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REVIEW

Immune senescence in non-small cell lung cancer management: therapeutic relevance, biomarkers, and mitigating approaches

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ABSTRACT

Introduction: Lung cancer and mainly non-small cell lung cancer (NSCLC) still remain a prevalent malignancy worldwide despite sustained screening approaches. Furthermore, a significant proportion of the cases are diagnosed at advanced stages when conservative therapy is often unsuccessful. Cell senescence is an endogenous antitumor weapon but when it is upregulated exerts opposite activities favoring tumor metastasizing and poor response to therapy. However, little is known about this dangerous relationship between cell senescence and NSCLC outcome or on potential approaches to mitigate its unfavorable consequences.

Areas covered: We discuss cell senescence focusing on immune senescence, its cell and humoral effectors (namely immune senescence associated secretory phenotype-iSASP), its impact on NSCLC outcome, and its biomarkers. Senotherapeutics as mitigating approaches are also considered based on the availability of experimental data pertinent to NSCLC.

Expert opinion: Characterization of NSCLC subsets in which immune senescence is a risk factor for poor prognosis and poor therapeutic response might be very helpful in supporting the addition of senotherapeutics to conventional cancer therapy. This approach has the potential to improve disease outcome but more studies in this area are necessary.

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1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide, with almost 2 million deaths in 2020 [1]. Furthermore, the global increase in life span leads to an increase of lung cancer incidence in the elderly population, as aging is paying its toll on the overall prognosis of cancer, becoming a relevant issue to be addressed in oncologic treatment responses [2]. From a pathogenic point of view, the link between aging and risk of cancer development is demonstrated by the fact that at molecular levels some of the aging pathways overlap with some of those leading to oncogenesis [2]. In terms of therapeutic relevance in NSCLC, senescence can be induced by various oncologic therapies, and thus, it constitutes the basis of their beneficial cytotoxic effects. However, these 'therapeutically aged' cells can act as tumorigenesis promoters, and therefore, may be involved in tumor relapse, and also responsible of chemotherapy-induced side effects such as fatigue [3]. Thus, cell senescence, and in particular immune senescence (IS), becomes a more and more important issue in the management of NSCLC. In this paper, the authors are going to describe the cell senescence and the immune senescence from both physiological and pathogenic points of view, its potential therapeutic impact and relevant biomarkers, and to review the appropriateness of the existing senotherapeutics in correcting the 'abnormal' cellular senescence including immune senescence.

1.1. Immune senescence in NSCLC: potential therapeutic impact

If we are to strictly relate immune senescence with overall aging, its relevance in clinical practice becomes obvious in the light of the fact that the median age of diagnosis for lung cancer patients is 70, making NSCLC a tumor of the elderly [4–6]. The key risk factors of lung cancer incidence in the elderly include smoking-related factors (smoking dose and frequency, time since quitting) and radon exposure, by promoting an increase in rate of somatic mutation [7–9]. In elderly subjects, lung cancer is associated with nonspecific symptoms such as malnutrition, cognitive impairment with depression, and reduced physical capability. Additionally, the prevalence of frailty (characterized by a progressive decline of many physiological systems, which increases the mortality risk) rises with age among lung cancer patients, with a median value of 45%, causing a significant negative impact on overall survival [10,11]. As such, assessing the state of the immune system that is affected not only by the malignant disease and other comorbidities, but also by the physiological aging process, is important, since it may influence the response to different types of treatments. Immune senescence is also relevant from a therapeutic point of view irrespective of age, as many studies indicate that cancer itself may affect the immune response and induce energy, tolerance or indifference of the immune system [12].

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Article highlights

- Lung cancer (mainly NSCLC) is still the most prevalent malignancy despite sustained screening programs and consequently the prevalence of advanced stages at first diagnosis is relatively high.
- Senescence in general and immune senescence in particular can be considered up to a point as an endogenous antitumor mechanism having as effectors adaptive and immune cells and their cytokine/chemokine byproducts labelled as senescence associated secretory phenotype (iSASP) .
- However 'pathologic' immune senescence can exist in such patients and can be related with increase invasiveness and with poor therapeutic response to onco treatments. This relationship is worth being considered especially in the setting of immune checkpoint inhibitors which are expensive and not widely available.
- Therefore immune senescence is worth being evaluated and mitigated with senotherapeutics.
- Senotherapeutics are broadly classified into senolytics (which are able to induce apoptosis of the senescent cells) and senomorphics (which are able to inhibit SASP) and many of them are currently investigated experimentally in lung cancer.
- Some of the experimental data report on the potential of such therapies to restore response to onco therapies especially in aggressive subtypes of NSCLC and therefore their further evaluation in a clinical setting is supported.

Another issue to consider when assessing the relationship between treatment response and immunity is the dynamic state of the immune system and its potential to respond differently and change, adapt or remodel in relationship to the tumor depending on the type of treatment used [13]. This section summarizes available data from preclinical and clinical studies evaluating the effect of IS on the outcome of various therapies currently approved for non-small cell lung cancer (NSCLC) such as cytotoxic agents, targeted driver genes mutations or immune therapies (checkpoint inhibitors, monoclonal antibodies or tyrosine kinase inhibitors) [14].

1.2. Immunosenescence and chemotherapy

The relationship between the status of the immune system and chemotherapy exposure has been widely discussed in literature. Several studies have suggested that the percent of senescent immune cells increases as a response to chemotherapy in different types of solid tumors, while others have linked IS to cancer in itself, irrespective of treatment type and exposure [15–18] . An exploratory study found that both naïve and central memory T cells are decreased and effector memory T cells are increased ($CD28^{-}CD45RA^{-}CCR7^{-}$) in heavily pretreated cancer patients, suggesting there is a correlation between T cell exhaustion and chemotherapy exposure [18]. Similar results were reported in another study in which significantly lower concentrations of $CD4^{+}$ naïve T cells and central memory CD8+ cells with a concurrent increase in effector memory $CD4^{+}$ cells were noted in patients treated with platinum-based chemotherapy compared to untreated patients [19]. In contrast, another study which compared community-dwelling older adults and elderly lung cancer patients found that stage IV lung cancer patients had a higher proportion of $CD28^{-}CD57^{+}$ $CD8^{+}$ T lymphocytes in peripheral blood samples. Additionally, the authors assessed this cell subpopulation both at baseline and throughout chemotherapy and found that chemotherapy treatment did not modify the proportion between different lymphocytic subgroups thus failing to identify a relationship between IS and exposure to chemotherapy [16]. The most likely hypothesis, however, is that both the tumor and the cytotoxic treatment modulate the patient's immune system throughout the cancer patient's journey. This is supported by the results of a study evaluating the efficacy of an epidermal growth factor vaccine in lung cancer patients, which additionally found a reduced blood CD4/CD8 ratio and a significant shift in lymphocyte populations following platinum-based chemotherapy with an increase in $CD4^{+}$ CD28 negative T cells [20].

Despite controversies regarding the exact mechanism of IS in chemotherapy-treated NSCLC patients, most experts agree that immune system impairment does not significantly correlate with chemotherapy response rate, even though it might be an independent predictor for shorter survival [19]. A study evaluating the prevalence of IS and its impact on platinum-based treatment efficacy, identified 11% of the 61 patients scheduled to receive chemotherapy as having a prominent IS phenotype (over 39.5% of the CD8 + T lymphocytes were $CD28^{-}CD57^{+}KLRG1^{+}$). No significant differences were found between the two groups in terms of objective response rate (ORR), disease clinical benefit (DCB), progression-free survival (PFS) and overall survival (OS), suggesting that immune senescence does not play a major part in predicting response to chemotherapy [13].

A recent study has identified a lung cancer tumor antigen, known as anti-lung-specific X protein (LUNX) which can be specifically targeted by monoclonal antibodies after chemotherapy-induced immunogenic senescence of tumor cells. Here, induction of cell senescence by chemotherapy is accompanied by increased translocation of LUNX to the plasma membrane, and thus, enhancing the immunogenic properties of cancer cells [21].

1.3. Immunosenescence and targeted immune therapy

IS becomes more relevant from a practical point of view when the treatment with immune checkpoint inhibitors (ICI) is considered in locally advanced or metastatic NSCLC patients [22]. The problem with this type of therapy is the fact that it is expensive and it can be ineffective in the presence of IS due to its mechanism of action linked to T cells. The main therapeutic effect of ICIs consists in disrupting the PD-1/PD-L1 axis, and thus, reactivating anergic lymphocytes and stimulating the cytotoxic potential of these cells. Unfortunately, the elderly population is generally less recruited in clinical trials, currently leading to insufficient data to conclude regarding the efficacy and safety of ICIs in geriatric subjects [6,23]. Interestingly, several clinical studies evaluating the efficacy of ICIs in elderly patients, in whom IS is more likely to be present, found that their survival rate was lower when compared to younger adults [24].

In the light of such data IS might be a plausible explanation for differences in response rate and survival and in fact, although in a different cancer setting (melanoma), such immune phenotypes were correlated with resistance to ICI treatment [25]. Such results suggest that IS might be helpful

for a better treatment selection in elderly with cancer, and that biomarker-guided diagnosis of this feature might become a part of personalized therapeutic approach in this setting [25]. This hypothesis is also supported by the demonstration of a senescent CD8 + T cell phenotype $CD28^{-}CD57^{+}KLRG1^{+}$ and of its correlation with worse therapeutic prognosis in NSCLC patients receiving ICI or conventional therapy [15]. Furthermore, the authors found no difference between baseline samples and samples taken after 1–3 months of ICI treatment, thus suggesting that this type of therapy cannot reverse IS [15]. It is also important to mention that telomerase reverse transcriptase (TERT) mutations and the tumor mutation burden (TMB) are increasingly considered as potential predictor biomarkers for ICI responses [26]. TERT mutations correlate with immune infiltration and TMB, and NSCLC patients with high TMB values obtained higher ORR and median PFS [27].

Other T-cell targeted therapies such as CAR-T cells or bispecific T cell engagers are theoretically believed to be influenced by IS and inflammaging, but more research data is needed for confirming this preliminary observation [28]. There are fewer data also regarding the potential IS associated with some other targeted therapies such as monoclonal antibodies (trastuzumab or bevacizumab) or tyrosin kinase inhibitors (TKIs). Interestingly, some hints come however from a study such as the one evaluating the efficacy of TKIs as the first line therapy in a Japanese sample of patients with NSCLC found that the subset of patients with high PD-L1 expression and high content of $CD8^{+}$ T cells in the tumor microenvironment had the poorest overall survival [29].

Given the potentially interfering role of IS in the therapeutic outcome of NSCLC patients, approaches able to reverse this are needed. These approaches might be represented by the group of senotherapeutics which are discussed in the specific section below.

2. Immune senescence: overview of cellular senescence and biomarkers of immune senescence

Given that the cancer itself might induce immune senescence and that this might interfere with response to cytotoxic agents or with newer therapies such as ICIs, the need to document it with biomarkers becomes evident. Therefore in the following section an overview of cellular senescence is firstly given, and then its particularization to the immune system is discussed in order to highlight potential biomarkers which might be used to document immune senescence dynamics over the disease (NSCLC) course.

2.1. Cellular senescence

Cellular senescence, a common hallmark of aging, is defined as an irreversible cell cycle arrest at G1 phase that prevents the uncontrolled cell proliferation events and limits the lifespan of mammalian cells [30,31]. However, the senescent cells remain viable and continue to be metabolically and transcriptionally active, becoming relatively resistant to apoptosis [32]. This process is likely a consequence of cell injury and plays important roles in assuring the tissue homeostasis and physiological development by limiting the growth of damaged cells. Cellular senescence has therefore beneficial effects and acts as an important antiproliferative mechanism that prevents oncogenesis and controls physiological conditions like aging, embryogenesis, wound healing and tissue repair, mainly after cancer therapy [30,32,33]. The cell injury is triggered by multiple and diverse internal and/or external environmental factors including telomere shortening (causing replicative senescence), oncogenic activation (causing oncogene-induced senescence), oxidative stress, chromatin and epigenetic changes, genomic instability, impaired proteostasis, inflammation and tissue damage signals, radiation and chemotherapy agents [30,32,33].

Senescence is nowadays seen as a highly dynamic process during which the senescent cells' properties progress after the initial cell-cycle arrest and vary based on stress triggers and environmental contexts [30,33,34]. Commonly, the senescent cells present several morphological and functional hallmarks: a) a permanent cell cycle arrest mediated via activation of one or both $p53/p21^{CIP1}$ and $p16^{INK4A}$/pRB tumor suppressors, important inhibitors for the kinase activity of cyclin D complexes (CDK4,6) [30,35]; b) changes in the general cellular morphology (enlargement and flattening) [36]; c) nuclear changes (multinucleation, breakdown of nuclear envelope due to Lamin B1 loss) [36,37]; d) alteration of cellular organelles (the most prominent changes are observed among mitochondria and lysosomes): decline in mitochondrial function results in dampened oxidative capacity and ATP production followed by significant increase in reactive oxygen species (ROS) generation [38]; progressive lysosomal deterioration (as numbers or activity) is reflected in the accumulation of lipofuscins, intense detection of the increased senescence associated beta-galactosidase (SA-β-gal) activity at pH 6.0 [35,39], both *in vivo* and *in vitro* and accumulation of unfunctional mitochondria due to consequent reduced mitophagy [40,41]. The accumulated ROS finally initiate the DNA damage response (DDR) signaling which promotes the acquisition of the pro-inflammatory senescence-associated secretory phenotype (SASP): soluble signaling factors such as cytokines and chemokines (IL-1α, IL-6, IL-8, and interferon gamma – IFNγ), and growth factors (vascular endothelial growth factor VEGF, and insulin-like growth factor IGF – binding proteins), secreted proteases (metalloproteinases – MMPs, cathepsin B), and components of the extracellular matrix (ECM). While SASP factors play crucial roles in wound healing and embryogenesis, the long-term effects are deleterious, as they can modulate the neighboring cells (inducing proliferation or senescence, activation or inhibition), including immune cells (macrophages, natural killer (NK), T cells etc.) or may turn fibroblasts into pro-inflammatory cells [30,35,42]. For instance, pro-inflammatory cytokines and MMPs enhance cell proliferation, and are associated with tumor cell migration and invasion, while the VEGF may stimulate angiogenesis required for tumor formation [30,35,42]. Most of those secretory molecules are transcribed by NF-kB with additional input from other key transcription factors (C/EBPβ, STATs) and further translated in an mTOR-dependent manner [43,44]. The existence of SASP and mTOR activity is one of the key characteristics that distinguishes senescence from other forms of growth arrest, such as quiescence (no SASP, and mTOR is inhibited) [43,45].

Therefore, in oncology, cellular senescence from a physiologic point of view is an endogenous mechanism consisting of cell arrest occurring in tissues with high regeneration potential and ensuring an appropriate cell turnover, and prevention of related organ aging or tumorigenesis [46,47]. However, in the tumor setting, cell senescence and more specifically immune senescence become 'pathologic' and provide the appropriate background for tumor expansion and resistance to various types of anticancer therapies. This immune senescence can be targeted with various senotherapeutics which are subsequently discussed in this paper. Biomarkers of immune senescence discussed in the following section might be helpful to detect the immune senescence and to monitor the effects of various senotherapeutics.

2.2. Biomarkers of immunosenescence: immune cell biomarkers and immune senescence associated secretory phenotype (iSASP)

The progressive decline of immune functions with age observed in elderly, characterized by a lower proliferative capacity of immune cells with a concomitant lower capacity to neutralize newly encountered antigens, was largely named immunosenescence [48]. This is determined by genetic predisposition, which associate altered gene expression and epigenetic regulation, and is influenced by external factors that impact on immunosenescence severity [9,49]. Importantly, these age-induced changes determine metabolic reprogramming in distinct immune cells, ultimately characterized by altered functions [50]. While these processes cause an ineffective immune response against developing tumors, it also creates a favorable environment for tumorigenesis. The central features of faulty immune processes seen in elderly rely on an impaired activity to properly respond to new antigens, mainly due to a reduction in the naïve population of

T cells (the main components of the adaptive immune system) with concurrent accumulation of the memory and terminally differentiated T and B cells which promote *via* SASP an enduring low-grade level of inflammation, named inflammaging [51]. The senescence-related changes of immune cells are summarized in Table 1, and the functional perturbations are revealed in Figure 1.

2.2.1. Cell biomarkers of immune senescence in adaptive immunity

T cells are mainly responsible for the cellular immunity component of the adaptive immune system, while B cells, after differentiation into plasma cells *via* their ability to secrete antibodies, mainly cover the humoral immunity [76].

Both T and B cells develop from hematopoietic stem cells present in the bone marrow. For T cell generation, the progenitor cells further migrate into the thymus, where they mature and undergo positive and negative selection processes. The surviving cells are the so-called naïve T cells (CD4 or CD8 single positive cells) and are released to the periphery to encounter the antigen for which they express specific T cell receptors (TCRs) [77]. With age, the thymus regresses being replaced by adipose tissue, resulting in a decline of both naïve T cell output and capacity to establish central tolerance to self [78]. The reduction in the naïve T cell pool explains the diminished capacity to respond to new antigens, while a defective induction of tolerance will facilitate the escape of self-reactive T cells to the periphery to boost inflammaging.

2.2.1.1. Senescent T cells. By assessing the expression of key surface markers (the long isoform CD45RA, CC-chemokine receptor 7 (CCR7) and co-stimulatory molecules CD28 and CD27 involved in T cell activation), distinct T cell subsets may be delineated: naïve ($CD45RA^+CCR7^+CD28^+CD27^+$), central memory ($T_{CM}$, $CD45RA^+CCR7^-CD28^+CD27^{\pm}$), effector memory ($T_{EM}$, $CD45RA^-CCR7^-CD28^{\pm}CD27^{+/}$) and terminally differentiated effector memory (T_{EMRA}, $CD45RA^+CCR7^-CD28^-CD27^{\pm}$) [52,53]. With age, the senescent memory and late-differentiated T cells accumulate, as they lose the expression of the co-stimulatory molecules CD28 and CD27 which causes the up-regulation of the cyclin-dependent kinase inhibitors p21 and p16, leading to cell cycle arrest in G1 phase and replicative senescence [54,71]. These cells also acquire specific surface markers of senescence (CD57

Table 1. Biomarkers of senescent immune cells.

Category	Marker	Senescent immune cells	Activity	References
Cellular markers				
Surface markers	CD27, CD28, CCR7, CD45RO, CD95	T cells	↓	[52–55]
	CD57, CD45RA, KLRG1	T cells	↑	[52,53,56,57]
	PD1, LAG-3, CTLA-4, TIGIT, TIM-3, (exhaustion markers)	T cells	↑	[58–62]
	CD27	B cells	↓	[63,64]
	DNAM-1, NKp30/ NKp46, NKG2A	NK cells	↓	[65,66]
	CD57, KIR, NKG2C	NK cells	↑	[65,66]
	CD62L, CD38, CD115, HLA-DR, CX3CR1, TLR1/4	Monocytes/ macrophages	↓	[42,67]
	CD16, CD11b	Monocytes/ macrophages	↑	[42,67]
Effector molecules	Perforin, Granzyme B	CD8 + T cells	↑	[68–70]
	IL-2, IL-4	CD4 + T cells	↓	[68–70]
Metabolic changes	Mitochondrial function	T cells	↓	[68–70
	Glycolysis, ROS	T cells	↑	[68–70]
General senescent markers	Telomerase activity	All	↓	[30,33,34]
	SA-β-gal activity	All	↑	[35,39]
	Cell cycle arrest (P16, P21, P53)	All	↑	[30,35,71]
Secretory-associated markers				
Pro-inflammatory markers	Cytokines and chemokines: TNF, IL-6, IL-8	B and T cells	↑	[65,72,73]
	Cytokines and chemokines: osteopontin, IFN-γ, CCL3, CCL4	T cells	↑	[65,72,73]
	Micro-RNAs: miR-16, miR-155, miR181a	B and T cells	↑	[65,72,73]
Inhibitory factors	TGF-β, IL-10	T cells and MDSCs	↑	[74,75]

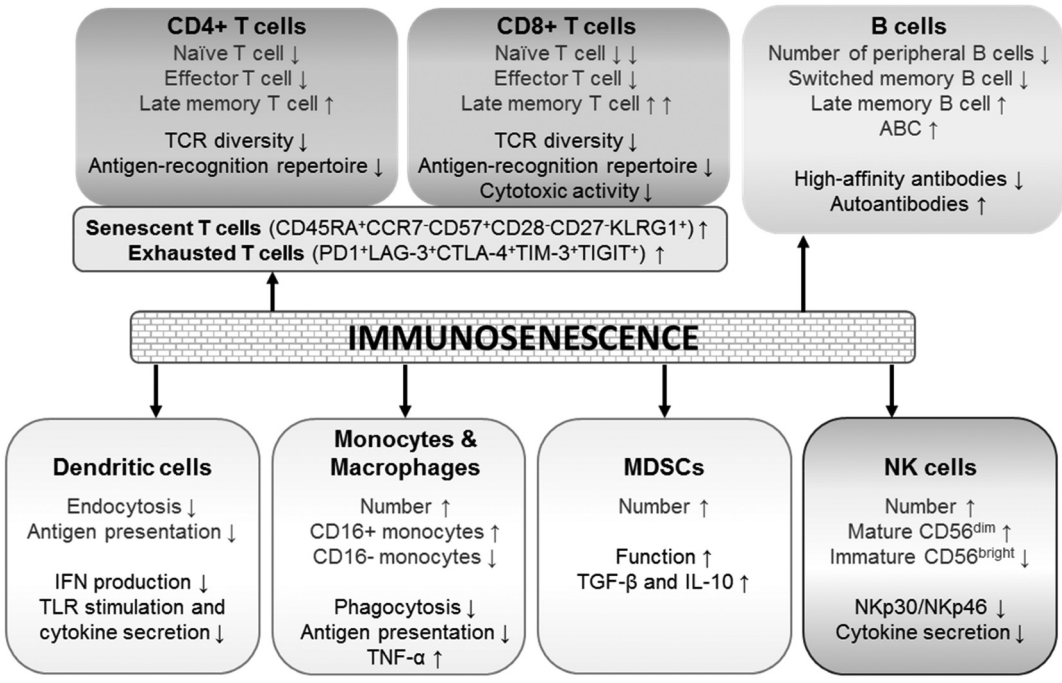

Figure 1. Overview of the immunosenescence-derived changes in various cells of the adaptive and innate immune systems. Changes in the adaptive immune system: the number of both T and B cells is reduced in elderly individuals, but the number of late memory T and B cells is increased. The antigen recognition repertoire is lowered due to the decrease in TCR diversity. The internalization and antigen presentation capacities of antigen presenting cells, such as dendritic cells and monocytes/ macrophages, are diminished with age. The number and function of MDSCs are enhanced, while the NK function is impaired despite an increase in the total number with age.

and co-inhibitory killer-lectin-like receptor G1 (KLRG1)) which correlates with enhanced cytolytic potential, but reduced sensitivity to cytokines and proliferative capacity [56,57]. This senescent T_{EMRA} is further delineated by the reduced expression of the apoptotic receptor CD95 (APO-1/Fas), making them less prone to spontaneous apoptosis, tending to pile up in aged individuals [55]. The accumulation of T_{EMRA} at the expense of naïve cell subset as seen in elderly is more noticeable for the $CD8^+$ if compared to the $CD4^+$ T cells as they acquire a senescent phenotype faster due to increased mitochondria damage [68]. The increase in $CD8^+CD28^-$ senescent T cells further suggests an expansion in the cytotoxic activity of the immune system with increasing age, as these cells feature a higher expression of the lysosomal-associated membrane protein-1 (LAMP-1/ CD107a), perforin and granzyme B [69]. In advanced lung cancer patients, the $CD8^+CD28^-CD57^+$ T cell subset, characterized by dysfunctional antitumor activity and less proliferative capacity, accumulate at the expense of central memory cell subset, which is the one efficient in providing the specific antitumor response [70]. Actually, after tumor resection or in long-term complete remission, the senescent T cell subset tends to decrease [79,80]. Among the $CD4^+$ T cells, the $CD25^+$Tregs gradually accumulate with age, and apparently, $CD25^+Foxp3^+$Tregs infiltration is higher in the elderly group than in the younger one in both human patients and murine lung cancer models [81,82].

2.2.1.2. Exhausted T cells. Some studies also documented the increase of exhausted T cells with age. T cell exhaustion is usually triggered by chronic antigen stimulation either through chronic infection or tumor development, and is characterized by progressive loss of effector function and enhanced expression of multiple inhibitory receptors known as markers of exhaustion [58]. The best-known markers are programmed cell death protein 1 (PD-1), lymphocyte-activation gene 3 (LAG-3), cytotoxic T-lymphocyte-associated-protein 4 (CTLA-4), T cell immunoreceptor with Ig and ITIM domains (TIGIT) or T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) [59–62]. When expressed, they are associated with a suppressive microenvironment and loss of the anti-tumor response function of the adaptive immune system.

2.2.1.3. Senescent B cells. In humans, the proportion and number of $CD19^+$ B cells in peripheral blood have been shown to significantly decrease with age [83,84]. Similarly, a significant decrease in the percentage of B cell precursors was documented in the bone marrow of patients with or without tumors [85]. Several studies identified in the bone marrow of old mice an increase of a pro-inflammatory B cell subset (called age-associated B cells, ABC) which secretes high levels of TNF-α which impedes the B cell ontogeny [86].

This general reduction of peripheral $CD19^+$ B cell number is observed concomitant with changes in its subsets. Based on the surface expression of IgD and CD27, the CD19 + B cells are divided into four major subsets: naïve (IgD^+CD27^-), IgM or unswitched memory (IgD^+CD27^+), switched memory (IgD^-CD27^+), and double negative (IgD^-CD27^-) memory B cells. Aging causes a significant decline in the proportion of switched memory B cells (the cells responsible for the generation of rapid and robust secondary antibody responses), while the percentage of naïve and double negative memory B cells significantly increases [63,64]. The function of switched memory

B cells is altered as reflected by the decreased expression of the autoimmune regulator (AIRE) and autoantigens in thymic B cells which are crucial for the proper generation of self-tolerant T cells [65,87]. The double negative memory B cells, also called late-memory or tissue-like memory cells, resemble the ABC described in mice, being the most pro-inflammatory B cell subset and showing a decreased ability to produce high-affinity protective antibodies against tumor antigens in elderly [72].

2.2.2. Cell biomarkers of immune senescence of the innate immunity

The adaptive immune system is tightly linked to the innate immunity, as T cells require the presence of antigen presenting cells (APC) for their proper activation: these specialized cells are able to process intracellularly and display the antigen bound by major histocompatibility complex (MHC) proteins on their surface, in order to be recognized by the TCRs of T cells. Among APCs, the dendritic cells (DCs) are the most potent activators of naïve T cells, and therefore they may be considered as the central coordinators of the immune response, playing a key role in tolerance maintenance [65]. DCs also suffer important functional changes with age, characterized by impaired internalization (eg. endocytosis), reduced antigen presentation capacity and IFN production [65,87]. There are age-related changes seen also in the mononuclear system: the fraction of pro-inflammatory monocytes ($CD16^{+}$) increases, while the number of phagocytic classical monocytes ($CD16^{-}$) is reduced [67]. The inflammaging is additionally boosted by age-modified tissue-specific macrophages known to mediate the local immunosuppression. Preclinical studies report that myeloid-derived suppressor cells (MDSCs) were increased in the bone marrow, blood and local regions of tumor-bearing aged-mice, inducing general and local immunosuppression which impaired the tumor cell clearance and favored metastasis [74,75]. Cells of the innate immunity directly involved in the anti-tumor response, such as NK cells, also suffer age-related changes. For instance, despite an increase in the total NK cells' number, a shift between distinct subsets is reported: the immature immunoregulatory subset ($CD56^{bright}$) is reduced at the expense of the highly differentiated NK cell fraction ($CD56^{dim}CD57^{+}$) [66]. The NK cell function is additionally altered in elderly individuals, being characterized by reduced cytokine secretion and diminished target cell cytotoxicity consequently to a lower expression of activated receptors (DNAM-1, NKp30/NKp46) [66].

2.3. Immune senescence associated secretory phenotype (iSASP)

Senescence-associated secretory phenotype (SASP) is considered the effector arm of cell senescence and is represented by the battery of inflammatory mediators, extracellular vesicles etc., which are able to propagate inflammation and senescent cell apoptosis. SASP composition and activating signals are very heterogeneous, depend on the cell type, and when it comes of immune senescence-related SASP, this is the result of both T and B cells senescence and has the role of boosting inflammaging [88,89]. Therefore it can be assumed that SASP associated to the IS may exhibit a particular pattern and that it might have different effects on innate respectively adaptive immunity

In order to better circumscribe the SASP-related discussion to immune senescence, we label this subtype immune senescence-related SASP (iSASP). The existence of such an iSASP is supported for example by the results of a study in which CD8+ EMRA T cells were found to secrete increased quantities of cytokines such as TNF $-\alpha$, IL-18, CCL-16 or ADAM28 [90]. Additionally, CD4+ Tregs and late-memory B cells directly modulate those processes as they also show a clear higher expression of pro-inflammatory cytokines in elderly individuals (see Table 1) [65,72].

However, in the particular setting of immune senescence more studies are needed to better document iSASP.

2.4. iSASP: pathogenic role in NSCLC

Interleukin-6 is an iSASP nonspecific biomarker with a demonstrated role in lung cancer development and metastasis [91]. Some other mediators such as IL-1 family or such as chemokines have demonstrated carcinogenic potential for example interleukin-1 receptor accessory protein (IL-1 Racp) was found to be involved in the development of lung adenocarcinoma, whereas CXCR2 was identified as a potent angiogenesis stimulator in lung cancer [92,93]. Other mediators are involved in drug-resistance development in NSCLC and one such example is represented by the insulin-like growth factor which was demonstrated to be upregulated in tyrosine kinase (EGFR) inhibitor resistant ENSCLC [94]. More recently extracellular vesicles containing nucleic acids such as micro RNA for example were identified as novel iSASP effectors which might be involved in lung cancer development [95].

Therefore, given the complex role of pathogenic iSASP in lung cancer development, metastasis and drug resistance, the use of so called senolytic therapies in this setting represents a plausible approach.

3. Mitigating approaches for immune senescence

This section refers to various types of senotherapeutics according to senescence component targeted (eg senescent cells or SASP) and to the mechanism of action. These senotherapeutics were selected based on the availability of experimental data which backs up their effect in lung cancer.

Senotherapeutics is a more recently coined group of approaches targeting senescence with senolytics which are therapies able to kill senescent cells or with senomorphics/senostatics which are therapies that reverse senescence by inhibiting SASP. Senoprobes are prodrugs conjugated with various moieties for example with galactose-based oligosaccharides in order to increase their penetrability at senescent cell level [39]. A third senotherapeutic approach is represented by therapies able to stimulate the clearance of senescent cells by the immune system, but this is not discussed in this review.

3.1. Senolytic compounds of potential interest in lung cancer

This section discusses various senolytic drugs according to the mechanism of action and novelty of the approach. Thus

'conventional' antiaging molecules such as aspirin, curcumin or quercetin are described together with anticancer drugs more recently being investigated for their senolytic effects or with newer more spectacular potential therapies such as antiaging vaccines [96]. Table 2 summarizes these data.

3.1.1. BCL-2 inhibitors

BCL protein family is a modulator of cell survival, BCL-2 in particular being a pro-survival group of proteins while BH3 is a pro-apoptotic group of proteins [122]. Navitoclax targets BCL-2 and BCL-XL and BCL-W based on its properties to mimic the activities of BH3 proteins being considered as a potential anticancer therapy[122]. Navitoclax was evaluated in lung cancer for its potential to reverse taxane (paclitaxel) resistance and was found to be effective [97]. The main limiting factor for its wider use in clinical practice is represented by platelet toxicity at therapeutic doses and therefore some other formulations which allow lower dosages of navitoclax to be at least equally effective as compared with the currently used one are needed. In fact such formulations are discussed below as improved senolytic therapies. When assessed in its 'native' form as a potential senolytic, navitoclax was found to exert senolytic effects on senescent umbilical vein epithelial cells, human lung fibroblasts, or murine embryonic fibroblasts [123]. A novel formulation of navitoclax, using the proteolysis targeting chimera (PROTAC) approach which is based on its property of inducing enzymatic degradation of a protein of interest (in this case, endogenous 'aged' proteins) by trapping the former with an E3 ligase is currently considered as a senolytic approach able to overcome navitoclax toxicity (especially on platelets) [124–127].

ABT-737 is another BCL-2 inhibitor which is currently evaluated as a potential senolytic therapy [128,129]. Klotho

Table 2. Senotherapeutics of potential interest in lung cancer.

Generic mechanism of action/ Pharmacologic class	Active compound	Therapeutic target	Stage of evaluation in lung cancer	Senotherapeutic effects in lung cancer setting	References
Senolytics					
BCL-2 inhibitors	Navitoclax, PROTAC-Navitoclax ABT-737 Cardiac glycosides	BCL-2 protein inhibition, BH3 mimetic Integrin/AkT/mTOR pathway	Experimental	Reversal of taxanes (paclitaxel resistance)	[97]
	a-klotho protein	BCL-2/Insulin-like growth factor-1 inhibition	Experimental	Cancer cell proliferation inhibition	[98]
AKT inhibitors	Dasatinib Cardiac glycosides	AkT inhibition, ROS species inhibition, LIMK1	Experimental	Inhibition of lung cancer cells proliferation	[99]
Antioxidant flavonoids	Quercetine Acacetine	ROS species inhibition	Experimental	Cancer cell apoptosis, inhibition of metastasis development	[100,101]
Piperlonglumine and synthetic analogues	Piperlongumine	ROS species activation and NF-kB pathway inhibition Immunoproteasome (eg FOXM1, NLRP3) inhibition	Experimental	Cancer cell apoptosis and reversal of gemcitabine resistance in KRAS mutated lung cancer cells	[102–104]
Heat shock proteins	Geldanamycin (17-AAG) Tansepymicin (17-DMAG)	HSP90 inhibition	Not yet tested as a senolytic approach in lung cancer	Cytotoxic effects on lung cancer cells uncertain	[105]
Polysenolytic molecules	Curcumin, aspirin		Experimental	Cancer cell apoptosis in adenocarcinoma	[106,107]
Cardiac glycosides	Proscilaridin A, ouabain, digoxin	LIMK1 inhibition	Experimental	Cancer cell apoptosis	
Senomorphics					
Antiinflammatory polyphenols					
Flavonoids	Apigenin/ Luteolin Kaempferol	Nrf-2 inhibition, PDL-1 inhibition	Experimental	Reduction of inflammation, increase in radiosensitivity	[108–110]
Other polyphenols	Resveratrol	ROS inhibition, mTOR inhibition	Experimental	Lung cancer cell apoptosis	[111]
mTOR inhibitors	Rapamycin	Nrf-2 inhibition, PDL-1 inhibition	Experimental	Inhibition of proliferation	[112]
JAK inhibitors	Momelotinib, ruxolitinib	JAK inhibition	Experimental	Inhibition of myelofibrosis	[113,114]
Oral antidiabetics	Metformin	YAP oncogene inhibition	Experimental	Inhibition of metastasis	[115]
Mixed senolytics and senomorphics					
Antioxidant flavonoids	Fisetin	ROS species inhibition(senolytic) mTOR pathway/monocyte chemotactic protein 1 (MCP-1) inhibition(senomorphic)	Experimental	Lung cancer dissemination, SASP inhibition	[116,117]
Green tea alkaloids	Epigallocatechin gallate	CLOCK protein, AkT/mTOR, BcL inhibition	Experimental	Lung cancer cell invasion	[118,119]
Senoprobes					
Galactoconjugates	Rapamycin-G Navitoclax-G	Additional inhibition of senescence associated lysosomal galactosidase	Experimental	Potentiation of chemotherapy effects	[120,121]

protein which occurs endogenously is another senolytic approach which was found to inhibit lung cancer proliferation via BCL-2 pathway inhibition [98].

3.1.2. AkT inhibitors

AkT pathway is involved as a part of integrin/AkT/mTOR network in tumor progression and metastasis [130]. AkT is a tyrosin kinase which stimulates cell proliferation and is known to play a relevant role in oncogenesis. Therefore its inhibition with compounds such as dasatinib could be beneficial and is currently being evaluated in both preclinical and clinical studies. In an experimental study targeting lung cancer in particular, dasatinib was found to induce apoptosis of cancer cells in vitro and in mice with xenografted lung cancer [99]. Dasatinib in combination with quercetine was evaluated as a potential therapy for pulmonary fibrosis and for diabetic kidney disease [131,132].

3.1.3. Antioxidant flavonoids

Flavonoids have been long considered as antiaging therapies but the mechanisms leading to this effect was not deciphered until recently. There are various flavonoids which are able to interfere with the senescence, some of them are able to kill the senescent cells, some are able to inhibit SASP. Therefore the below included discussion differentiate them according to these two generic mechanisms of action. Quercetine, fisetin and acacetin are evaluated in this section for their senolytic activity in NSCLC.

3.1.3.1. Fisetin. Fisetin is present in various fruits and vegetables such as strawberries or onions and there is a large body of data demonstrating its in vitro and in vivo anti-inflammatory effects translating into functional improvements of various tissues such as liver, nervous fibers, etc.[133]. Its senolytic effect is mediated via the inhibition of reactive oxygen species (ROS) whereas its senostatic on SASP effects are reported to be exerted via mTOR pathway respectively monocyte chemotactic protein 1 (MCP-1) inhibition [116].

Its potential senolytic effects in lung cancer were demonstrated indirectly in vitro, fisetin being able to interfere with senescence features such as epithelial-mesenchymal transition by inhibiting pro-inflammatory pathways leading to its development such as STAT3 or NF-kB [117].

Unfortunately the use of 'raw' fisetin extracts is limited by the poor hydrosolubility of the isolated molecule which limits its absorption at digestive tract level and therefore currently it is studied in various nanoformulations as an anti-aging therapy [134].

3.1.3.2. Quercetine. Quercetine is the first flavonoid that has been studied for its senolytic properties in both preclinical and clinical settings, its senolytic activity being exerted via NF-kB pathway inhibition [135]. In an in vitro study using 549 NSCLC cell line quercetine was demonstrated to stimulate apoptosis of senescent cells [100]. Senolytic activities of quercetine were also proved in real life clinical setting during COVID-19 and are currently evaluated in combination with dasatinib for a number of therapeutic indications.

3.1.3.3. Acacetin. Acacetin is a flavonoid which came into attention of researchers more recently, as a potential senolytic therapy alternative to fisetin and in an in vitro study on A549 and HI1299 NSCLC cells it surpassed the latter in terms of synergic antitumor effect when combined to doxorubicin [101].

3.1.4. Piperlonglumine and its synthetic analogues

Piperonglumine is an alkaloid derived from pepper corn plants which was demonstrated to exert senolytic activities by inducing ROS-related apoptosis of senescent cells in various experiments in lung cancer setting this being of particular potential value in overcoming gemcitabine resistance in KRAS mutated lung cancer [102,103]. Another ROS-independent mechanism of action related to the inhibition of immune proteasome (e.g. FOXM1, NLRP3) might be of particular therapeutic interest in alleviating immune senescence in NSCLC [104,136].

3.1.5. Heat shock protein inhibitors

Heat shock proteins (HSP90) are cellular components which are involved in repair and regeneration processes of the tissues. They can increase pathologically with age or in various conditions such as cancers, for the latter category their therapeutic inhibition being currently under investigation. The problem is that such 'generic' inhibitors can exhibit cytotoxic effects on normal cells and therefore, more recently, organelle-specific (e.g. mithocondrial or endoplasmatic reticulum) HSP90 inhibitors were developed and tested as senolytic drugs [137]. In fact, in a recent experimental study, several such HSP90 inhibitors were tested in in vitro and in vivo models of progeroid- like cellular/animal phenotypes. Geldanamycin and 17-AAG (tanespymicin) respectively 17 DMAG were found to exert senolytic effects [138]. Such senolytic effects are actually those which might prompt further clinical testing of this class in the future, because its efficacy in cancers in general and in lung cancer in particular as cytotoxic agents and stand-alone therapy are still questionable.

3.1.6. Green tea alkaloids

Epigallocatechin gallate is a green tea alkaloid with a potent antioxidant effects which was found to be both senolytic and senostatic in various studies [119]. In NSCLC cell line A549 and HI1299, epigallocatechin gallate was found to induce apoptosis whereas in a xenograft model it was found to exert a similar effect on tumor stem cells by acting in particular on CLOCK protein [118].

3.1.7. Curcumin, and aspirin

These senolytic 'therapies' are grouped together in this discussion due to their well-known antioxidant and anti-inflammatory properties which qualify them as 'polysenolytics' and were found to be effective in experimental studies regarding lung cancer [106–108].

3.1.8. Cardiac glycosides

Cardiac glycosides such as proscillaridin A, ouabain or digoxin were demonstrated to kill A549 lung cancer in which senescence was induced after bleomycin exposure and are also considered as potential senolytic in lung fibrosis [139]. These

molecules were also found to inhibit the migration of lung cancer cells and the consequent metastasis development [140].

3.2. Senomorphics

As mentioned in the beginning of this section, senomorphics are able to reverse or to halt the senescence development by inhibiting SASP. In the following discussion included are some compounds which are also senolytic. A dual senolytic/senomorphic effect is also therapeutically useful probably in situations with a higher senescence burden such as for example advanced NSCLC and therefore highlighting this aspect in this discussion is of particular relevance.

3.2.1. Apigenin and luteolin

Apigenin is a naturally occurring flavonoid and a derivative of luteolin, with demonstrated anti-inflammatory effects which can be exerted on SASP. In lung cancer setting in particular apigenin was found to inhibit PDL-1 pathway and this might be useful in establishing synergic combinations with checkpoint inhibitors which are of particular value especially in therapy resistant phenotypes [105].

3.2.2. Kaempferol

Kaempferol is another ubiquitous flavonoid which can be found in tea tree, capers, vegetables or fruits and which was initially studied for its potent antioxidant properties qualifying it for therapy in cardiovascular, inflammatory diseases or cancer prevention. More recently, the inhibitory effects of kaempferol on SASP were demonstrated in an experimental study with in vitro and in vivo components: in vitro in bleomycin induced senescence in BJ fibroblasts and in vivo at kidney level in aged rat, kaempferol was found to reduce SASP-derived inflammation by interfering with NF-kB pathway [141]. As far as the role in cancer therapy is concerned, kaempferol was found to induce in vitro apoptosis of NSCLC cell lines by inhibiting the Nrf2 pathway and was also found to render such cells radiosensitive in another study [109,110].

3.2.3. Rapamycin

Rapamycin is an mTOR inhibitor currently used in transplant therapy and considered for some rare diseases in which this pathway plays a prominent role. In aging setting, rapamycin was demonstrated to interfere with NrF2 pathway associated with cell senescence [142]. In an in vitro study, rapamycin was found to inhibit the proliferation of NCI-H446 cells and to increase senescent cell apoptosis in a dose-dependent manner [112]. Based on the fact that it is able to target senescence mediated β-galactosidase rapamycin is also a candidate for prodrug (senoprobe, see below) conjugation [112].

3.2.4. JAK inhibitors

Such compounds evaluated for a large range of chronic inflammatory diseases were also found to be strong modulators of SASP by acting at the level of aged adipocytes and preadipocytes this being demonstrated in both in vitro and in vivo studies [143,144]. In an in vitro experiment inhibition of JAK pathway was found to reverse cisplatin-resistance in lung cancer cells and ruxolitinib, a JAK1 inhibitor by itself was found to have direct therapeutic potential in an ex vivo study involving organoids from patients with therapy naïve lung cancer [113,114]. Another JAK1/2 inhibitor, momelotinib, is currently under investigation in cancer settings and in particular in myelofibrosis.

3.2.5. Metformin

Metformin is an oral antidiabetic widely used for this purpose. The fact that the concomitant use of metformin in lung cancer patients improved their survival, prompted the evaluation of this molecule as an anticancer drug. In the onco-senescence setting, metformin inhibits activation of YAP oncogene and thus inhibits NSCLC proliferation and metastasis [115].

3.2.6. Resveratrol

Resveratrol is a naturally occurring polyphenol mainly found in red skin grapes with antioxidant properties, which is currently considered as a potential senostatic therapy. In experimental studies this effect was found to be mediated via the inhibition of AkT/mTOR pathway inhibition respectively inhibition of p38-MAPK pathway [111].

3.3. Senoprobes (prodrugs): galactoconjugate senolytics

The rationale behind developing these drugs (senoprobes) is represented by the fact that in senescent cells there is an upregulated activity of senescence-associated lysosomal β-galactosidase which uses galactose as a substrate and that by targeting this cell vulnerability it is possible to induce senescent cell death via a senolytic approach or it is possible to trace its activity via a theranostics approach [145].

Another advantage of this approach is the selectivity for senescent cells: one study in which gemcitabine was galactoconjugated and given to mice found that this was able to kill only senescent cells and in this manner to increase viability of mice receiving it [120].

On the other hand galactoconjugate form of navitoclax which in a recent study was demonstrated to have an improved senolytic index compared to the non-conjugated compound (ie specificity for senescent cells) thus protecting non-senescent cells. The conjugate was also found to be less toxic for platelets [121]. Furthermore when applied in combination with cisplatin in A549 lung cancer cells navitoclax galactoconjugate was found to increase the cytotoxicity of cisplatin [121]. Other similar approaches were tested for 5 fluorouracil or for duocarmycin [121].

4. Conclusions

NSCLC remains a therapeutic challenge despite the availability of screening programs and despite the existence of many therapeutic options. One of the aspects making therapy challenging is the lack of robust predictors of response to systemic therapy. One such predictor might be represented by the immune senescence, especially when immune checkpoint inhibitors are to be considered for therapy. Therapy-induced cell senescence is also a challenging issue because up to a point this is a beneficial therapeutic outcome and beyond that point is a risk factor for tumor recurrence. Immune

senescence can be assessed with the aid of biomarkers and can be reversed with senotherapeutics. This pharmacological approach includes senolytics which are able to kill senescent cells (including immune senescent cells) respectively senomorphics which are able to inhibit pathogenic SASP. There are many experimental data available for such potential therapies in the setting of NSCLC but some pieces of this senescence-related puzzle are still missing.

5. Expert opinion

NSCLC is challenging in terms of therapy especially when unknown limiting factors have to be identified and specifically considered. One such factor might be senescence and by immune senescence in particular which can be associated with poor survival, resistance to chemotherapy or to ICI and with tumor invasiveness. Therefore, in NSCLC there is a need to document senescence with appropriate biomarkers for various purposes. One purpose is to establish patient prognosis (speed of tumor progression, tumor invasiveness). Another is to better predict therapeutic response to the regimen being considered for a patient's management. The last purpose, which is closely linked to the previous one, is represented by the consideration of senotherapeutics in order to improve therapeutic prognosis of such patients. The problem with senescence and with SASP is the fact that they are actually endogenous antitumor mechanisms and up to that point it might be even dangerous to inhibit them. But where is that point? How can we define the threshold of pathogeny for senescence and SASP? Do we have markers for pathogenic senescence? In addition, is it enough to have a cellular marker of immune senescence? Or is it enough to have a biomarker of SASP? Some studies focused on SASP biomarkers and their correlation with frailty, but in NSCLC it is of particular importance to document the immune senescence and it is also worth studying and validating biomarkers of SASP which are associated with worse prognosis, especially in advanced NSCLC [146].

Once they are validated the next step is to coin the population of patients with NSCLC in whom to evaluate senescence as an appropriate step in selecting the most effective therapy. Is it enough and, more importantly, is it cheap enough to look for it in any patient? Or perhaps elderly patients or younger patients with 'senescence predisposing' comorbidities are the most adequate beneficiaries of this approach? Another issue is the use of senescence once diagnosed as a therapeutic target (ie having pathologic significance) and its integration in the oncologic management. For instance, one could routinely investigate the CD4/CD8 ratio together with the expression of PD-1 and CTLA-4 biomarkers on late-differentiated T cells, as well as the serum levels of pro-inflammatory cytokines and chemokines, such as TNF-α, IL-18, CCL-16 for early detection of immunosenescence onset. In this scenario, does this mean that senescence should be inhibited with senotherapeutics in all NSCLC patients? Or it is better to use one of the approaches currently recommended which consists of considering senotherapeutics only if there is a high risk of tumor recurrence [147]. One final question is the choice of the right senotherapy from the plethora of compounds currently under investigation in cancer as well as in other chronic conditions. Perhaps the use of biomarkers can also help with the best choice: for example, if immune senescence is detected than a senolitic drug is appropriate, if pathogenic SASP is detected a senostatic approach is needed and if both are present; a dual senotherapeutic is the best option.

To conclude, the identification of senescence as a potential prognostic factor in patients with NSCLC is also worth considering in order to allow the choice of the best senotherapeutic modality that can improve survival in such patients. Until then, many studies are needed to shape the pieces of this puzzle and then to assemble them.

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