ameliorate the efficacy of cancer vaccines in older patients.

The evidence associating senescent T cells (or senescent immune cells in principle) with advanced cancer disease, poor response to therapy and dismal prognosis renders their effective clearance or their reinvigoration an attractive perspective for cancer treatment. Apart from their implication in cancer progression, immune senescent cells have been shown to be involved in various other organismal processes such as aging [192] and the development of age-related diseases, by disrupting tissue and organ homeostasis [192], as well as to compromise the efficacy of vaccination strategies [188,193,194].

Initial attempts related to *ex vivo* reversing of senescent-like T cell phenotypes have been reported [129,190]. Interestingly, a recent study by Liu et al. reported that SA-b-Gal^+ senescent T cells present a dysregulated lipid metabolism and its *ex vivo* normalization may inverse the senescent phenotype [140]. However, pharmacological targeting of T cell senescence in the clinics still remains elusive. Senotherapeutics, the field of pharmacological elimination of senescent cells has rapidly expanded in the last decades, however, consistent with the heterogeneity of senescent cells, these regimens are often cell type- and concentration-dependent [195], confer adverse effects [196] or have off-target effects [195]. Therefore, application of senolytics for clearance of senescent T cells may be rather perplexing. Towards this direction, we have recently developed an innovative senolytic platform able to overcome these obstacles and selectively eliminate senescent cells exhibiting limited systematic effects [197]. In this context, an important issue that should be taken into account relates to the fact that effector T cells share common requirements/features with tumor cells (e.g the preference to glycolytic pathway) and therefore manipulations resulting in senescence "reversal" although beneficial among senescent T cells, can turn out detrimental for the non-immune compartment (Fig. 5). As an example, in the case of the circadian regulator *BHLHE40*, its up-regulation in fragile Tregs has been shown to suppress tumor growth [170], suggesting its potential in "reversing" the senescence program within T cells, rendering them again functional, at least to some extent. In contrast, *BHLHE40* overexpression in epithelial cells led to escape from senescence, promoting cancer progression [198]. Thus, future therapeutic interventions should aim in activating "senescence escape/bypass" routes in the immune cells, while eliminating the non-immune senescent population (Fig. 5). Li et al., provided proof of this concept by administrating epigenetic regimens of *BHLHE40* activation *in vivo*, eventually resulting in T cell fitness maintenance [199]. Another option might be the use of bifunctional molecules that selectively deliver drugs within the cell type of interest [197].

Beyond the context of cancer, as aging and senescence progress prevention, rather than treatment, is crucial for maintaining a healthy lifespan. Indeed, quality nutrition has been proven to be a precious tool for maintaining the fitness of T cells in the course of aging. For example, reduced chemotherapy induced T cell senescence was observed in well-nourished patients [155]. The so-called Mediterranean diet (large quantities of rich in anti-oxidants fruit and vegetables) has been recently demonstrated to delay emergence of immune senescence [200]. In addition, moderate caloric restriction and intermittent fasting activate metabolic pathways critical for T cell activation, such as AMPK, mTOR, NFkB [201] and FOXO1 [202]. Nutrition derived senolytics may exert immunomodulatory actions. Inhibition of the mTOR pathway by flavonoids favors Treg phenotypes (reviewed by [203]). Finally, resveratrol, a common and well-studied polyphenol abundant in grapes and berries, conferred metabolic reprogramming of CD4 T cells and enhanced effector actions [204].

In conclusion, although cellular senescence has an established role in cancer, immune senescence is recently gaining attention. This can be attributed (at least in part) to the absence of selective and specific markers for their identification, the complex, heterogeneous nature of cellular senescence and the phenotypic plasticity of immune cells. Despite the accumulating literature dealing with T cell senescence, the term is often misused or intertwined with other dysfunctional states, mainly exhaustion. Therefore, the need for accurate and precise identification of these immune cell subtypes is urgent and should always rely on the detection algorithm proposed by the senescence community. Undoubtedly, T cell fitness is vital for cancer prevention, progression and therapy and thus in-depth characterization and understanding of the T cell senescence program would pave the way for successful T cell reinvigoration and maximum efficacy.

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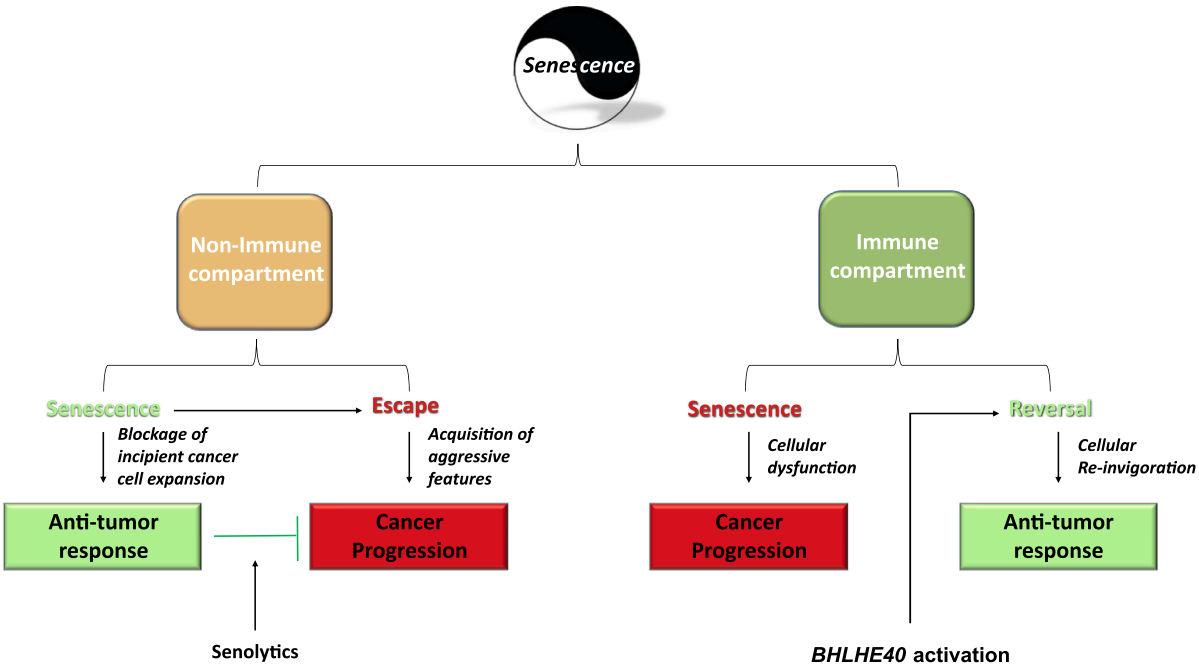

Fig. 5. The yin-yang nature of senescence in the immune and non-immune compartments. Senescence in homeostastic conditions is beneficial for the epithelial compartment and serves as an anti-tumor barrier protecting from malignant transformation. However, when it persists, senescent cells may escape from this state and re-enter the cell cycle, leading to malignant transformation. In the immune compartment, senescence associates with dysfunction and impaired anti-tumor responses. Elimination of senescent cells using senolytics inhibits tumor progression and relapse via the senescence escape phenomenon. On the other hand, senescence reversal (for instance by *BHLHE40* activation) is expected to reinvigorate immune cells and re-establish cell fitness.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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Data Availability

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

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