

Review

Old Hosts, Young Models: Rethinking Cancer Immune Evasion in Aging

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ABSTRACT: Cancer is largely a disease of older adults, yet the framework used to explain how tumors evade immunity was built almost entirely on young, specific-pathogen-free mouse models and on clinical trials that under-enroll older adults. This review examines whether that framework holds when the host is old. Rather than surveying cancer immunology and aging comprehensively, it focuses on one question: whether the four host capacities the standard account of immunoediting and checkpoint blockade assumes still hold in the aged host. These are a naive T-cell repertoire wide enough to generate tumor-specific clones, a stromal environment that does not suppress priming, functional natural killer [NK] cell surveillance, and an immune baseline free of chronic inflammation. Aging alters all four, but not uniformly. Thymic involution and NK cell decline result in the immune system operating at reduced capacity, representing a shift in severity rather than a fundamental change in mechanism. The NK cell axis is disproportionately significant, as no approved therapies currently restore its function. In contrast, aged stromal senescence and inflammaging represent qualitative changes: the tissue environment becomes suppressive prior to tumor development, rather than as a consequence of tumor presence. The clinical evidence neither confirms nor refutes this interpretation. Older and younger patients gain similar benefit from checkpoint blockade, which is easily read as age being immunologically irrelevant. We argue instead that chronological age bundles aging changes acting on response in opposite directions. What predicts response is more accurately captured by immunological age than by chronological age. This reframing has a clear translational consequence. Therapeutic approaches should not only target the release of suppressed immune responses but also address the correction of the aged microenvironment. This hypothesis is currently being evaluated by senolytic strategies, which have been tested in an initial clinical trial and are supported by converging preclinical evidence.

Keywords: immunosenescence, tumor microenvironment, immune checkpoint blockade, inflammaging, cellular senescence, senolytics

1. Introduction

Cancer is a disease that predominantly affects older adults, and the global epidemiology of the disease is increasingly shaped by population aging. According to a recent systematic analysis based on the GLOBOCAN 2020 and Global Burden of Disease 2019 databases, of the 19.3 million new cancer cases reported globally in 2020, adults aged 60 years and older accounted for 64% of all

cancer diagnoses and for 71.3% of cancer-related deaths [1]. Cancer progression is shaped by both tumor-intrinsic events, such as the cumulative acquisition of oncogenic alterations, and host-extrinsic factors, including the progressive functional decline of the immune system [2]. The immunological role of this decline has been formalized through the cancer immunosurveillance hypothesis [3, 4] and refined in the cancer immunoediting framework [5, 6].

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Despite this epidemiological reality, the foundational experimental work supporting the dominant framework of tumor immune evasion has largely been conducted in young experimental systems. As Murphy [2016] noted in a frequently cited commentary, the use of "young, lean, inbred mice housed under specific-pathogen-free conditions does not mirror the human cancer scenario," and the field has been described as "penny-wise but pound foolish" in its preclinical assessment of immunotherapeutics [7]. Nearly a decade after this critique, the gap remains largely unaddressed: recent experimental work in age-matched preclinical models has shown that aged hosts exhibit altered tumor immune infiltrates and varying responses to immune checkpoint blockade compared with their younger counterparts [8, 9]. That last condition matters more than it might seem specific-pathogen-free mice, never having met the microbial world, carry immune systems that look more like a human newborn's than an adult [10]. The clinical correlate of this preclinical bias is the persistent underrepresentation of older adults in the trials that shape immunotherapy practice. In an FDA analysis of more than 224,000 patients enrolled in cancer drug registration trials between 2005 and 2015, only 12% were aged 75 or older [11], a disproportionate representation that has been shown to persist in contemporary cancer trials [12].

This preclinical and clinical bias carries considerable biological implications. Four immune alterations characterized in aged hosts are of particular relevance to tumor immune evasion and form the analytical core of this review: thymic involution and the contracted naive T-cell repertoire, the senescence-associated secretory phenotype [SASP] of aged stromal cells, the functional decline of natural killer [NK] cells, and inflammaging as a baseline immune state [2, 13, 14]. Whether these alterations represent merely milder forms of the same evasion processes operating in younger hosts, or constitute qualitatively distinct mechanisms, is a question that the present review aims to address.

Our study argues that this framework, built largely on young-host experimental systems, does not fully transfer to the immune evasion landscape in older patients. The main contribution of this work is a reinterpretation of the prevailing framework of tumor immune evasion as conditional on host age, with direct implications for the design of immunotherapy in older patients. This review does not provide an additional catalogue of immunosenescence mechanisms, as comprehensive accounts are already available. Immunosenescence has been examined by cell type as a driver of tumor progression and therapy resistance [2], organized into a taxonomy of molecular hallmarks with associated remodeling of the tumor microenvironment [15], and reviewed from the perspective of geriatric oncology [16].

Most recently, age-related effects across immunity, the tumor microenvironment, immunotherapy efficacy, and adverse events have been surveyed collectively [17]. The primary focus of this review is the conceptual framework, specifically immunoediting and checkpoint blockade, which are models developed and validated primarily in young, pathogen-free hosts.

To this end, we examine four points at which the standard model does not hold in an aged host, assess the clinical evidence on whether age modifies immunotherapy outcomes, and discuss emerging senolytic strategies that aim to correct the aged tumor microenvironment rather than enhance existing immune responses. Taken together, these shortfalls amount to more than a quantitative extension of the young-host model; they approach a qualitative reframing of what immune evasion is in an aged host. The scope is restricted to solid tumors.

2. The Standard Model of Tumor Immune Evasion: Structure and Host-Dependent Assumptions

2.1 The immunoediting framework as a host-conditional model

The hypothesis that the immune system constrains tumor development was first articulated by Ehrlich [1909] and developed by Burnet [1957] and Thomas [1959]. It was later framed more fully by Burnet [1970] as the cancer immunosurveillance theory [18]. The hypothesis was revived in the late 1990s through experimental work in IFN- γ receptor-deficient and RAG2-deficient mice, which established that adaptive immunity and interferon γ [IFN- γ] signaling constrain tumor outgrowth in immunocompetent hosts [19-21]. Building on these findings, Dunn, Old, and Schreiber extended the hypothesis into the cancer immunoediting framework, comprising three phases: elimination, equilibrium, and escape [5, 22, 23].

Elimination depends on three principal mechanisms. First, IFN- γ signaling, mediated through signal transducer and activator of transcription 1 [STAT1], is required for the elimination of nascent transformed cells [19]. Second, CD8⁺ T-cells eliminate transformed cells through perforin- and granzyme-mediated cytotoxicity [24]. Third, NK cells recognize transformed cells via the NKG2D receptor, engaging stress-induced ligands on their surface [25]. Equilibrium is the longest and most hypothetical of the three phases. It has been shown to require CD4⁺ and CD8⁺ T-cells together with IFN- γ and IL-12, and has not been shown to depend on natural killer cells under the experimental conditions tested [26]. The strongest human evidence remains the recurrence of donor-derived melanoma in immunosuppressed

transplant recipients sixteen years after the donor's apparent cure [27]. Escape encompasses several distinct strategies, which can be usefully separated into tumor-intrinsic and tumor-extrinsic mechanisms. Tumor-intrinsic escape includes major histocompatibility complex [MHC] class I downregulation and Janus kinase 1/2 [JAK1/2] loss-of-function mutations, which disable IFN- γ signaling and have been documented as a mechanism of acquired resistance to programmed cell death protein 1 [PD-1] blockade in melanoma [28, 29]. In contrast, tumor-extrinsic escape includes the recruitment of regulatory T-cells [Tregs] and myeloid-derived suppressor cells [MDSCs], among other mechanisms involving the broader tumor microenvironment [30, 31].

Each of these phases relies on certain capacities in the host: a naive T-cell repertoire capable of recognizing neoantigens, a permissive stromal context that does not actively suppress effector function, functional NK-mediated innate surveillance, and a baseline immune state free of chronic inflammatory tone. These conditions were not explicitly stated in the original framework because, in practice, they were already present in the young, inbred, pathogen-free mice commonly used in experiments. As a result, the concept of immunoediting does not offer a universal, host-independent view of tumor-immune interactions – instead, it reflects what happens in a specific kind of host.

2.2 Immune checkpoint blockade and its conditional logic

The therapeutic translation of the immunoediting framework rests on a clinical observation. Tumors exploit physiological inhibitory pathways that, under normal conditions, maintain self-tolerance and limit autoimmunity [32]. The conceptual breakthrough was that these pathways could be pharmacologically blocked to release suppressed anti-tumor T-cell responses [33].

Cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] and programmed cell death protein 1 [PD-1] act at different stages of the T-cell response, and this temporal separation explains why the two checkpoint pathways have distinct therapeutic profiles. CTLA-4 functions primarily during the T-cell priming phase in secondary lymphoid organs, where it competes with CD28 for the shared ligands CD80 and CD86, thereby raising the threshold for naive T-cell activation [34]. PD-1, by contrast, acts later, on effector T-cells in peripheral tissues, where engagement by programmed death-ligand 1 [PD-L1] expressed on tumor cells and on host antigen-presenting cells in the tumor microenvironment attenuates cytotoxic function [32, 35, 36].

The clinical application of these mechanisms progressed sequentially. Anti-CTLA-4 therapy was

initially validated with ipilimumab in a phase 3 trial that demonstrated improved overall survival in metastatic melanoma [37], resulting in Food and Drug Administration [FDA] approval in 2011. Anti-PD-1 agents received approval in 2014, followed by anti-PD-L1 agents from 2016 onward. These therapies have subsequently been applied to a wide range of tumor types [33, 35].

Despite this expansion, the population-level benefit of immune checkpoint blockade remains modest. Population-level analyses of US cancer patients estimate that the proportion eligible for immune checkpoint inhibitor [ICI] therapy rose from approximately 44% in 2018 to approximately 57% in 2023, while the proportion deriving a measurable response increased from approximately 12% to 20% over the same interval [38, 39]. Even among treated patients, durable responses are observed in only approximately 25% across solid tumors, and predictive biomarkers capable of identifying responders before treatment remain incomplete [40].

Therefore, the conceptual framework underlying immune checkpoint blockade is based on two key assumptions. The first is that a tumor-specific T-cell response is already present and is suppressed by the targeted pathway. The second is that, once released, this response maintains sufficient effector capacity to eliminate tumor cells. Both assumptions are intrinsically linked to host factors. The first relies on a diverse T-cell repertoire capable of generating tumor-specific clones, while the second requires intact T-cell effector mechanisms that have not been impaired by senescence, exhaustion, or metabolic dysfunction.

2.3 Four host-dependent assumptions

Immunoediting depends on a host capable of mounting and sustaining adaptive immune pressure [5, 6]. Checkpoint blockade depends on the existence of a tumor-reactive T-cell response that has been suppressed but is recoverable, and on T-cells whose effector machinery remains functional once that suppression is released [32, 33, 35]. A recent comprehensive formulation classifies cancer-cell-intrinsic immunoevasive mechanisms under a "three Cs" framework of camouflage, coercion, and cytoprotection. While the framework is presented as a synthesis of how malignant cells evade tumor-targeting immunity, its scope statement explicitly excludes three categories of host-level mechanisms from consideration: host polymorphisms, immunological alterations of the tumor microenvironment driven by non-malignant cells, and "defects in the whole-body ecosystem that are not elicited by neoplastic cells" [41]. Aging-related alterations to the host immune system fall predominantly within the second and third of these excluded categories.

The exclusion is appropriate to the authors' stated scope but illustrates how comprehensive frameworks of cancer immune evasion can be built without engaging the host dimension, leaving the question of how host aging modifies these mechanisms outside the analytic frame in which they are typically discussed.

Four host conditions warrant particular attention, as these are the conditions most susceptible to compromise with aging [2, 14]. The first is the maintenance of a naive T-cell repertoire sufficiently diverse to generate tumor-specific clones in response to an evolving antigen landscape. Both de novo elimination and the pre-existing responses targeted by checkpoint blockade depend on this diversity. The second condition involves dendritic cell antigen presentation within a stromal environment that does not actively suppress T-cell priming. The third is natural killer cell-mediated surveillance, which detects tumors independently of MHC-restricted T-cell responses. This redundancy allows the framework to predict immune control even when tumors downregulate MHC class I to evade CD8⁺ T-cells. The fourth condition is a baseline immune tone that has not shifted toward chronic inflammation. The framework assumes that tumor-specific responses originate from a homeostatic resting state, rather than from a chronically activated baseline that has already compromised its effector capacity. These four conditions are typically present in young, immunocompetent hosts. Thus, the sections that follow examine each in turn, asking whether aging alters a capacity the framework already represents or introduces one it does not.

3. How Host Aging Reshapes the Tumor Microenvironment

This section addresses two recurring departures from the young-host model, distinctions that should be made clear at the outset. First, a change is classified as one of degree when the existing framework already includes a variable for the affected host capacity and aging simply modifies its value, resulting in the same mechanism operating but at a reduced magnitude. In contrast, a change is considered one of kind when aging introduces a new state not represented in the original framework. This scenario necessitates an extension of the model, rather than a simple re-parameterization. Notably, a change may be extensive at the molecular level yet still qualify as one of degree if the framework already accounts for diminished capacity. Conversely, a change may involve mediators present in young-host biology but still be one of kind if its causal and temporal structure, chronic rather than acute, tumor-independent rather than tumor-provoked, does not fit within the existing model. As will be demonstrated in the following sections, these two types of changes are

interrelated: qualitative alterations in the aged microenvironment contribute directly to the quantitative decline of the effector compartment.

This criterion is distinct from descriptive taxonomies of age-related immune change. The most comprehensive of these, Age-Related Immune Dysfunction [ARID], was introduced to encompass the full spectrum of age-related immune alterations, including changes in quantity, quality, direction, emergence of novel cell subsets, and shifts in inflammation [17]. While such taxonomies classify the specific changes occurring in the aged immune system, the degree versus kind distinction addresses a different issue: whether the young-host framework already accounts for the affected capacity. These two axes are independent. For example, an alteration classified by ARID as a change in immune quality may still represent a change of degree if the existing framework already includes the variable that is degraded. The objective here is not to re-describe the biology of the aged immune response, as ARID and related syntheses already provide a comprehensive vocabulary for this purpose, but rather to evaluate the adequacy of the framework within which this biology is assumed to function. Figure 1 previews this evaluation, comparing each young-host assumption with the aging change that alters it across the four axes examined in turn below.

3.1 Thymic involution and the contracted naive T-cell repertoire

The first host condition the framework suggests is a naive T-cell repertoire diverse enough to generate tumor-specific clones against an evolving antigen landscape. Both de novo elimination and the pre-existing response that checkpoint blockade aims to release depend on this diversity. The thymus atrophies from early childhood, with thymic epithelial tissue progressively replaced by adipose tissue, and T-cell production declining exponentially with a half-life of approximately 15.7 years [42-44]. The translational importance of this parameter is considerable. Palmer and colleagues demonstrated that a model relying exclusively on the immune escape threshold, determined by declining T-cell output, predicts age-specific incidence across multiple cancer types with greater accuracy than the conventional power-law model of mutation accumulation. This approach utilizes the empirically derived involution rate of 0.044 per year instead of a fitted parameter. Consequently, the model attributes age-related cancer risk primarily to the host-extrinsic decline in immune surveillance rather than to the accumulation of intrinsic genomic damage [45].

Direct quantification of the human TCR β repertoire by deep sequencing in 39 donors aged 6 to 90 years

showed that diversity per million T-cells decreases linearly with age, with a significant reduction apparent by age 40. The percentage of naive T-cells declined in parallel until age 70, after which a survivor effect appeared: the oldest cohort, averaging 82 years, retained higher naive CD4⁺ fractions and greater TCR β diversity

than the 62-year-old group, suggesting that exceptional longevity is associated with preserved repertoire breadth [46], though this cross-sectional survivor pattern rests on a small cohort and does not establish that repertoire breadth is preserved within individuals over time.

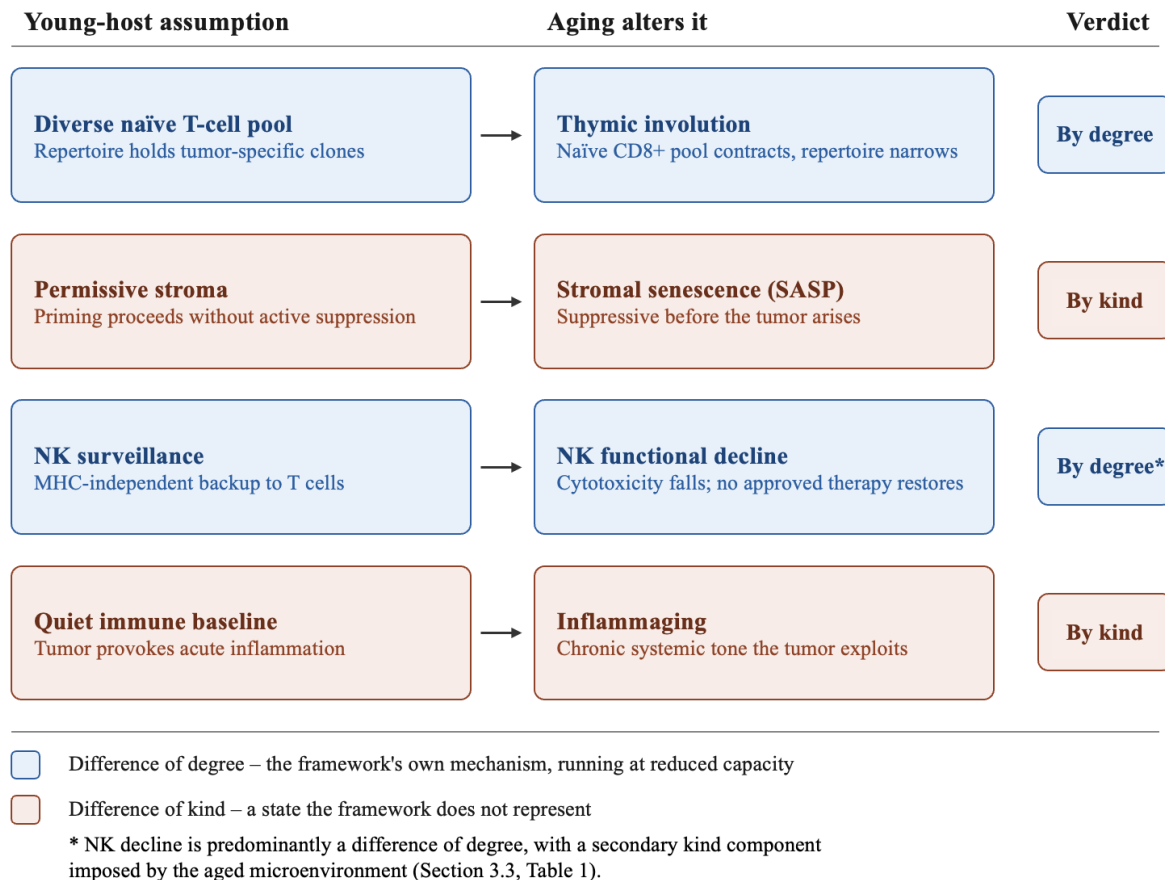


Figure 1. The four host-dependent assumptions of the tumor immune-evasion framework and how host aging alters each. Each young-host assumption (left) is paired with the corresponding change in the aged host (center) and a verdict on whether that change is a difference of degree or of kind (right). Blue denotes a difference of degree, in which a mechanism the framework already represents operates at reduced capacity; red denotes a difference of kind, in which aging introduces a state the framework does not represent. NK functional decline is predominantly a difference of degree with a secondary kind component imposed by the aged microenvironment (asterisk; Section 3.3, Table 1). Classification and supporting evidence for each axis are given in Table 1.

The mechanistic basis of contraction is complex and involves multiple layers. Goronzy and Weyand [2019] categorize T-cell aging into three primary domains: reduced self-renewal resulting from decreased thymic output, impaired regulation of cellular quiescence that leads to homeostatic proliferation of the remaining naive T-cell pool, and cellular senescence characterized by telomere shortening, increased DNA damage responses, and a senescence-associated secretory phenotype. The disproportionate loss of repertoire between CD4⁺ and CD8⁺ T-cell subsets represents the primary intersection of thymic involution with tumor immunity. Importantly,

naive CD8⁺ T-cells represent the most susceptible component of T-cell homeostasis. Their depletion serves as the most consistent and prominent indicator of immune aging in healthy older adults, regardless of comorbidities or chronic latent infection [47].

A longitudinal analysis of thirty adults from the Baltimore Longitudinal Study of Aging, sampled an average of nine years apart, quantified this asymmetry directly: naive CD8⁺ TCR β richness declined at 3.48% per year against 2.27% for naive CD4⁺, and paired $\alpha\beta$ repertoire richness fell significantly for total, naive, and memory CD8⁺ subsets while remaining stable across all

CD4⁺ subsets. The same study found that the aged memory CD8⁺ repertoire becomes not only smaller but also more rigid, with TCR sequence retention between sampling points roughly doubling in donors over 70 relative to those under 40. The cytotoxic compartment engaged by both immunoediting elimination and checkpoint blockade is therefore the compartment that aging most severely depletes and most strongly locks into a fixed set of specificities [48]. These longitudinal estimates derive from thirty individuals and should be read as indicative of direction rather than precise magnitude.

One qualification belongs here: naive T-cell numbers and functional repertoire diversity are not strictly proportional. Notably, simulations discussed by Goronzy and Weyand [2019] indicate that homeostatic proliferation can preserve functional diversity even when the naive CD8⁺ compartment contracts by more than half, so numerical loss alone does not produce large gaps in the repertoire [47]. The sequencing data nonetheless show diversity declining alongside cell number, and because both measures fall together in the CD8⁺ compartment, the decline is a real loss rather than a statistical artifact [46, 48].

Therefore, it can be concluded that TCR repertoire contraction is not absent in young hosts but reflects the same biology operating at a different magnitude, making it a shift in severity rather than a categorical change. The severity matters because the magnitude crosses thresholds the framework depends on. A repertoire broad enough to contain tumor-specific clones, and a naive CD8⁺ pool large enough that *de novo* priming remains a viable response mode, are not features that scale gracefully with age. When the substrate erodes below these thresholds, immunoediting and checkpoint blockade rest on resources the host no longer reliably possesses. The contraction described so far concerns thymic output and repertoire size. However, numerical contraction is not the only route by which the aged host loses T-cell competence. Regulatory T-cells and the suppressive milieu can drive naive and effector T-cells into senescence directly, producing growth-arrested, suppressive cells characterized by the loss of CD27 and CD28 and the induction of p16, p21, and p53 in human cells, both *in vitro* and *in vivo* [49]. Tumor-derived T-cell senescence of this kind is now more broadly recognized as a feature of the tumor microenvironment [50]. This represents a qualitatively distinct mechanism, which will be revisited in the synthesis concluding this section.

3.2 Aged stroma, SASP, and dendritic cell dysfunction

The second host condition the framework presumes is that dendritic cell antigen presentation operates within a stromal environment that does not actively suppress T-cell priming. The standard model treats the stroma as a neutral scaffold through which antigen is captured, transported, and presented. Aging challenges this assumption in a unique way. Instead of simply reducing an existing immune capacity, it transforms what should be a brief, self-limiting signal into a chronic, persistent feature of the microenvironment. This shift is driven by two main mechanisms: the emergence of a suppressive stromal-myeloid axis and the gradual breakdown of the dendritic-cell presentation machinery.

Senescent cells accumulate in aged tissues and release a set of signals known as the senescence-associated secretory phenotype [SASP], including interleukins, chemokines, growth factors, proteases, and matrix-remodeling enzymes. Interleukin-6 [IL-6] stands out as the most prominent SASP cytokine and is commonly used as a marker for overall SASP activity in tissue [51, 52]. The distinction that matters for this framework is timing. In young tissue, the SASP emerges briefly during wound healing or senescence surveillance, and then it fades away. But as tissues age, senescent cells continue to accumulate, and the SASP shifts from a short-lived burst to a chronic, ever-present feature of the microenvironment. Where young hosts encounter the SASP as a temporary signal, older hosts carry it as a persistent background condition.

The first mechanism is the suppressive stromal-myeloid axis, and the evidence for its causal role comes from genetic mouse models. Ruhland et al. activated senescence exclusively in the stromal compartment in the absence of any tumor and showed that senescent stroma alone was sufficient to recruit immunosuppressive myeloid-derived suppressor cells [MDSCs] and suppress CD8⁺ T-cell function. Interestingly, the neutralization of IL-6 reduced this myeloid accumulation. The authors framed senescence as a driver of immunosuppression distinct from the role played by tumor cells. In human samples, immune cells were localized near senescent stromal cells in aged, cancer-free individuals, consistent with the mouse mechanism but establishing an association rather than causation [53]. Independent work has shown that senescent cells also recruit MDSCs through CCL2, indicating that the suppressive stromal program does not depend on a single cytokine [54]. The claim that aged stroma is suppressive before and independently of the tumor, therefore, rests on direct causal evidence in mouse models and on correlative evidence in humans.

The second mechanism concerns the antigen-presentation machinery itself and operates at the level of the broader aged tumor microenvironment rather than the senescent stroma specifically. Chen et al. [2024]

demonstrated that the aged tumor microenvironment impairs the crosstalk among natural killer cells, cDC1, and CD8⁺ T-cells necessary for effective priming. This impairment is characterized by reduced XCL1-XCR1 and FLT3L-FLT3 signaling, decreased numbers of conventional type 1 dendritic cells in tumors and draining lymph nodes, and downregulation of antigen-presentation machinery [55]. In their model, aged hosts did not respond to neoantigen vaccination, with the defect attributed to the microenvironment rather than to intrinsic T-cell dysfunction. The study also identified a dysfunctional CD8⁺ T-cell signature in human pan-cancer datasets from older patients, indicating that this mechanism extends beyond the mouse model. This axis is distinct from, though related to, the stromal SASP, as it highlights a failure of dendritic-cell-mediated priming that does not necessarily result from stromal senescence alone.

A critical caveat must be noted for accuracy. The senescence-associated secretory phenotype [SASP] is context-dependent and not uniformly immunosuppressive. In precancerous tissue, SASP can promote senescence surveillance and tumor clearance. Additionally, individual factors such as IL-6 may exhibit either pro-tumorigenic or anti-tumorigenic effects depending on the specific context [54]. The qualitative claim is narrowly defined and specifically addresses the chronic, established stromal state in aged hosts, in which senescent fibroblasts and the associated myeloid compartment alter the priming environment to promote immunosuppression before tumor development.

This distinction represents a difference of kind rather than degree. In mouse models, the causal relationship is direct: aged stroma is sufficient to suppress priming independently of the tumor [53]. In humans, the evidence remains correlative but is consistent across independent datasets. The aged host does not merely exhibit a weaker priming response; instead, it primes T-cells within a chronically suppressive stromal environment. The standard model does not capture this condition, as it was developed from hosts in which stromal suppression arises only as a consequence of tumor development.

3.3 Natural killer cell decline as a separate immune evasion axis

The third host condition assumed by the framework is natural killer [NK] cell-mediated surveillance, which identifies tumors independently of major histocompatibility complex [MHC]-restricted T-cell responses. This independence provides redundancy within the framework: when tumors downregulate MHC class I molecules to evade CD8⁺ T-cells, they become susceptible to NK cells. NK cells detect the absence of self MHC class I through inhibitory receptors, resulting in the

loss of their restraining signal. This mechanism is known as the missing-self principle, whereby NK cells recognize MHC class I-deficient cells that lack inhibitory ligands for killer-cell immunoglobulin-like receptors [56]. The activating pathway, involving NKG2D engagement with stress-induced ligands such as MIC and ULBP, establishes a recognition logic distinct from T-cell antigen recognition [24].

Aging does not abolish this axis, and the manner in which its effectiveness is reduced provides valuable insight. In human peripheral-blood studies, total NK-cell numbers are largely preserved with age, rising modestly as a proportion of a shrinking lymphocyte pool while absolute counts are reported as stable or mildly increased [57]. Whether the composition of the pool shifts with age is not settled: some studies report no significant change in the CD56bright and CD56dim proportions, while others describe a relative decline of the cytokine-producing CD56bright subset and expansion of the cytotoxic CD56dim subset, with reduced per-cell cytotoxicity and IFN- γ output [57-60]. Notably, stable NK-cell counts can coexist with a markedly reduced production rate, reflecting accumulation of long-lived cells rather than true homeostatic preservation [57].

At the receptor level, the senescence marker CD57 accumulates while the activating receptors NKp30, NKp46, and DNAM-1 are downregulated, the inhibitory receptor KLRG1 rises, and perforin and granzyme expression fall [59-61]. An important qualification applies: this remodeling is only partly age-intrinsic. The accumulation of CD57 on CD56dim NK cells is associated with chronic cytomegalovirus seropositivity rather than aging as such, and because CMV prevalence is high among older adults the specific effects of age and CMV are difficult to separate [57, 61, 62]. At the level of individual receptors, reduced DNAM-1 tracks with chronological age whereas reduced NKp30 is more closely associated with CMV infection [62]; CMV status nonetheless does not account for all age-associated NK changes [57]. This is therefore predominantly a severity shift: the same recognition machinery, operating less effectively, in a population that has not numerically collapsed.

The consequence, however, is not proportionate to the magnitude. The framework treats NK surveillance as the backup that holds when the T-cell axis is evaded, but two features of aging remove that backup precisely when it is most needed. First, the aged tumor microenvironment actively drives NK senescence through myeloid-derived suppressor cells, regulatory T-cells, and the cytokines transforming growth factor-beta [TGF- β] and interleukin-6, so the decline is not merely cell-intrinsic but reinforced locally [63]. Direct evidence supports this: the effector suppression that marks NK aging can be reproduced in

healthy human NK cells by microenvironmental TGF- β , reversibly and through chronic tumor contact, with effector function restored when TGF- β is blocked [64]. Part of what presents as NK aging is therefore the standing suppressive environment acting on the NK compartment, rather than cell-intrinsic decline alone. Second, the approved checkpoint inhibitors that define current practice act on the T-cell axis; programmed cell death protein 1 [PD-1] is expressed at very low levels on NK cells, so anti-PD-1 therapy largely bypasses them. Checkpoint strategies directed at the NK axis exist but operate through different receptors. For example, blockade of NKG2A, the inhibitory receptor that reads the same non-classical MHC class I signal, HLA-E, exploited in missing-self recognition, releases both NK and T-cell effector functions and showed early promise in combination with T-cell-directed therapy [65]. These NK-directed agents remain investigational rather than approved, and their clinical translation has so far been uncertain: the lead anti-NKG2A antibody, monalizumab, did not improve survival in a phase 3 solid-tumor trial [66] and is not part of standard care. NK senescence markers have been proposed as predictors of immunotherapy response, although direct studies of NK senescence and checkpoint-inhibitor efficacy are lacking; elevated CD57⁺ NK-cell proportions correlate with poor clinical prognosis [63]. The redundancy the framework assumes is thus doubly compromised in the aged host: the backup axis weakens with age, and the therapies in routine use do not restore it.

3.4 Inflammaging as a tumor-permissive baseline

The fourth host condition the framework presumes is that the inflammatory dynamics shaping anti-tumor immunity are driven by the tumor itself. Acute, antigen-specific inflammation arises in response to transformation, recruits effector cells, and resolves. The framework's logic, inflammation as a tumor-mounted attack and the immune response as the reply, depends on this temporal structure: inflammation is something the tumor provokes in a host that begins from an inflammatorily quiet baseline. Aging departs from that assumption by introducing a feature that the framework does not represent.

Inflammaging is the chronic, sterile, low-grade systemic inflammation that develops with age and contributes to the pathogenesis of age-related diseases [13]. Each of those features sets it apart from the inflammation the framework represents. It is sustained by endogenous stimuli including cell debris, misplaced self molecules, and gut microbial products rather than by an active pathogenic or transformative trigger. This phenomenon persists as a baseline state rather than

emerging as a discrete event. It is systemic, manifesting in circulating cytokines and the immune compartment well before any tissue-specific challenge occurs. The framework's representation of inflammation as acute and locally provoked does not contain this category.

Inflammaging shares a mechanistic source with the stromal senescence discussed earlier [Section 3.2]. Senescent cells accumulate in aged tissues and secrete the SASP, and this secretion [sustained across decades rather than resolved over days] is one of the principal drivers of the chronic inflammatory baseline [13]. In young tissue, certain signals remain local and transient; however, in aged individuals, these signals enter the circulation and sustain a systemic inflammatory state that cannot be attributed to any single acute event. Andonian et al. [2024] describe this phenomenon as a transdisciplinary inflammatory state that links cellular senescence to clinical aging outcomes, including frailty and mortality. They also discuss interventions targeting this baseline state, including senolytics and senomorphics [67].

A key consequence for tumor immunity is that this baseline falls outside the established framework. Chronic inflammation has long been recognized as a predisposing factor for malignancy, a concept originating from Virchow's nineteenth-century observation that tumors frequently develop at sites of chronic irritation. This association is supported by mechanistic and observational evidence indicating that an inflammatory microenvironment provides growth factors, survival signals, angiogenic factors, and matrix-remodeling enzymes that facilitate cellular transformation and tumor progression [68]. Inflammaging further extends this concept by establishing that a tumor-permissive inflammatory state can exist independently of tumor presence. In aged individuals, this pro-inflammatory condition is constitutively present prior to malignancy, so that tumors may arise within an inflammatory milieu they did not need to induce [69].

This represents the clearest example of qualitative addition among the four conditions. The first three conditions primarily involve aging-related changes that distort, weaken, or restructure mechanisms already represented within the framework, even when, as in the case of NK cell decline, some changes are imposed by the aged environment. In contrast, inflammaging introduces a state not represented by the framework: a systemic, chronic, sterile inflammatory tone that exists in the host independently of tumor presence and is exploited, rather than provoked, by the tumor. This baseline influences how the aged host responds to immunotherapy [70] in ways that an acute-inflammation model cannot predict. The nuances and clinical implications of this shift are discussed further in Section 4.

Collectively, the four assessments should not be viewed as independent categories. Paracrine senescence serves as the connecting mechanism: senescent cells can induce senescence in neighboring cells via the secretory phenotype, with TGF- β family ligands acting as principal mediators [71]. This phenomenon has been primarily demonstrated in stromal and epithelial cells, rather than within the lymphoid compartment. Furthermore, direct evidence that the microenvironment can induce senescence in NK and T-cells is derived mainly from studies of the tumor microenvironment, rather than from aged hosts specifically. The relevance to the current context is that aged hosts exhibit a similarly suppressive, TGF- β - and IL-6-rich environment prior to tumor

development. This is evident in the aforementioned findings: senescent stroma alone can suppress CD8⁺ T-cell function even in the absence of tumors [Section 3.2]. In this framework, both degree changes, such as thymic involution and the cell-intrinsic component of NK cell decline, and kind changes, such as stromal senescence and inflammaging, are interconnected. The persistent suppressive environment in aged hosts contributes to reducing the effector compartment below the thresholds required by the framework. Thus, the classification is best understood as layered rather than strictly partitioned. Table 1 summarizes each axis, the criteria applied, and the strength and provenance of the supporting evidence.

Table 1. Host-aging changes to the four framework assumptions: classification as degree or kind, with supporting evidence.

Framework Assumption	Aging Change	Degree / Kind	Key Evidence	Predominant Model System	Strength Of Causal Inference	Human-Cancer Relevance
Naive T-cell repertoire broad enough to generate tumor-specific clones	Thymic involution and TCR repertoire contraction; environmentally imposed T-cell senescence	Degree (repertoire variable; value falls) + kind component (imposed senescence)	42, 45 (modeling); 46; 48; 49; 50 (imposed)	Human sequencing + population modeling; human <i>in vitro/in vivo</i> (imposed)	Correlative + quantitative modeling; causal for imposed senescence	High
Stromal priming environment that does not suppress priming	Stromal senescence / SASP	Kind (pre-existing suppressive environment; not represented)	52-55	Mouse (causal) + human (correlative)	Causal in mouse; correlative in human	Moderate-High
NK MHC-independent surveillance (backup axis)	NK senescence: receptor remodeling, effector reprogramming, TME-imposed senescence	Degree-dominant (surveillance machinery at reduced capacity) + kind component (TME-imposed)	57; 61-63 (CMV vs age); 64 (TGF- β -imposed);	Human correlative + mechanistic; human <i>in vitro/ex vivo</i> (imposed)	Human correlative, partly CMV-confounded; causal (reversible) for TGF- β -imposed suppression	High
Inflammation-free baseline (acute, tumor-provoked inflammation)	Inflammaging (chronic, sterile, systemic, tumor-independent)	Kind (pre-existing inflammatory baseline; not represented)	67; 69; 72	Human + conceptual synthesis	Conceptual / associative	Moderate

Footnote: Paracrine senescence [71] provides a mechanistic bridge linking several "kind" changes (e.g., stromal senescence and TME-induced senescence) to downstream "degree" changes in immune function, with TGF- β representing a recurring mediator across multiple pathways.

4. Age and Immunotherapy Response: What the Clinical Evidence Shows

The previous section proposed that host aging alters the tumor microenvironment along four dimensions not fully captured by the standard framework. If this hypothesis is correct, a clinical implication follows: older patients would be expected to respond less effectively to immune

checkpoint blockade, as the therapeutic substrate is compromised. However, the clinical literature does not unequivocally support this prediction, and the nature of this discrepancy provides more insight than a simple confirmation or refutation.

Meta-analyses consistently indicate that the survival benefit of checkpoint inhibition is broadly comparable between older and younger patients, which challenges the

mechanistic hypothesis. The earliest pooled analyses of age subgroups across randomized trials found no significant difference in hazard ratios between these groups [73]. In advanced lung cancer, overall-survival hazard ratios were nearly identical, with estimates of 0.81 [95% CI 0.69-0.97] for older patients and 0.78 [0.66-0.93] for younger patients [74]. Subsequent pan-cancer analyses reached the same conclusion, reporting no difference in survival benefit by age, although efficacy may vary by inhibitor type [75]. This pattern persisted in studies of checkpoint-inhibitor combinations for non-small-cell lung cancer, although subgroup analyses of overall survival revealed differences not apparent in the primary comparison [76].

At the population level, chronological age does not abolish the benefit of checkpoint blockade, and withholding these therapies solely on the basis of age is not supported by trial evidence. Nevertheless, this finding should be interpreted with caution. Registration trials enroll disproportionately fit older patients, with those over 75 significantly under-represented relative to their share of the cancer population [12], so pooled estimates of benefit reflect the subset of older patients who qualify for trials rather than the broader aged population. A further limitation is that both clinical and mechanistic evidence are concentrated in melanoma, lung, and breast cancers, the tumor types where checkpoint blockade is most active and most studied. Thus, its efficacy in less immunogenic solid tumors remains largely uncharacterized.

Mechanistic studies introduce additional complexity to this issue. These studies do not consistently demonstrate that aging impairs checkpoint response. Instead, the effects appear to depend on tumor type, model system, and therapeutic agent, and do not follow a uniform pattern. For example, in melanoma, older patients have responded more favorably to anti-PD-1 therapy than younger patients, a difference attributed to age-related changes in intratumoral T-cell populations, specifically a reduction in suppressive regulatory T-cells in tumors of older patients [77]. In contrast, triple-negative breast cancer has exhibited the opposite trend: in aged tumor-bearing mice, increased immune dysfunction limited the efficacy of checkpoint blockade due to reduced IFN signaling and antigen presentation, a deficit also observed in patient samples [78]. The choice of therapeutic agent is also significant. In one aged-mouse model, anti-PD-L1 therapy lost efficacy entirely, anti-CTLA-4 retained only modest activity, while anti-PD-1 maintained its effect [79]. Although these studies are not directly comparable due to differences in tumor type and reliance on human versus murine data, they collectively suggest that aging does not influence checkpoint response in a single, consistent direction.

This divergence could be dismissed as noise awaiting resolution by larger studies. We suggest the opposite: the divergence is itself informative. The aging changes characterized in the preceding section need not act together on checkpoint response. The reduced regulatory T-cell suppression that favors response in Kugel's older melanoma patients and the loss of IFN signaling that impairs it in Sceneay's breast tumors are both consequences of aging, and they operate in opposite directions [77, 79]. Chronological age combines such effects into a single variable, and when opposing mechanisms are grouped under one broad measure, the population-level signal can be reduced or cancelled even when each underlying effect is real. The comparable benefit reported by the meta-analyses is therefore not evidence that aging is immunologically irrelevant to checkpoint response, but close to what one would expect when opposing mechanisms are averaged across a varied patient population.

The same point applies to tumor mutational burden [TMB], which is the most established predictor of checkpoint response and also varies with age. In a large pan-cancer cohort, TMB increases significantly with age, demonstrating a 2.4-fold difference between ages 10 and 90, although the magnitude and even the direction of this trend differ by tumor type [80]. In tumor types where TMB rises with age, this increase would be expected to enhance checkpoint response in older patients, which contrasts with the negative effects attributed to age-related microenvironmental changes described previously. Erbe et al. [2021] directly investigated these competing influences across TCGA and GENIE cohorts, reporting that older patients exhibit higher TMB, increased checkpoint-gene expression, and stronger IFN- γ signaling, but also reduced T-cell receptor diversity. Thus, both response-promoting and response-impairing changes are present simultaneously [81].

This has a methodological implication. Stratifying by chronological age, as trials necessarily do, may be among the least informative ways to ask whether aging affects immunotherapy. The more answerable questions are mechanistic: which specific aging change is present in a given tumor, in which direction it shifts the response, and whether the therapy can accommodate it. NK senescence before treatment, for instance, is a specific and measurable state of the kind this framework identifies as informative; whether it predicts response better than chronological age remains untested [63]. These questions can be operationalized. Table 2 organizes candidate immunological-age measures by the four framework axes, together with integrated composite metrics, and states, for each, the host property it indexes and its principal practical limitation. Several already appear in this review as markers of their respective axes [Sections 3.1-3.4]; they

can in turn be integrated into composite immune-age metrics such as IMM-AGE, derived from high-dimensional peripheral-blood profiling, which describes

immune status better than chronological age and predicts all-cause mortality beyond established risk factors [82].

Table 2. Candidate measures for immunological-age stratification, organized by framework axis.

FRAMEWORK AXIS	CANDIDATE MEASURE(S)	WHAT THE MEASURE INDEXES	PRINCIPAL PRACTICAL LIMITATION
Naive T-cell repertoire (3.1)	TCR repertoire diversity; CD8 ⁺ senescence markers (CD27/CD28 loss, p16/p21)	Capacity for <i>de novo</i> priming – whether the repertoire remains broad enough to contain tumor-specific clones and the naive CD8 ⁺ pool is large enough for priming to remain a viable response mode (Section 2.1).	Systemic measures may not reflect, and can even invert, the intratumoral state (Section 3).
Stromal priming environment (3.2)	SASP signature; IL-6; MDSC abundance	Composition and activity of the stromal secretory environment in which priming occurs (54).	Most directly assessed in tumor tissue rather than blood.
NK surveillance (2.3)	NK receptor profile (CD57 ⁺ , DNAM-1 ⁺ , NKp30 ⁺)	NK surveillance capacity; an elevated CD57 ⁺ NK proportion correlates with poor clinical prognosis (63).	No universally accepted definition of NK-cell senescence or established phenotypic markers in oncology (63); CMV confounds several markers (Section 2.3); PD-1-axis agents largely bypass NK cells (Section 2.3); no direct evidence links NK senescence to checkpoint-inhibitor response (63).
Inflammatory baseline (3.4)	Circulating IL-6	Tumor-independent inflammatory tone – the TGF- β - and IL-6-rich environment present in aged hosts before tumor development (Section 2.4).	Nonspecific: elevated IL-6 is associated with and predictive of many aging phenotypes, and the causal role of inflammaging remains largely unknown (74).
Integrated	Composite immune-age clocks (e.g., IMM-AGE) (84)	Overall systemic immune status; describes immune status better than chronological age and predicts all-cause mortality beyond established risk factors (82).	Requires high-resolution immune profiling (mass cytometry, phospho-flow cytometry, transcriptomics), the scarcity of which has hindered application in existing cohorts and often necessitated gene-expression surrogates; requires CMV adjustment; systemic and blood-based rather than tumor-specific (84).

Footnote: Table 1 classifies each host-aging change as one of degree or of kind and records the strength of the evidence behind it; Table 2 addresses what could be measured in a patient to detect that change, and what limits each measurement in practice. The two tables share the same four axes by design. Predictive value for checkpoint-blockade response is largely untested.

Two important caveats apply to these measures. From a practical perspective, the composite metrics depend on high-resolution immune profiling, such as mass cytometry, phospho-flow cytometry, and transcriptomics. The limited availability of these technologies has already impeded the application of such metrics in existing cohorts and necessitated the use of gene-expression surrogates. Additionally, several constituent markers require adjustment for cytomegalovirus serostatus [82].

From a conceptual standpoint, these measures are primarily systemic and blood-based. However, the effect of age on checkpoint response is both tumor-type- and mechanism-specific, and may act in opposite directions across different tumors. For example, reduced regulatory T-cell suppression in aged melanoma can favor response, whereas diminished IFN signaling in aged triple-negative breast cancer can impair it [Section 3]. This divergence between systemic and intratumoral states is supported by

evidence: in the melanoma series discussed above, the age-associated decrease in intratumoral regulatory T-cells was not observed in the spleen, where regulatory T-cells were instead elevated [77]. Therefore, a single systemic immune-age value is unlikely to be applicable across tumor types. The microenvironmental state that most directly governs response is best assessed in tumor tissue, which is not always available prior to treatment. Immunological age is therefore best suited to complement, rather than replace, tumor-level assessment. The most informative question is which axis is affected in a given tumor, rather than relying on a single global immune-age score.

The clinical evidence thus does not weaken the case that host aging matters to tumor immunity. It shifts that case from age as a demographic category to the specific changes age brings, changes that determine not only whether a tumor responds but whether an older patient can tolerate treatment, which the next section addresses.

5. Response and Tolerance in the Older Patient

Section 4 demonstrated that chronological age performs poorly as a predictor of checkpoint-blockade response because it conflates opposing biological mechanisms within a single variable. This conflation also limits its utility as a guide for treatment decisions in older adults for a second reason: treatment decisions require consideration of two distinct questions, namely, whether the tumor will respond to therapy and whether the patient can tolerate the treatment. Chronological age serves as a weak proxy for both. These questions are influenced by different determinants and require separate assessments. Tumor response is influenced by the tumor microenvironment and the immune compartment targeted by therapy. In contrast, treatment tolerance is determined by the patient's physiologic reserve and competing health risks, which are estimated through comprehensive geriatric assessment across domains such as physical function, comorbidity, nutrition, polypharmacy, and geriatric syndromes including sarcopenia [83]. Performance status, although still the most commonly used measure in oncology, frequently overestimates the health of older patients and does not detect impairments that are only apparent through more comprehensive assessment [84, 85].

On the response side, neither age nor frailty is a reliable predictor. A prospective study of patients aged 65 and older receiving anti-PD-1 monotherapy found no association between frailty, or the number of impaired geriatric domains, and clinical benefit [85], and reviews of the frailty-specific literature report shortened overall survival in frail patients but no lower response rate [84]. Worse survival in frail patients is therefore not a failure of tumor response; it reflects competing risks arising from the patient's overall health rather than from the tumor's behavior under therapy.

Toxicity shows a parallel pattern. The larger recent studies do not find that severe immune-related toxicity tracks age or frailty: in the prospective cohort, grade 3 or higher events occurred in 18.0% of frail compared to 16.4% of non-frail patients [$p = 0.814$], with no geriatric-assessment component associated [85], and a population study of 2,737 patients found frailty unassociated with immune-related hospitalization. This study further distinguished between the two variables, identifying frailty as associated with acute-care use but not immune-related hospitalization, while age showed the opposite pattern. The authors concluded that age and frailty should be considered independently [86].

In the context of frailty, the primary distinction lies not in the incidence of severe events but in patients' tolerance and the overall burden experienced. Frail patients are more likely to discontinue treatment earlier,

despite comparable rates of severe toxicity [87, 88]. Furthermore, frailty is strongly associated with increased all-cause hospitalization and mortality [odds ratio 3.98 and hazard ratio 5.23], a relationship largely attributable to pre-existing vulnerabilities unrelated to immunotherapy rather than to treatment toxicity itself [85]. This dissociation is supported by a plausible biological rationale. Older individuals typically exhibit a chronic inflammatory state [Section 3.4], elevated autoantibody production, and a higher prevalence of autoimmune conditions [84]. Although this profile might be expected to increase the incidence of immune-related toxicity, evidence does not support this; instead, aging-associated inflammation, impaired tissue repair [Section 5], and reduced physiological reserve may act on the tolerance and resolution of toxicity, rather than its frequency. Consequently, even low-grade adverse events can disproportionately impair functioning in frail patients [89]. Therefore, frailty should prompt anticipation of supportive-care needs rather than serve as a contraindication to treatment. Current guidelines recommend that treatment decisions be based on comprehensive geriatric assessment rather than age or performance status alone [90].

These clinical findings strengthen the central argument of this review rather than limit it. The observation that neither chronological age nor frailty reliably predicts treatment response or severe toxicity aligns with expectations when host aging is assessed at the demographic level, as discussed in Section 4. Treatment response is determined by the mechanistic changes outlined in Section 3, while tolerance depends on physiologic reserve, which is directly measured by geriatric assessment. These are distinct outcomes with separate determinants. Immunological age serves to complement, rather than replace, geriatric assessment. Integrating both measures has been identified as a research priority for older patients receiving immunotherapy [88]. The following strategies target the response determinant directly by addressing the aged microenvironment, rather than solely evaluating a patient's fitness for treatment.

6. Senolytic Strategies: Mechanistic Correction as a Testable Hypothesis

Senolytic therapy follows from a different premise than checkpoint blockade. If the aged tumor microenvironment suppresses anti-tumor immunity due to the accumulation of senescent cells and their secretory products, as suggested by stromal and inflammaging theories, then eliminating these cells may address the underlying substrate rather than merely enhancing the immune response within it. While checkpoint inhibitors release an

existing T-cell response, senolytics seek to restore the environment in which this response occurs.

The pharmacological basis for this approach was established by Zhu et al. [2015], who identified the combination of dasatinib and quercetin [D+Q] as the first senolytic regimen through a hypothesis-driven search for agents that selectively eliminate senescent cells [91]. Dasatinib induces apoptosis in senescent cells, and quercetin complements its activity, the pair together depleting senescent cells across multiple tissues.

The therapeutic logic requires that senescent-cell burden is not merely a marker of aging but a causally modifiable contributor to its pathologies, and this was demonstrated when D+Q clearance improved physical function and extended lifespan in aged mice [92]. The relevance to tumor immunity follows from the stromal senescence described earlier: if senescent stromal cells impose a chronically suppressive, MDSC-recruiting, inflammatory microenvironment, then depleting them, or suppressing their secretory phenotype, should lift that suppression.

Among the first clinical tests of this logic in cancer is the COIS-01 trial reported by Liu et al. [2025]. In a single-arm phase 2 study, 24 patients with resectable head and neck squamous cell carcinoma received neoadjuvant anti-PD-1 therapy [tislelizumab] combined with dasatinib and quercetin. Four patients [16.7%] achieved a pathological complete response and a further four [16.7%] a major pathological response, for a combined response rate of 33.3% [95% CI 16.6-54.7%], with a low incidence of grade 3-4 adverse events [4.2%] [93]. The authors set this against historically reported major pathological response rates of roughly 7-13.9% for anti-PD-1 monotherapy in comparable neoadjuvant settings [94-96]. That comparison is suggestive rather than conclusive: the historical rates come from separate studies with different patient selection, staging, and checkpoint agents, so the apparent improvement could in part reflect differences between cohorts rather than the senolytic addition alone. What matters for this review is the mechanistic interpretation. The authors attribute the observed benefit to senolytic clearance of senescent cells and suppression of their pro-tumorigenic senescence-associated secretory phenotype [SASP], as supported by single-cell profiling of the immune compartment. This evidence suggests that the intervention modifies the aged microenvironment instead of exerting a direct effect on the tumor or T-cell checkpoints. Nevertheless, the trial does not directly demonstrate, in these 24 patients, that microenvironmental correction occurred or that such correction was responsible for the observed response. The proposed causal chain from senolytic exposure to SASP suppression and subsequent improved outcomes remains an interpretation by the authors, grounded in mechanistic

data rather than direct measurement across the trial population. Independent preclinical work supports the same logic in a different setting. In prostate cancer models, senolytic clearance of p21-positive senescent stromal cells with a BCL-xL inhibitor blocked the SASP, reactivated antitumor CD8⁺ T-cell immunity, and reduced tumor growth, in a CD8⁺ T-cell-dependent manner [97]. Suppression of BCL-xL or of p21 itself also potentiated anti-PD-1 checkpoint blockade. The clearance logic proposed for COIS-01 is thus reproduced in a separate tumor type and through a different senolytic mechanism, which supports the underlying principle beyond a single clinical trial.

These results should be interpreted with consideration of their limitations. The study is a single-arm trial involving 24 patients with a single tumor type, lacking a randomized comparator. Additionally, pathological response serves as a surrogate endpoint, and its relationship to long-term survival in this context has not been established. It remains uncertain whether the observed effect generalizes beyond head and neck squamous cell carcinoma or persists when compared to a randomized control rather than a historical one. The trial provides proof of concept but does not establish a change in standard of care.

In addition to limitations in trial design, senolytic strategies carry biological risks that temper support for microenvironmental correction. Cellular senescence is highly context-dependent. The same program that promotes tumor development in aged tissue also serves as an early tumor-suppressive barrier and supports homeostatic processes such as wound healing and tissue repair. Therefore, indiscriminate clearance of senescent cells may eliminate both protective and pathological functions [98-100]. This duality is supported by evidence: senescence surveillance and the anti-tumor component of the SASP can restrain malignancy in certain contexts, with SASP factors including CCL2, IL-15 and CXCL1 recruiting macrophages, lymphocytes and NK cells to tumor sites [98, 99, 101]. The interaction with cytotoxic therapies is also significant, as chemotherapy and radiotherapy induce senescence. This provides a rationale for administering senolytics after such treatments, but also underscores the importance of timing and context in their use [98]. The combination of senolytics with checkpoint blockade, as examined here, is based on a single small trial and supporting preclinical studies, rather than established synergistic effects.

Furthermore, senolytic agents exhibit inherent on-target toxicities. BCL-xL inhibition, the mechanism utilized in the prostate cancer models discussed above, also induces thrombocytopenia by affecting platelets. This hematologic on-target liability has restricted the clinical use of navitoclax and has driven the development

of more selective BCL-xL inhibitors [99, 100]. A distinction is worth drawing here, since the two are often conflated: senolytics eliminate senescent cells, whereas senomorphics [also known as senostatics] suppress the SASP without inducing cell death [99, 100, 102]; the evidence discussed here pertains to senolytics, while senomorphic strategies, which retain senescent cells, are being investigated separately. Collectively, these considerations indicate that senolytic correction of the aged tumor microenvironment remains a mechanistic hypothesis under early clinical investigation, rather than an established therapeutic effect.

Despite these limitations, the conceptual significance of the findings is considerable. All therapies discussed in this review thus far operate within the framework's assumptions: checkpoint blockade releases a suppressed T-cell response, and its efficacy depends on host capacities that are diminished by aging. The senolytic combination represents the first strategy examined that directly targets one of these impaired capacities. If the previously developed host-conditional account of immune evasion is accurate, this therapy aligns with its predictions: rather than simply enhancing the aged immune response, it seeks to modify the environment that restricts it [103].

7. Conclusion

The framework of tumor immune evasion that organizes contemporary immunotherapy was built largely in young hosts, and this review has argued that it does not transfer cleanly to the aged hosts in whom most cancer occurs. Aging does not undermine the framework uniformly, though: of the four host-dependent assumptions examined, two are violated by degree and two by kind. Thymic involution and natural killer cell decline are severity shifts, the framework's own mechanisms running at diminished capacity, with the natural killer axis carrying a structural consequence that exceeds its magnitude because no approved therapy restores it. In contrast, aged stromal senescence and inflammaging are qualitative additions: a priming environment that is suppressive before the tumor arises, and a chronic systemic inflammatory tone that the tumor exploits [14]. The cumulative effect is not a quantitative correction to the young-host model but a reframing of what immune evasion is in an aged host.

Current clinical evidence does not definitively support or contradict this interpretation. Chronological age encompasses multiple aging processes that affect immunotherapy response in divergent ways, making it an insufficient stratification variable. The comparable benefit of checkpoint blockade observed across different age groups supports this perspective, as opposing

mechanisms may offset each other when summarized by a single metric. This finding underscores the necessity for more refined stratification approaches. Immune status represents a more accurate determinant of response, with age functioning only as an approximate surrogate. Measures of immunological age, obtained through comprehensive immune-cell profiling, have demonstrated superior assessment of immune status compared to chronological age and predict all-cause mortality beyond standard risk factors [84]. Whether immunological age also predicts immunotherapy response more effectively than chronological age remains untested, but this question is both apparent and addressable with existing methodologies.

Several limitations bound this argument. This review is deliberately scoped: it is organized around four host-conditional assumptions rather than as a comprehensive account of cancer immunology and aging, a structure that favors analytical clarity over completeness. Further dimensions of immune aging fall outside these four assumptions and are therefore not addressed here, though each has a recognized role in the aging tumor-immune relationship and may matter as much as the axes examined: the aging of the gut microbiome as a regulator of systemic immune tone, B-cell aging and the humoral compartment, the tertiary lymphoid structures through which intratumoral immune responses are organized, and the myeloid skewing of the aged immune system. Each represents a direction in which the host-conditional account developed here would need to be extended.

The evidence supporting the four verdicts is also uneven: the stromal-senescence claim rests on direct genetic mouse models, whereas the inflammaging argument leans more heavily on conceptual synthesis, and the verdicts should be weighted accordingly. Much of the mechanistic spine derives from murine work with only partial human validation. From a therapeutic perspective, clinical evidence for senolytic correction is currently limited to a single, small, single-arm trial. Although converging preclinical studies in a second tumor type support the underlying principle, the clinical case remains provisional, even when the mechanistic rationale is robust. This limitation does not undermine the central claim that host aging reshapes immune evasion through specific mechanisms rather than uniformly. However, these constraints delineate the extent to which the claim can presently be advanced.

The constructive implications are both methodological and therapeutic, and several can be stated as recommendations. Since the young-host model does not transfer effectively, preclinical research should prioritize aged and pathogen-experienced systems that align with the target populations, rather than relying on young, specific-pathogen-free animals. As chronological

age can obscure opposing mechanisms, clinical trials should prospectively collect immunological-age biomarkers [Table 2], rather than recording age alone. Outcomes should be stratified by immune state and, separately, by frailty to avoid conflating response and tolerance within a single demographic variable. Given that senescent-cell correction remains a mechanistic hypothesis rather than an established effect, senolytic and senomorphic combinations should be evaluated in randomized studies instead of single-arm designs. Furthermore, because the benefit observed in the only available trial was inferred from response rather than directly measured, future studies should assess microenvironmental correction using the senescence and secretory markers specified by the mechanism. This approach would allow a positive clinical result to be attributed to the proposed cause rather than assumed. Thus, this review suggests that addressing these gaps for the aged host is essential for extending the benefits of immunotherapy to the patients who bear the greatest cancer burden.

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Conflict Of Interest

The authors declare no conflict of interest.

Use of Artificial Intelligence

During the preparation of this manuscript, the authors used Grammarly for grammar and language checking. The authors reviewed and verified all content, including all scientific claims, citations, and interpretations, and take full responsibility for the final manuscript.

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