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HIV PATHOGENESIS AND TREATMENT (AL LANDAY AND NS UTAY, SECTION EDITORS)

Senotherapeutics and HIV-1 Persistence

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Abstract

Purpose of Review To review the potential use of senotherapeutics, pharmacologic agents that target senescent cells, in addressing HIV-1 persistence.

Recent Findings Treated HIV-1 infection results in a state of immune exhaustion, which may involve reprogramming of infected and bystander cells toward a state of cellular senescence. Aging research has recently uncovered pathways that make senescent cells uniquely susceptible to pharmacologic intervention. Specific compounds, known as senotherapeutics, have been identified that interrupt pathways senescent cells depend on for survival. Several of these pathways are important in modulating the cellular microenvironment in chronically and latently infected cells. Strategies targeting these pathways may prove useful in combating both HIV-1 persistence and HIV-1-associated immune exhaustion.

Summary Senotherapeutics have recently been described as potential therapeutics for aging-associated diseases driven by senescent cells. Recently, correlations have emerged between HIV-1 infection, senescence, lifelong chronic infection, and viral persistence. New insights and therapies targeting cellular senescence may offer a novel strategy to address both HIV-1 persistence and immune exhaustion induced by chronic viral infection.

Keywords HIV · Senescence · Senotherapeutics · Persistence · Latency · Eradication

Introduction

Through the advent of antiretroviral therapy (ART), HIV-1 has been transformed from a fatal disease to a chronic, manageable illness [1, 2]. However, the persistence of HIV-1 in both circulating latently infected $CD4^+$ T cells and tissue-based myeloid cells, and the associated chronic inflammatory state of treated HIV-1 infection have led to the recognition that new strategies to combat viral persistence and its systemic effects are needed [3–6]. In recent years, two new classes of pharmacologic agents, termed senolytics and senomorphics, have been investigated for their ability to interrupt cellular senescence [7]. These compounds demonstrate anti-inflammatory and/or anti-proliferative effects in vitro and in vivo, and a select few have advanced to pilot clinical trials [8••]. Two defining features of chronic, treated HIV-1 infection, namely viral persistence of latently infected $CD4^+$ T cells through homeostatic proliferation and chronic, low-level immune activation and exhaustion, suggest that senolytic and senomorphic therapies may prove clinically useful in augmenting ART [9–11].

In this review, we will outline the barriers to HIV-1 eradication and the current state of cure strategies. With a focus on HIV-1 latency and persistence, we will discuss how chronic HIV-1 infection mirrors a state of advanced aging. We will summarize current theories surrounding how this senescent phenotype may contribute to HIV-1 persistence and those co-morbidities associated with chronic HIV-1 infection. Finally, we will outline the most recent advances in the use of senolytic and senomorphic compounds, their use in the context of HIV-1, and discuss how these may play a role in HIV-1 cure efforts.

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Aging-Associated Diseases Are Driven by Cellular Senescence

Mounting evidence supports a role for cellular senescence, a state of stable pro-inflammatory cell cycle arrest, in driving

diseases of aging including cardiovascular disease (CVD), neurologic disorders, and a syndrome of generalized physiological decline known as frailty [12, 13]. The correlation between cellular senescence and age-related diseases has been demonstrated in natural aging as well as in disease states that drive premature or pathologic aging, including chronic viral infection [7, 14, 15].

Cellular senescence has been identified as an anti-oncogenic pathway, in which pre-neoplastic cells undergo cell cycle restriction and unrestrained cellular proliferation is curbed [16–18]. While senescence can be advantageous, or even essential in the case of embryologic development, the accumulation of senescent cells has been shown to contribute to age-related diseases [12, 19]. In some cases, such as idiopathic pulmonary fibrosis, senescence is thought to have a direct causal relationship with disease progression, and senolytics are actively being evaluated in this context [8••, 20].

The role of cellular senescence in driving age-related diseases is hypothesized to occur through local or systemic release of pro-inflammatory mediators, collectively known as the senescence-associated secretory phenotype (SASP) [7, 21]. The ability of senescent cells to transmit pathological (pro-inflammatory, pro-apoptotic) signals is thought to rely heavily on these inflammatory mediators, suggesting that the presence of even relatively few senescent cells may have important effects on distant organ systems [22, 23]. It has long been recognized that chronic HIV-1 infection gives rise to a state that has been characterized as accelerated aging, and more recently, a correlation between senescence in circulating $CD4^+$ T cells and chronic HIV-1 infection has been established [15, 24]. Therefore, senolytic/senomorphic therapies may play an important role in the treatment of "inflamm-aging" associated with chronic HIV-1 infection [25].

Senolytics Directly Target Senescent Cells

The ability of senescent cells to perpetuate pro-inflammatory signaling is enhanced by a state of cell cycle arrest and an increased threshold to apoptosis. While a variety of events can trigger activation of cellular senescence, these pathways converge on a relatively narrow group of mediators thought to be responsible for the production of SASP. The two major cell-intrinsic mechanisms leading to senescence are the p53/p21 and $p16^{INK4A}$/Rb pathways, both well-defined strategies for tumor suppression that simultaneously activate anti-proliferative and anti-apoptotic programs in response to cellular stress [26, 27]. Thus, pharmacologic strategies that target pathways crucial for the induction and maintenance of senescence represent exciting candidates for their ability to reduce the burden of senescent cells in various diseases and disease models.

Elimination of senescent cells as a strategy to promote healthspan and lifespan was first validated using a transgenic mouse model [12]. More recently, senolytic compounds such as ABT-199, ABT-263, and ABT-737 have been shown to selectively kill senescent cells via inhibition of the BCL-2 pathway which circumvents apoptosis [28–30]. Additionally, through pathways that are incompletely defined, the combination of dasatinib, a broadly active tyrosine kinase inhibitor (TKI), and quercetin, a plant flavonoid, have been shown to selectively kill senescent fibroblasts in mouse models of idiopathic pulmonary fibrosis (IPF) and hepatic steatosis and have shown clinical benefit in IPF patients in a small pilot trial [8••, 31].

The discovery of β-galactosidase and $p16^{INK4A}$ as cellular biomarkers of senescence has allowed the field to assess the ability of senolytic compounds to selectively target these cells in vitro an in vivo, and has identified numerous additional candidates [13, 32]. Some senotherapeutic drugs are non-selective compounds, such as broadly active TKIs, with numerous off-target effects [33]. However, many compounds under investigation for senolytic/senomorphic potential demonstrate far greater specificity, allowing these to act on a limited number of targets that are expressed disproportionately in senescent cells [32]. These are reviewed in Table 1 and discussed in more detail below.

Treated HIV Is a Disease of Chronic Inflammation

The immune system in aviremic HIV-1-infected individuals on ART is marked by chronic immune activation despite the partial recovery of adaptive immunity and elimination of AIDS-related infections [46–48]. In addition to inflammation, chronic, treated HIV-1 infection is associated with increased risk of both end-organ impairment and non-AIDS-associated malignancies [49]. Cardiovascular disease (CVD) risk is elevated among individuals living with treated HIV-1 infection [50–52]. Frailty, an integrative measure identifying patients at high risk of adverse clinical outcomes from aging-related conditions, is common among people living with treated HIV-1 infection [53] and is an important HIV-associated, non-AIDS complication in people living with HIV (PLWH) [54, 55].

Despite the knowledge that chronic HIV infection resembles a state of accelerated aging, a causal association of senescence or senescent cell types remains unclear [25]. Latently infected $CD4^+$ T cells, the major source of HIV-1 persistence in patients on ART, are one potential candidate for targeting by senolytic/senomorphic intervention. However, T cells are not the only cell type susceptible to HIV-1 infection in vivo [56]. Tissue macrophages harbor HIV-1 infection despite ART, and are less susceptible to viral cytopathic effects [57]. HIV-1-infected myeloid cells secrete high concentrations of cytokines in vitro including IL-6 and TNFα, as well as numerous additional pro-inflammatory mediators and cellular responses consistent with induction of senescence [58•, 59].

Table 1 Selected senotherapeutic approaches applicable to HIV-1 cure

Drug	Mechanism(s) of action	Senotherapeutic Behavior	Anti-reservoir mechanism	Clinical status	References
Panobinostat	HDAC inhibitor	Senolytic	Latency reversal	FDA approved for multiple myeloma	[34, 35]
Navitoclax (ABT-263)	BCL-2 antagonist	Senolytic	Targeted apoptosis	Experimental	[32]
Venetoclax (ABT-199)	BCL-2 antagonist	Senolytic	Targeted apoptosis	FDA approved for CLL	[36]
Dasatinib	Broadly active TKI	Senolytic	Anti-proliferative	FDA approved for CML	[37, 38]
Ruxolitinib	JAK1/JAK2 inhibitor	Senomorphic	Anti-proliferative	FDA approved for myeloproliferative diseases	[39–42] NCT02475655
Everolimus	mTOR inhibitor	Senomorphic	Anti-proliferative	FDA approved for immune suppression	NCT024298699
Rapamycin	mTOR inhibitor	Senomorphic	Anti-proliferative	FDA approved for immune suppression	[43, 44], NCT02440789
Metformin	AMPK agonist and glycerophosphate dehydrogenase (mGPD) inhibitor	Senolytic/senomorphic	Unknown	FDA approved for T2DM	[45]

HDAC histone deacetylase, *BCL-2* B cell lymphoma 2 protein, *TKI* tyrosine kinase inhibitor, *JAK* Janus kinase, *mTOR* mechanistic target of rapamycin, *AMPK* 5′ adenosine monophosphate–activated protein kinase, *FDA* Food and Drug Administration, *CLL* chronic lymphocytic leukemia, *CML* chronic myelogenous leukemia, *T2DM* type II diabetes mellitus, *NCT* national clinical trial database (clinicaltrials.gov)

Thus, chronic, treated HIV-1 infection provides two major candidates for senolytic intervention—the latently infected $CD4^+$ T cell and infected tissue macrophages that contribute to chronic inflammation.

Strategies to Target HIV Persistence and Senescence

The first trials aimed at HIV-1 eradication induced non-specific T cell activation, which was ineffective and poorly tolerated [60–62] (reviewed in [63]). Targeted latency reversal is the most highly investigated strategy to date. Often referred to as "shock and kill," this strategy relies on pharmacologic interventions using latency reversal agents (LRAs) which function to activate transcription of the silently integrated HIV-1 provirus in $CD4^+$ T cells. As shown in Fig. 1, alternative HIV-1 eradication strategies include targeted apoptosis and blocking cellular proliferation. Table 1 details several of the candidate pharmacologic agents used in these strategies that have also been explored as senotherapeutics, and these are discussed further below.

Latency Reversal

Latency reversal strategies rely on pharmacologic interventions which activate transcription of the silently integrated HIV-1 provirus in $CD4^+$ T cells. Latency reversal induces virus production in cells which can then be targeted by the immune system. Carried out in the presence of ART, these strategies aim to activate the virus to reproduce while inhibiting new infections in uninfected bystander cells. Histone deacetylase (HDAC) inhibitors have been evaluated as LRAs in several clinical trials [64, 65]. Panobinostat, which is FDA-approved for the treatment of multiple myeloma, has senolytic properties that are being actively explored in the context of directed killing of cancer cells expressing senescent markers. Trials of panobinostat for HIV-1 eradication demonstrated modest anti-reservoir effects [34]. In one trial, a significant decrease in SASP was observed after 8 weeks of dosing, suggesting that panobinostat, and perhaps other HDAC inhibitors, may play an adjuvant role as senotherapeutics [35].

Targeted Apoptosis

Selective killing of latently infected cells with senolytics requires that they share features of senescent cells. One of the consequences of cellular senescence is a reliance on anti-apoptotic pathways for survival. These pathways have been targeted by senolytics that counteract BCL-2 family–induced apoptosis threshold modification. These BCL-2 family inhibitors include ABT-199, ABT-263, and ABT-737 (reviewed in [32]). The major cell type responsible for maintaining the HIV-1 reservoir, the memory $CD4^+$ T cell, is resistant to cell death induced by both exogenous stimuli and HIV-1 replication due to the increased expression of anti-apoptotic and

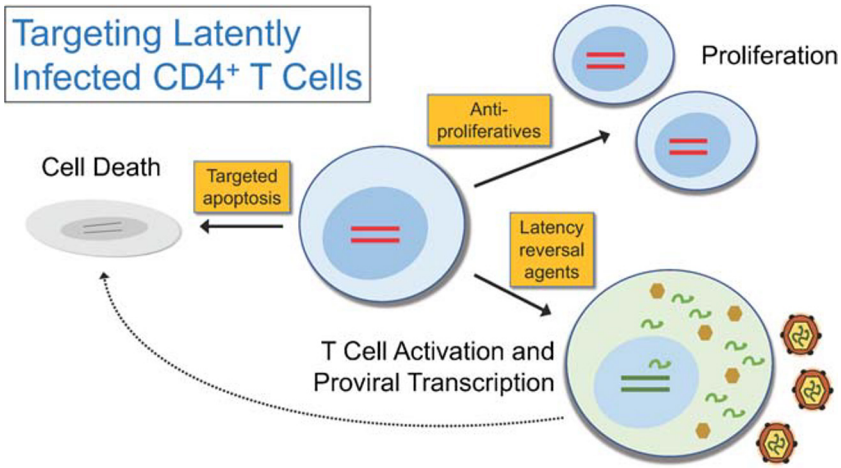

Fig. 1 Senotherapeutic mechanisms that can target latently infected $CD4^+$ T cells. Potential pharmacologic strategies to reduce the HIV-1 latent reservoir in resting memory $CD4^+$ T cells include activation of the latent provirus with latency reversal agents (LRAs), targeted apoptosis of latently infected cells, and interrupting homeostatic proliferation. Senotherapeutic agents, some of which are known to selectively induce cell death or block cellular proliferation, may be employed for their targeted anti-proliferative and pro-apoptotic activities as means to reduce the $CD4^+$ T cell reservoir

decreased expression of pro-apoptotic mediators [36]. It has been shown that latently infected cells can be sensitized to apoptosis upon viral reactivation by pre-treating cells with BCL-2 inhibitors. Importantly, due to their reliance on anti-apoptotic pathways for survival, inhibition selectively kills reactivated cells while leaving uninfected bystander cells unharmed. The BCL-2 inhibitor venetoclax (ABT-199), FDA-approved for treatment of chronic lymphocytic leukemia and acute myeloid leukemia, has been shown to decrease reservoir size and proliferation in an in vitro latency model [66]. Venetoclax counteracted IL-7- and CD3/CD28-driven proliferation, viral reactivation, and new rounds of infection. Targeting the apoptosis threshold of latently infected cells with these senolytic agents holds promise but has yet to be tested clinically.

Anti-proliferatives

One major mechanism contributing to lifelong HIV-1 persistence is homeostatic proliferation [9]. This process allows HIV-1 to persist through division of $CD4^+$ T cells containing HIV-1 provirus driven by γ-c cytokines IL-2, IL-7, and IL-15 in the absence of proviral reactivation [67]. These proliferative stimuli drive kinase cascades (many involving JAK-STAT signaling) that ultimately induce proliferation without cellular activation. Anti-reservoir strategies to date have not adequately addressed the cellular mechanisms responsible for persistence.

The ability to target cellular proliferation was first investigated as a cancer treatment strategy and has become a major mechanism by which many blood-borne cancers are treated. Many of the agents currently in clinical use involve small-molecule TKIs, as many hematopoietic cancers are driven by activating mutations or duplication events within tyrosine kinases responsible for normal cellular proliferation [68]. While TKIs were initially developed to specifically target mutated kinases, these compounds tend to possess off-target effects and thus can inhibit the activity of wild-type kinases [69]. Recently, dasatinib, an FDA-approved TKI used in Philadelphia chromosome-positive chronic myeloid leukemia (CML), has been investigated for its anti-HIV effects. We and others have shown that this molecule prevents infection in major HIV-1 target cell types, and new evidence suggests it may also be useful in inhibiting cytokine-mediated homeostatic proliferation [37, 38]. Dasatinib represents one leading candidate among many TKIs which may prove useful in targeting both the mechanisms responsible for HIV-1 persistence as well as deleterious immune activation observed during chronic infection. Importantly, dasatinib is currently the subject of one clinical trial involving senescence in chronic kidney disease [NCT02848131], and in combination with a quercetin (a plant flavonoid), is being assessed for its potential role in treating Alzheimer's disease [NCT04063124].

T cell homeostasis and cytokine-mediated proliferation rely on signaling intermediates that relay extrinsic signals driven by γ-c cytokines at the cell surface to enact changes in gene expression responsible for cell division [70]. Chief among these is the JAK-STAT pathway, which are critical intracellular mediators of $CD4^+$ T cell proliferation, but are also directly responsible for altering HIV-1 reservoir dynamics, including a correlation between activated JAK-STAT and higher levels of proviral DNA [39]. Compounds targeting JAK signaling thus may present one potential treatment modality for reducing overall proviral burden and preventing homeostatic proliferation leading to HIV-1 persistence. Ruxolitinib, a JAK1/JAK2

inhibitor approved for use in myelofibrosis and polycythemia vera, and tofacitinib, a JAK1/JAK3 inhibitor approved for use in rheumatoid arthritis and ulcerative colitis, have recently been tested and shown to interfere with HIV-1 reservoir seeding an γ-c cytokine-mediated CD4+ T cell proliferation in vitro [39]. Additionally, JAK inhibition has been shown to inhibit cytokine release and global T cell activation in the context of HIV-1 latency reversal, suggesting that these compounds may be useful either alone or in the context of alternative strategies to combat HIV-1 persistence [40]. JAK1/2 inhibition has further been shown to relieve age-related disease including adipose tissue and stem cell dysregulation and reduce measures of frailty in mice [41, 42]. A phase 2 randomized clinical trial evaluating the anti-reservoir and anti-senescence effects of ruxolitinib in chronic, treated HIV-1 infection has recently been completed [NCT02475655]; however, results are not yet available.

Another approach to combat reservoir homeostasis and proliferation is through targeting the mechanistic target of rapamycin (mTOR) pathway, a master regulator that governs cell cycle and metabolism [71]. Previous reports have shown that mTOR inhibitors including sirolimus (rapamycin) and everolimus uncouple cytokine release and HIV-1 reactivation in activated T cells [43]. Rapamycin was associated with a smaller reservoir of HIV-1 DNA-containing cells in patients following transplantation relative to individuals receiving other forms of immune suppression [44]. Taken together, these results suggest that modulating the replicative potential of cells harboring proviral DNA through mTOR inhibition, such as that observed the context of post-transplant immunosuppression, may be a useful and well-tolerated option for reservoir reduction. Currently, two clinical trials are underway to test this hypothesis [NCT02440789 and NCT024298699]. Due to the remarkable overlap of mTOR-centric pathways dictating aging, cell survival, cytokine-driven homeostatic T cell proliferation, aging, and inflammation, mTOR inhibition is of great interest in HIV-1 eradication [72, 73].

Anti-inflammatory and anti-proliferative properties have been ascribed to metformin, a medication approved for the treatment of type 2 diabetes mellitus [74]. It has also been shown to increase health and lifespan in numerous models of aging and age-related disease, and recent evidence suggests that metformin may exhibit senomorphic activity in the context of chronic HIV-1 infection [75–77]. This is currently the subject of a trial which will evaluate the effect of metformin therapy on reservoir reduction and inflammation in non-diabetic individuals [45].

Conclusion

Despite the success of ART, people living with HIV-1 require lifelong treatment due to viral persistence in long-lived cellular reservoirs and remain at elevated risk of aging-associated diseases including cardiovascular disease and non-AIDS-related malignancies. The inability to address these clinically relevant shortcomings of ART represents a critical knowledge gap in the management of HIV-1 infection. Intensive efforts to perturb the latent reservoir via pharmacologic latency reversal or immune-based therapies targeting latently infected cells have not produced positive results to date. Similarly, attempts to directly address the chronic immune activation observed in chronic, treated HIV-1 infection have yielded modest returns. Though in an early stage, the development of senotherapeutics offers a number of promising candidates that may target both HIV-1 persistence and its clinical consequences.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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