Inflammation and Regeneration

REVIEW

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Natural killer cells: gatekeepers of healthy aging in longevity medicine

Joanna Y. Yang[1†], Doris T. Tu[1†], Jun-Cheng Liao[1†] and Oscar K. Lee[1*]

Abstract

Natural killer (NK) cells are innate lymphocytes that provide rapid immune surveillance through the recognition and elimination of virally infected, malignant, and stressed cells. Beyond their established roles in host defense, accumulating evidence indicates that NK cells undergo profound age-associated remodeling affecting subset distribution, receptor balance, metabolic programming, and effector function. These changes, collectively referred to as NK immunosenescence, contribute to impaired clearance of senescent cells, dysregulated inflammation, and increased susceptibility to cancer, infection, and metabolic disease. In this review, we integrate current knowledge of NK cell aging into the emerging framework of longevity medicine. Rather than introducing NK cells as a newly identified determinant of aging, we synthesize evidence positioning them as key immune effectors whose functional state reflects and influences biological aging processes. We highlight how NK cells participate in senescence surveillance, tissue homeostasis, and immunometabolic regulation across organs, and how their dysfunction intersects with multiple hallmarks of aging. We further discuss the potential utility of NK-related phenotypic and functional metrics as complementary biomarkers of immune aging, while acknowledging current limitations in specificity and prognostic validation. Finally, we examine therapeutic strategies aimed at preserving or restoring NK competence, ranging from lifestyle and nutritional interventions to cytokine-based therapies, immune checkpoint modulation, and emerging cellular platforms. While many advanced NK-targeted approaches remain investigational—particularly outside oncology settings—we outline a translational roadmap linking NK biology to actionable interventions and measurable outcomes relevant to healthspan. By situating NK cells within a systems-level view of immune aging, this review frames them as a tractable component of precision longevity medicine rather than a singular regulator of aging.

Introduction

Longevity medicine is an emerging discipline at the interface of geroscience, precision health, and translational biomedicine. It seeks to delay, prevent, or even reverse the biological processes of aging through targeted interventions that extend healthspan—the period of life free from chronic disease and disability—rather than focusing solely on prolonging lifespan [1–4]. Unlike traditional geriatric medicine, which emphasizes management of age-related diseases after their clinical onset, longevity medicine highlights proactive strategies: early monitoring of biological age, personalized intervention plans, and mechanistic targeting of pathways that drive aging across tissues. In this framework, the immune system plays a central role because it both reflects the pace of aging and actively shapes the aging trajectory through surveillance, repair, and regulation of inflammation.

Among immune compartments, natural killer (NK) cells are particularly relevant to longevity medicine. NK cells are cytotoxic innate lymphocytes that recognize and eliminate virally infected cells, transformed tumor cells, and, importantly, senescent cells without prior antigen

[†]Joanna Y. Yang, Doris T. Tu and Jun-Cheng Liao contributed equally to this work.

*Correspondence:
Oscar K. Lee
oscarlee9203@gmail.com
[1] Department of Biotechnology Medicine, MacKay Memorial Hospital, Taipei, Taiwan

priming. This frontline role positions NK cells as sentinels of tissue integrity and guardians against malignant and senescent burden. In addition, NK cells exert regulatory functions through secretion of cytokines such as IFN-γ, TNF-α, and GM-CSF, which influence dendritic cells, macrophages, and T cells [5–7]. Thus, NK cells sit at the crossroads of innate and adaptive immunity, shaping both immediate defense and long-term immunological tone. The word "gatekeeper" in the title of this article refers to the functional capacity of NK cells to regulate the burden of senescent, malignant, and dysfunctional cells, thereby modulating tissue integrity and systemic inflammatory tone, rather than implying exclusive or hierarchical control over the aging process.

With advancing age, however, NK cells undergo profound remodeling in numbers, subset distribution, receptor repertoires, and effector competence, a process collectively termed NK immunosenescence [8–11]. This remodeling is complex; while total NK cell numbers often remain stable or even increase, their composition shifts toward terminally differentiated $CD57^+$ NK cells with reduced proliferative capacity. Activating receptors such as NKG2D and DNAM-1 are downregulated, while inhibitory receptors including NKG2A and TIGIT become more prominent. Functionally, aged NK cells display impaired cytotoxic synapse formation, reduced degranulation, and diminished cytokine secretion. These defects compromise their ability to eliminate senescent and malignant cells, contributing to the persistence of senescent cell populations, exacerbation of systemic inflammation, and increased susceptibility to cancer and infection.

This decline links NK dysfunction directly to several hallmarks of aging [1]. Inadequate clearance of senescent cells exacerbates cellular senescence and alters intercellular communication. Impaired metabolic flexibility and mitochondrial dysfunction in NK cells reflect deregulated nutrient sensing and diminished proteostasis. Failure to constrain inflammation accelerates stem cell exhaustion and tissue dysfunction. Thus, NK cells not only age themselves but also influence aging in surrounding tissues and organs, amplifying systemic decline.

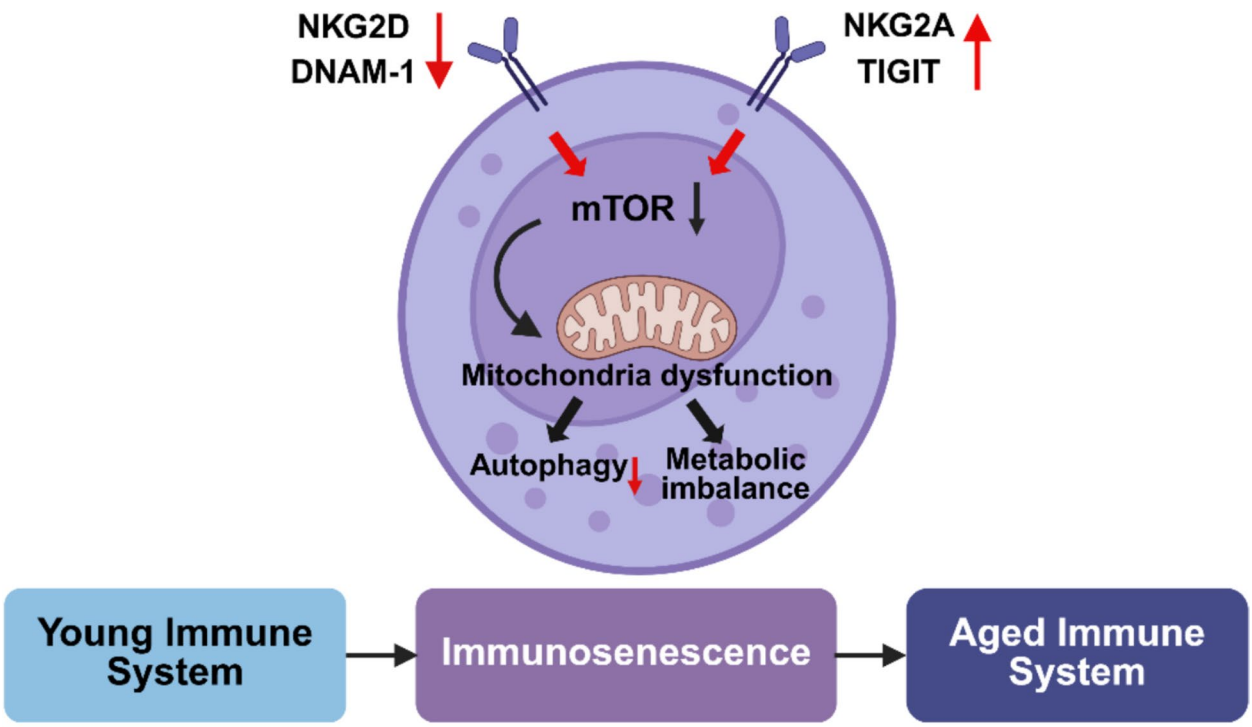
The idea that NK cells act as endogenous "senolytic" agents has transformed how their role in longevity is understood. Senescent cells, though initially protective by halting proliferation of damaged cells, become deleterious when chronically retained. They secrete a senescence-associated secretory phenotype (SASP) that drives fibrosis, inflammation, and tumorigenesis. NK cells can recognize stress ligands such as MICA/B and ULBP on senescent targets and eliminate them, functioning as natural senotherapies. With aging, reduced NK function results in accumulation of these harmful cells, thereby fueling age-related pathologies. This mechanistic link places NK biology squarely within the scope of longevity medicine.

Recent advances in geroscience further underscore the immune system's central role in determining healthspan and lifespan [2–4]. For example, longitudinal studies show that measures of immune function such as NK cytotoxicity predict morbidity and mortality in older adults independent of chronological age [12]. Experimental rejuvenation of NK activity in animal models extends healthy lifespan, reduces tumor burden, and improves metabolic parameters. These insights highlight NK cells not only as biomarkers of biological age but also as tractable therapeutic targets for healthspan extension.

Importantly, NK cells differ from other immune effectors in ways that make them especially suitable for integration into longevity medicine. T cells require antigen presentation and clonal expansion, processes slowed by thymic involution and clonal senescence. B cells suffer from impaired somatic hypermutation and reduced antibody diversity with age. By contrast, NK cells provide antigen-independent, immediate effector responses. Their ability to target senescent cells, pathogens, and tumors without prior sensitization is a unique advantage for interventions aiming to broadly reduce age-related disease burden. Moreover, NK cells can be expanded, engineered, and adoptively transferred, opening the door to cellular immunotherapies specifically designed for aging populations.

The study of NK biology across the lifespan is therefore foundational for building NK-centered strategies in longevity medicine. Key questions include the following: How do NK cells remodel across tissues such as liver, adipose, and bone marrow with age? Which molecular pathways—metabolic, epigenetic, receptor-mediated—govern NK immunosenescence? How can NK competence be restored or enhanced safely in older adults? And how should NK function be integrated into composite biomarkers of biological aging? Addressing these questions is critical for translating NK biology into interventions that extend human healthspan.

In this review, we do not propose NK cells as a newly discovered determinant of aging. Rather, we integrate established knowledge of NK cell immunosenescence, senescence surveillance, and metabolic regulation into the emerging framework of longevity medicine. By positioning NK cells at the intersection of immune aging, tissue homeostasis, and translational intervention, we aim to provide an operational roadmap linking NK biology to measurable biomarkers and actionable strategies for healthspan extension (Fig. 1).



Cell Populations	Receptors	Metabolism	Function
CD56 bright ↓ CD56 dim ↑	NKG2D↓ DNAM-1↓ NKG2A↑ TIGIT↑	mTOR↓ Mitochondria function↓ Autophagy↓ Metabolic imbalance	Degranulation / cytokine production↓ Zombie cell clearance↓ Infection / Tumor risk ↑ Chronic inflammation ↑

Fig. 1 Hallmarks of NK-cell aging and metabolic change. This diagram shows how aging changes NK cells: their subsets, receptors, and metabolism. As the immune system goes from young to old, the share of $CD56^{bright}$ cells goes down, and $CD56^{dim}CD57.^{+}$ cells go up. At the same time, activating receptors (such as NKG2D and DNAM-1) go down, and inhibitory receptors (such as NKG2A and TIGIT) go up. These changes reduce ITAM-based signals and the PI3K–AKT–mTOR pathway. Lower mTOR is linked to weak mitochondrial function, less glycolysis, and poor autophagy/mitophagy. Then, NK cells degranulate less and make fewer cytokines (such as IFN-γ and TNF)

Natural killer cells and immunosenescence

NK cells are innate lymphocytes that provide rapid cytotoxic and regulatory responses against virally infected, transformed, and stressed cells, functioning without antigen-specific receptors generated by somatic recombination but instead integrating signals from a diverse array of activating and inhibitory receptors to balance responsiveness and tolerance [5–7]. Key receptor families in humans include killer-cell immunoglobulin-like receptors (KIRs) recognizing HLA class I molecules, C-type lectin-like receptors such as NKG2A and NKG2C that sense HLA-E, and natural cytotoxicity receptors (NKp30, NKp44, NKp46) that bind stress ligands [6, 7]. NK cells originate from common lymphoid progenitors in the bone marrow under the influence of IL-15 and transcription factors including Eomes and T-bet, and they differentiate into $CD56^{bright}$ cytokine-secreting NK cells, which predominate in lymphoid tissues, and $CD56^{dim}$ cytotoxic NK cells enriched in blood and peripheral sites [5–7]. In youth, NK cells effectively eliminate senescent and transformed targets via perforin- and granzyme-mediated cytotoxicity and by producing cytokines such as IFN-γ and TNF-α, orchestrating adaptive immunity.

With advancing age, however, NK cells undergo profound remodeling—termed NK immunosenescence—marked not only by decline but also by compensatory adaptations [8–11]. Hallmark features include shifts in subset distribution with expansion of $CD56^{dim}CD57^{+}$ terminally differentiated NK cells and reduction of $CD56^{bright}$ immunoregulatory cells, impaired degranulation and cytokine secretion leading to reduced clearance of senescent and malignant cells [8–12], receptor remodeling with downregulation of activating molecules like NKG2D and DNAM-1 and upregulation of inhibitory checkpoints such as NKG2A and TIGIT [13–15], metabolic reprogramming with impaired mTOR signaling, mitochondrial dysfunction, and defective autophagy, and epigenetic remodeling that stabilizes exhaustion-like states [13–15]. Chronic infections, particularly cytomegalovirus, strongly influence these trajectories by driving the accumulation of adaptive or memory-like NK cells characterized by NKG2C expression and epigenetic imprinting, subsets with enhanced cytotoxicity but restricted diversity [16–18]. Moreover, NK immunosenescence exhibits tissue specificity. In the liver, age-related dysfunction of resident NK cells promotes fibrosis; in adipose tissue, NK cells transition from homeostatic to pro-inflammatory roles driving metabolic disease; in the uterus, decidual NK cells orchestrate pregnancy-related vascular remodeling though their aging biology remains less understood; and in barrier tissues such as lung and skin, impaired NK function reduces pathogen defense. Paradoxically, aging also yields persistent memory-like NK subsets with strong cytotoxicity but limited breadth, underscoring that immunosenescence is a remodeling rather than uniform decline. The net effect is impaired clearance of senescent and malignant cells, increased infection susceptibility, and propagation of systemic inflammation, all converging to

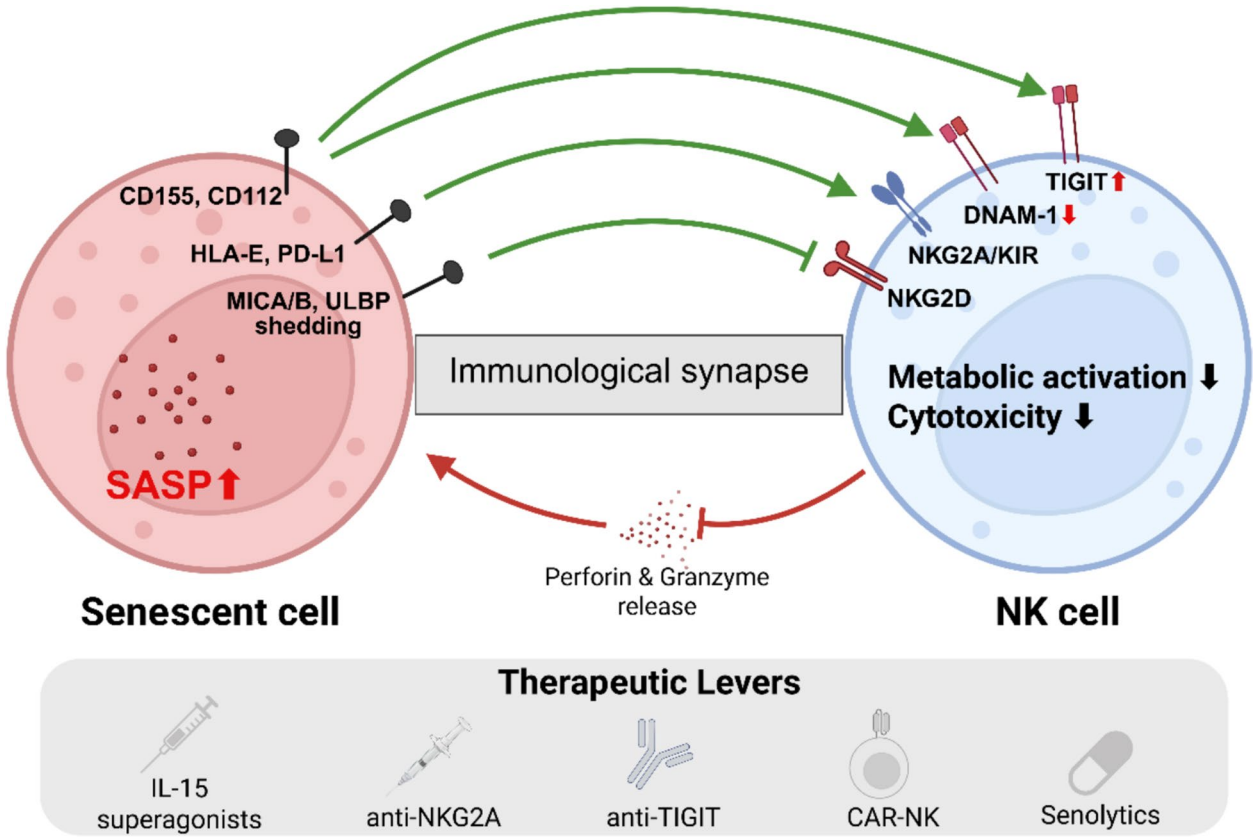


Fig. 2 Senescent cell–NK cell crosstalk at the immunological synapse and therapy options. This diagram shows two-way interaction between senescent cells and NK cells by activating and inhibitory receptor–ligand pairs. Senescent cells increase stress ligands (MICA/B, ULBPs) and adhesion molecules (CD155, CD112). They also increase checkpoint ligands (HLA-E, PD-L1), but they shed MICA/B and ULBPs, and they show more inhibitory ligands, so NK killing goes down. On NK cells, DNAM-1 and NKG2D signals go down, and TIGIT and NKG2A/KIR binding goes up. So metabolic activation goes down, and mTOR activity goes down. Then, release of perforin and granzyme goes down. Senescent cells also make SASP cytokines (TGF-β, IL-6, IL-10), and these reduce NK function. The lower panel shows therapy options: IL-15 superagonists, anti-NKG2A, anti-TIGIT, CAR-NK, and senolytics

accelerate hallmark aging phenotypes such as cancer, fibrosis, and metabolic dysfunction (Fig. 2) [12, 19, 20].

NK cells in senescence and cancer surveillance

A defining feature of NK cells is their ability to recognize and eliminate senescent cells, a process central to tissue homeostasis and organismal aging. Senescent fibroblasts, hepatocytes, endothelial cells, and other stressed cell types upregulate stress-induced ligands such as MICA, MICB, and ULBPs, which engage activating receptors like NKG2D and DNAM-1 on NK cells, triggering perforin- and granzyme-mediated cytolysis [21–23]. Through this mechanism, NK cells act as endogenous senolytics that restrict the accumulation of dysfunctional cells and limit the propagation of the senescence-associated secretory phenotype (SASP) [24–26]. Experimental evidence supports this role: genetic or antibody-mediated depletion of NK cells accelerates accumulation of senescent hepatocytes, promotes fibrotic progression, and increases tumorigenesis in mouse models, whereas enhancing NK activity through cytokines such as IL-15 or through adoptive NK transfer restores clearance and mitigates pathology [23–26]. Despite this potential, senescent cells evolve immune evasion strategies that closely parallel those used by tumor cells. These include shedding of soluble NKG2D ligands (MICA/B) that desensitize NK receptors, upregulation of HLA-E to engage the inhibitory receptor NKG2A, and secretion of SASP-derived immunosuppressive mediators such as TGF-β and IL-10, which blunt NK function and recruit suppressive myeloid populations [27–29]. These adaptations not only allow persistence of senescent cells but also exacerbate inflammation, fibrosis, and paracrine senescence of neighboring cells [28–30]. The parallels with cancer are striking, as malignant cells exploit similar escape mechanisms, including downregulation of activating ligands, checkpoint engagement, and remodeling of the tumor microenvironment [29, 31–35]. Thus, NK dysfunction with aging simultaneously drives both senescence accumulation and oncogenesis. Human studies further highlight this intersection: reduced NK cytotoxicity correlates with increased incidence of hematologic and solid tumors, while longitudinal cohorts demonstrate that baseline NK competence predicts infection-related mortality and cancer risk [31–33]. A clinically important dimension is therapy-induced senescence (TIS), in which chemotherapy and radiotherapy eliminate proliferating tumor cells but also induce senescence in stromal and immune compartments, generating SASP-driven inflammation and relapse potential [36–38]. Although NK cells are capable of targeting TIS cells, treatment-related immunosuppression often diminishes their activity. Strategies to preserve or augment NK surveillance during anticancer therapy may therefore improve both immediate cancer outcomes and long-term healthspan. The recognition that NK biology links senescence surveillance and tumor immunosurveillance suggests that interventions originally designed for oncology may also serve as senotherapies. Cytokine agonists (e.g., IL-15 superagonists), checkpoint blockade (e.g., NKG2A or TIGIT inhibition), adoptive transfer of cytokine-induced memory-like NK cells, and CAR-NK approaches targeting stress ligands represent promising strategies to restore NK competence [35, 39–50]. Moreover, combining NK activation with pharmacological senolytics such as dasatinib, quercetin, or fisetin has shown synergistic clearance of senescent populations in preclinical models [51–62]. Collectively, these findings highlight NK cells as critical effectors at the intersection of aging and cancer, whose age-related dysfunction undermines surveillance and accelerates multimorbidity. Therapeutically enhancing NK competence offers a dual opportunity: reactivating the natural senolytic axis that maintains tissue youthfulness while reinforcing antitumor immunity, thereby positioning NK cells as true gatekeepers of healthy aging.

Of note, current evidence supporting engineered NK cell platforms, including CAR-NK and other genetically modified NK approaches, is derived predominantly from oncology and preclinical disease models. In cancer settings, these strategies have demonstrated potent cytotoxic activity and, in some cases, improved safety profiles compared with CAR-T cells. However, their extension to longevity or preventive medicine remains conceptual rather than established. In the context of aging, fundamental questions remain unresolved, including appropriate target selection for senescent but otherwise non-malignant cells, the long-term persistence and reversibility of engineered NK activity, and the risk of off-target effects in tissues affected by chronic low-grade inflammation. Consequently, CAR-NK and related engineered NK strategies should presently be regarded as future-facing senotherapeutic concepts that require rigorous preclinical validation and carefully designed clinical studies before their incorporation into healthspan-oriented interventions (Fig. 3).

In a conceptual framework, we depict how lifestyle, pharmacologic, and cellular interventions converge on NK cell regulation to support healthy longevity. Inputs consist of lifestyle interventions (exercise, fiber and polyphenol-rich diet, circadian alignment, microbiome modulation), pharmacologic or biologic agents (IL-15 superagonists, methathione analogs, mTOR or epigenetic modulators, immune checkpoint inhibitors, and senolytic combinations), and advanced cell therapies (CIML-NK, iPSC-derived NK, CAR-NK, and armored or tunable NK products). The downstream clinical results will be

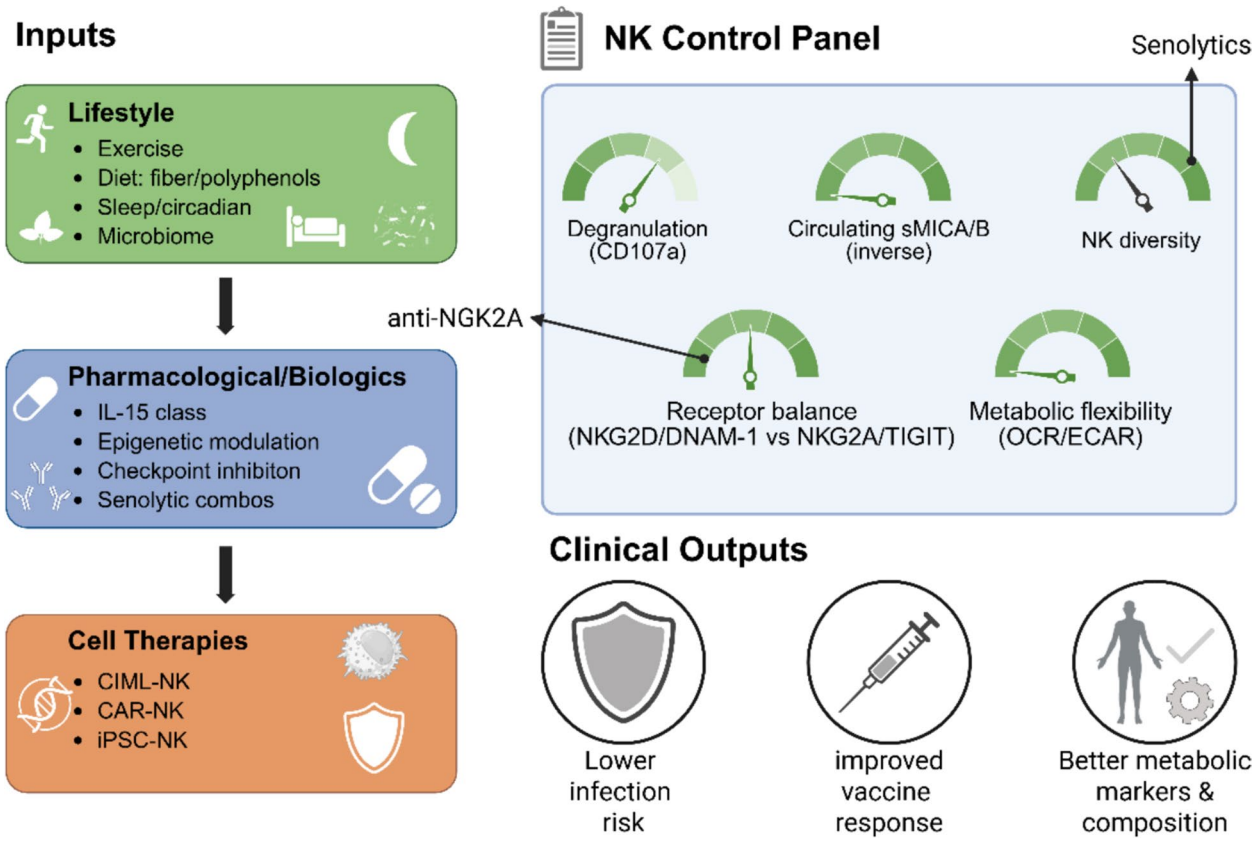


Fig. 3 Conceptual framework for integrating natural killer (NK) cells into longevity medicine. This schematic illustrates a tiered translational framework linking NK cell biology to healthspan-oriented strategies across the lifespan. At the foundational level, lifestyle and metabolic factors—including physical activity, nutrition, circadian regulation, and stress—shape NK cell development, metabolic fitness, and effector capacity. Intermediate interventions, such as cytokine modulation (e.g., IL-15–based strategies) and immune checkpoint regulation, aim to preserve or restore NK functional competence during aging. At the frontier level, advanced cellular approaches—including cytokine-induced memory-like NK cells, iPSC-derived NK cells, and CAR-NK platforms—represent future-facing strategies derived largely from oncology and preclinical disease models. While these engineered NK cell approaches demonstrate therapeutic promise, their application in preventive or longevity medicine remains speculative and will require rigorous evaluation of long-term safety, reversibility, ethical considerations, and context-specific risk–benefit profiles before use in otherwise healthy aging populations. Together, this framework positions NK cells as a tractable, but non-exclusive, immune component within precision longevity medicine

decreased risk of infection, better vaccine responsiveness, and optimized metabolic health and body composition, forming a comprehensive route for translational longevity medicine.

It should be emphasized, however, that the application of engineered NK cell platforms in preventive or longevity medicine remains speculative, as human data outside oncology settings are extremely limited and long-term safety in otherwise healthy individuals has not been established.

NK cells in tissue and metabolic aging

Beyond their canonical role in pathogen and tumor surveillance, NK cells regulate a broad spectrum of tissue and metabolic processes that are directly relevant to aging and longevity. As tissues accumulate damage and metabolic stress, NK cells act as regulators of homeostasis, either by eliminating dysfunctional stromal cells or by shaping local immune–metabolic crosstalk. With age, however, tissue-specific NK subsets undergo remodeling that contributes to impaired regeneration, metabolic dysfunction, and organ-specific pathologies.

Adipose tissue provides a clear example of the dual role of NK cells in health and disease. In lean states, NK cells participate in remodeling and support adipose tissue homeostasis, while in obesity and aging, they adopt a pro-inflammatory phenotype, producing IFN-γ that recruits and activates M1-like macrophages [63–65]. This shift amplifies local inflammation, disrupts insulin signaling, and contributes to systemic insulin resistance.

Depletion of NK cells in obese mouse models ameliorates glucose intolerance, whereas adoptive transfer of activated NK cells exacerbates metabolic dysfunction [63, 65]. These findings underscore how aging-associated NK remodeling contributes to immunometabolic dysfunction, a hallmark of metabolic aging. NK cells do not operate in isolation within aging tissues but function as part of a distributed immune–stromal network that collectively shapes tissue homeostasis. In adipose and metabolic tissues, NK cells interact closely with macrophages, stromal cells, and endothelial compartments, influencing inflammatory tone primarily through cytokine-mediated crosstalk rather than direct hierarchical control. Macrophages and monocyte-lineage cells remain major drivers of chronic low-grade inflammation in aging tissues, while NK cells act as modulatory effectors whose impact depends on local metabolic stress, cytokine gradients, and tissue context. Accordingly, age-related metabolic dysfunction reflects the integrated behavior of multiple immune and non-immune cell types, with NK cells contributing as context-dependent regulators rather than singular determinants.

In the liver, NK cells surveil hepatic stellate cells and eliminate activated populations through NKG2D- and TRAIL-dependent pathways, thereby restraining fibrosis [66, 67]. With chronic injury or aging, NK surveillance weakens, leading to progression of hepatic fibrosis and increased risk of cirrhosis and hepatocellular carcinoma. Experimental restoration of NK cytotoxicity has been shown to reduce fibrosis and tumor initiation in preclinical models [66, 67]. Thus, NK dysfunction contributes not only to systemic immune decline but also to age-related liver disease, a leading cause of morbidity in older populations.

NK cells also influence regeneration and repair in musculoskeletal tissues. In skeletal muscle, NK-derived cytokines coordinate immune–myogenic interactions during injury repair. Aged animals with impaired NK recruitment display delayed myofiber regeneration, increased fibrosis, and loss of functional capacity [68]. In the bone marrow, NK cells interact with osteoclasts and stromal niches to influence bone remodeling and hematopoietic stem cell (HSC) function [69, 70]. Dysregulated NK activity may promote clonal hematopoiesis of indeterminate potential (CHIP), a process linked to both cardiovascular disease and hematologic malignancies, thereby bridging immune aging and systemic multimorbidity [69, 70].

Cardiovascular aging highlights the paradoxical contributions of NK cells. On the one hand, NK cells exacerbate vascular injury by releasing pro-inflammatory cytokines and cytotoxic mediators within atherosclerotic plaques. On the other hand, they play a protective role by clearing senescent endothelial and smooth muscle cells, which can stabilize lesions and reduce rupture risk [29, 71]. The balance of these effects likely depends on local microenvironmental cues, including lipid metabolism, hypoxia, and cytokine gradients, which are altered with age.

Emerging evidence suggests that NK cells also modulate brain aging and neurodegeneration. Senescent astrocytes and microglia accumulate in aged brains and secrete neurotoxic SASP factors. NK cells have been detected in cerebrospinal fluid and at brain borders, where they may limit chronic microglial activation and protect neuronal networks [72]. However, excessive or dysregulated NK activity could also exacerbate neuronal injury. Clinical studies indicate that reduced peripheral NK cytotoxicity correlates with faster cognitive decline and increased dementia risk [73]. These findings highlight the need to better define the role of NK cells in neuroimmune aging and their potential as targets in neurodegenerative disease.

The gut microbiome further influences NK aging. Microbial metabolites such as short-chain fatty acids (SCFAs) regulate NK metabolism, enhancing glycolysis and IFN-γ production. With age, dysbiosis reduces SCFA availability, weakening NK surveillance and promoting systemic inflammation [74]. Restoring microbiome integrity through dietary fiber, probiotics, or fecal microbiota transplantation has been shown to rejuvenate NK function in animal models, linking microbiota-targeted interventions to NK-centered longevity medicine [75].

Lifestyle factors profoundly impact NK function across tissues. Exercise mobilizes NK cells into circulation, increases granzyme and perforin expression, and enhances vaccine responsiveness in older adults [76–79]. Caloric restriction and fasting-mimicking diets improve NK metabolic fitness by inducing autophagy and optimizing mitochondrial function [74]. Nutritional interventions, such as polyphenols and omega-3 fatty acids, further modulate NK cytotoxicity, while sleep deprivation causes rapid declines in NK activity, linking circadian integrity to immune surveillance [31, 32, 75, 80, 81]. These findings emphasize that NK cells integrate environmental inputs into immune–metabolic outcomes, and that lifestyle interventions represent tractable levers for maintaining NK competence during aging.

Taken together, NK cells are deeply embedded in the regulation of tissue homeostasis and systemic metabolism. Their decline with age compromises multiple organ systems, including adipose tissue, liver, skeletal muscle, bone, cardiovascular structures, and brain. This systemic dysfunction links NK immunosenescence to hallmark features of metabolic and tissue aging, including insulin resistance, fibrosis, sarcopenia, cardiovascular disease,

and cognitive decline. Conversely, preserving NK competence through lifestyle, microbiome-targeted interventions, or pharmacologic approaches may simultaneously protect multiple tissues. By situating NK biology within the framework of tissue-specific and systemic aging, NK cells emerge not only as effectors of immune defense but also as integrators of metabolic health and guardians of organ resilience.

Therapeutic interventions to harness NK cells

Harnessing NK cells for longevity medicine requires strategies that restore or augment NK function in the context of aging. Broadly, interventions fall into three categories: lifestyle-based modulation, pharmacological and biologic therapies, and cellular immunotherapies. Lifestyle interventions are among the most accessible and effective levers. Regular aerobic and resistance exercise mobilizes NK cells into circulation, enhances perforin and granzyme expression, and boosts cytokine secretion, with effects observable even in older adults [82–85]. Exercise also improves vaccine responsiveness and reduces infection risk by enhancing NK competence. Nutritional interventions, including caloric restriction, fasting-mimicking diets, and diets enriched in polyphenols or omega-3 fatty acids, optimize NK metabolism through induction of autophagy, improved mitochondrial function, and modulation of mTOR signaling [75]. Sleep integrity and circadian alignment are equally critical, as sleep deprivation can reduce NK activity by up to 70% within 24 h, whereas restoration of circadian rhythm normalizes NK cytotoxicity [80, 81]. Together, these findings highlight that modifiable lifestyle factors represent first-line tools for preserving NK function and delaying immunosenescence.

Pharmacological approaches to NK rejuvenation are advancing rapidly. Cytokine-based therapies, particularly IL-15 superagonists (e.g., N-803), have shown potent effects in enhancing NK proliferation, survival, and cytotoxicity in preclinical and early-phase clinical studies [86–88]. Combinations of IL-12 and IL-18 can generate cytokine-induced memory-like NK cells with enhanced persistence and activity, offering another route to restore NK responses [89]. Checkpoint inhibition provides another strategy, as NK cells upregulate inhibitory receptors such as NKG2A, TIGIT, and PD-1 with age. Antibodies blocking these pathways (e.g., monalizumab for NKG2A) reinvigorate NK cytotoxicity against senescent and malignant targets [90–92]. Small-molecule modulators are also under investigation, including mTOR inhibitors to restore metabolic flexibility, epigenetic reprogramming agents to reverse exhaustion-like states, and senolytics to synergize with NK activity [55–62]. Importantly, pharmacological senolytics such as dasatinib, quercetin, and fisetin can reduce senescent cell burden, but their efficacy may be incomplete without NK surveillance. Thus, combined strategies pairing NK activation with pharmacological senolytics are likely to achieve more durable rejuvenation of tissue microenvironments [93–100].

Cellular immunotherapies represent perhaps the most transformative avenue. Adoptive NK transfer has long been studied in oncology, but the field has now advanced to next-generation NK platforms that may be repurposed for longevity applications. Cytokine-induced memory-like NK cells generated by IL-12/15/18 priming demonstrate enhanced cytotoxicity, persistence, and recall responses compared with conventional NK cells [101–106]. These cells have shown efficacy in clinical trials for leukemia and may also be harnessed for senescence clearance in older adults. Induced pluripotent stem cell (iPSC)-derived NK cells represent another breakthrough, offering a renewable, standardized, and off-the-shelf source of NK products [107–109]. These cells can be genetically engineered for enhanced activity, such as CAR-NK platforms designed to recognize stress ligands or senescence-associated antigens, and can be manufactured at clinical scale. The possibility of developing CAR-NK therapies targeted not at tumors but at senescent cells opens an entirely new dimension in senotherapeutics. Furthermore, "armored" NK cells engineered to secrete IL-15 or resist TGF-β–mediated suppression could overcome inhibitory tissue environments typical of aged organs [108–110].

Another frontier involves biomarker-guided NK therapies. Advances in single-cell transcriptomics, proteomics, and metabolomics now allow precise profiling of NK function across tissues. Integration of these data with machine learning approaches may enable personalized NK rejuvenation strategies, where individuals are stratified according to NK cytotoxic capacity, receptor expression, or metabolic signatures [111, 112]. This approach would allow preventive deployment of NK-based therapies before overt multimorbidity emerges. Clinical translation will also benefit from the development of NK fitness biomarkers as surrogate endpoints in longevity trials, enabling shorter and more efficient study designs.

Importantly, therapeutic interventions must be framed within the context of safety and feasibility in aging populations. Unlike oncology, where cytotoxicity against tumors outweighs concerns about collateral damage, longevity medicine requires careful balancing of risk and benefit. Excessive NK activation could, in principle, promote autoimmunity or exacerbate tissue injury, particularly in organs with ongoing low-grade inflammation. Therefore, strategies for NK rejuvenation must prioritize tunability and reversibility. Approaches such as transient

cytokine pulses, titratable CAR constructs, or tissue-targeted delivery systems may provide ways to harness NK cytotoxicity safely in otherwise healthy older adults.

Collectively, these therapeutic approaches highlight the translational potential of NK biology in longevity medicine. Lifestyle optimization provides accessible tools to preserve NK competence, while pharmacological and biologic therapies offer scalable ways to rejuvenate NK function. Cellular immunotherapies, including iPSC-derived and CAR-engineered NK cells, represent frontier technologies with the potential to redefine senolytic medicine. By combining these interventions with biomarker-guided precision strategies, NK-centered therapies may move from experimental concepts to routine tools for extending healthspan. In this framework, NK cells are not merely targets of age-related decline but are reimagined as therapeutic effectors that can be enhanced, engineered, and deployed to maintain tissue integrity and delay the onset of multimorbidity. While advanced cellular approaches, including cytokine-induced memory-like NK cells, iPSC-derived NK cells, and CAR-NK platforms, offer compelling therapeutic potential, their application in longevity or preventive medicine remains highly preliminary. Most supporting evidence for these strategies originates from oncology and preclinical disease models, where risk–benefit considerations differ substantially from those in otherwise healthy aging populations. Key challenges—including appropriate target selection for senescent but non-malignant cells, control of long-term persistence, reversibility of NK activation, and the risk of off-target tissue injury—remain unresolved. Accordingly, such engineered NK cell approaches should presently be regarded as future-facing or investigational strategies in the context of healthspan extension, requiring rigorous preclinical validation, long-term safety assessment, and ethical oversight before broader application in aging interventions (Fig. 4).

Clinical translation and biomarkers

For NK cell–based longevity medicine to move from conceptual framework to clinical practice, robust biomarkers are needed to assess NK fitness, stratify individuals by biological age, and monitor therapeutic interventions. NK cells can be evaluated at multiple levels: phenotypic, functional, transcriptional, and systemic. Phenotypically, flow cytometry and mass cytometry enable profiling of NK subsets based on markers such as CD56, CD16, CD57, NKG2A, NKG2C, and KIRs, revealing distributional shifts associated with immunosenescence [8–11, 31–33]. The expansion of $CD56^{dim}CD57^{+}$ terminal NK cells, decline of CD56^bright cytokine-secreting subsets, and altered balance of activating versus inhibitory receptors have been correlated with frailty, poor vaccine responsiveness, and increased infection risk [19, 31]. Functional assays, such as chromium-release cytotoxicity assays, CD107a degranulation, and intracellular cytokine staining, provide direct measures of NK effector capacity but are technically demanding and not standardized for clinical use [32–34]. Advances in high-throughput single-cell transcriptomics and proteomics now allow comprehensive mapping of NK heterogeneity across tissues, identifying exhaustion-like transcriptional signatures, metabolic insufficiencies, and senescence-associated expression patterns [13–15, 111]. Such signatures can be integrated into biological age indices, offering a more precise measure of immunosenescence than chronological age alone.

Systemic biomarkers linked to NK activity are also emerging. Circulating levels of soluble NKG2D ligands (e.g., MICA/B), cytokines such as IL-15, and exosomal NK-derived microRNAs have been proposed as indicators of NK competence [112]. Elevated soluble NKG2D ligands correlate with impaired NK recognition and have been associated with both cancer risk and accumulation of senescent cells [27–29]. Similarly, reduced serum IL-15 levels in older adults predict poor NK homeostasis and increased frailty [100–102]. Integrating these systemic markers with cellular assays could provide multidimensional readouts of NK health. Moreover, the development of composite immune age scores, incorporating NK function alongside T- and B-cell parameters, is likely to refine assessment of biological aging trajectories [2–4].

From a translational perspective, NK biomarkers can serve both predictive and surrogate roles in longevity trials. Predictive biomarkers would identify individuals most likely to benefit from NK-centered therapies—for example, those with low baseline NK cytotoxicity or high levels of circulating SASP factors. Surrogate biomarkers would allow monitoring of intervention efficacy in shorter timeframes than clinical endpoints like mortality or multimorbidity. For instance, restoration of NKG2D expression, improved degranulation indices, or reduction of soluble MICA/B after therapy could serve as surrogate indicators of rejuvenated senescence surveillance [21–23, 55–62]. In this way, NK biomarker development aligns with the broader need for short, reliable, and mechanistically anchored endpoints in geroscience clinical trials. NK-based biomarkers are most informative in biological contexts where immune surveillance capacity, senescent cell burden, infection susceptibility, or cancer risk are dominant contributors to morbidity. In such settings, NK phenotypic and functional measures provide mechanistically anchored readouts of immune aging that are not captured by epigenetic clocks or clinical frailty indices alone. Conversely, NK metrics are not intended to function as universal predictors of biological age across

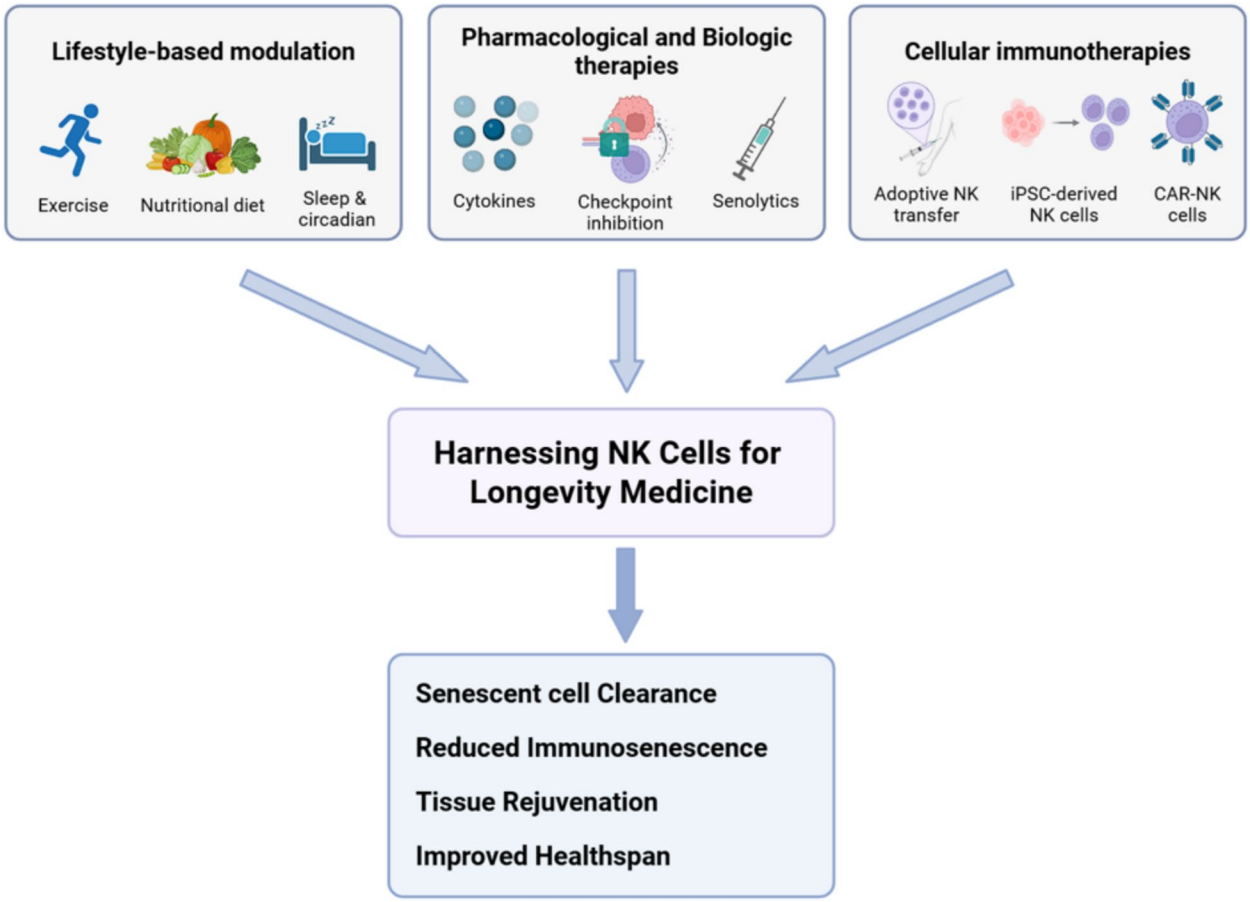


Fig. 4 Targeting natural killer cells in longevity medicine: from lifestyle to biologics and cell therapy. This schematic shows three classes of intervention increasing NK cell activity in aging. Lifestyle. Regular exercise. Diet low in calories and rich in omega-3 fatty acids. Optimized sleep and circadian rhythms. Modulation of the microbiome. All of these aspects enhance NK activation and maintenance of effector function. Drugs and biologics. Cytokine therapy such as IL-15 superagonists and IL-12/18-primed CIML-NK. Checkpoint blockades that target NKG2A or TIGIT. Senolytics such as dasatinib plus quercetin. These interventions lower inhibitory signals and raise NK activity. Cell therapy. Adoptive NK or CIML-NK transfers. iPSC-derived NK cells. CAR-NK cells. These products enhance target recognition and killing

all aging phenotypes, but rather as context-dependent indicators aligned with specific immune-mediated aging trajectories. At present, several limitations constrain the clinical deployment of NK-based aging biomarkers. Evidence supporting their independent prognostic value remains limited, and organ- or disease-specific associations between NK metrics and clinical outcomes are incompletely defined. Moreover, large-scale longitudinal cohorts integrating NK phenotypes with multimodal aging biomarkers—including epigenetic clocks, immune repertoire diversity, and clinical frailty indices—are still lacking. Addressing these gaps will be essential to determine the precise role of NK biomarkers within comprehensive aging assessment frameworks.

Clinical translation of NK interventions for longevity will require careful design of trial populations, dosing regimens, and safety monitoring. Unlike oncology or infectious disease, where patients are already at high risk of morbidity and mortality, longevity medicine may involve otherwise healthy older adults. This raises ethical considerations regarding acceptable risk thresholds and justifications for immunomodulation. Interventions may initially focus on high-risk subgroups, such as individuals with immunosenescence-associated multimorbidity, frailty, or clonal hematopoiesis, before expanding into general aging populations. Adaptive trial designs, in which biomarker-defined responders can be rapidly identified and therapy adjusted, may accelerate progress while ensuring safety [4, 111, 112].

Another challenge lies in ensuring equitable access and scalability. Advanced NK cell therapies, such as CAR-NK or iPSC-derived NK products, are resource-intensive and may be initially limited to specialized centers. To integrate into longevity medicine broadly, tiered strategies may be needed: lifestyle and nutritional interventions for population-level impact; pharmacological and

checkpoint-based approaches for at-risk older adults; and advanced cellular therapies for high-need subgroups. A layered approach could maximize benefit while minimizing disparities [67, 100–110].

Finally, regulatory frameworks will need to evolve to accommodate preventive NK interventions. Currently, most NK-based therapies are developed for oncology or viral infections, where endpoints are clear and risk–benefit ratios more favorable. Extending these therapies to aging populations will require dialogue between geroscientists, clinicians, and regulators to establish appropriate endpoints, monitoring systems, and long-term safety data. Ethical issues surrounding enhancement of immunity, potential overactivation, and allocation of advanced therapies must also be addressed [4]. Importantly, lessons can be drawn from the development of vaccines, which represent successful precedents for preventive immunotherapy in otherwise healthy individuals. Positioning NK interventions along similar lines may smooth regulatory pathways and societal acceptance.

Taken together, biomarkers and clinical translation strategies are critical enablers of NK-based longevity medicine. Biomarkers provide the means to measure immunosenescence, identify candidates for intervention, and track therapeutic efficacy. Clinical translation frameworks ensure that therapies can be deployed safely, equitably, and effectively. By combining robust biomarker platforms with adaptive trial designs and thoughtful regulatory strategies, NK-centered longevity interventions may transition from experimental concept to real-world preventive medicine. Ultimately, NK biomarker development does more than quantify immune health; it lays the foundation for integrating NK cells into the architecture of precision longevity medicine.

At present, NK-based metrics should be viewed as complementary immune-aging biomarkers rather than stand-alone predictors of biological age, with their greatest utility likely residing in contexts where senescence burden, infection susceptibility, or cancer risk dominate healthspan trajectories.

Ethical issues and future perspectives

The integration of NK cell biology into longevity medicine raises critical ethical, societal, and future-facing questions that extend beyond the laboratory and clinic. Unlike oncology or infectious disease settings, where NK-based therapies are deployed to treat acute pathology, longevity applications involve otherwise healthy older adults who may not yet manifest overt disease. This shift from treatment to prevention complicates the risk–benefit calculus and demands careful reflection. Immunotherapies, particularly cellular interventions such as CAR-NK or iPSC-derived NK products, carry risks of off-target effects, cytokine release, and long-term alterations to immune balance [100–110]. In preventive contexts, even low probabilities of adverse events must be weighed against uncertain benefits, as endpoints like delayed multimorbidity or extended healthspan unfold only over years or decades. Ethically, this raises the bar for informed consent, requiring that individuals understand both the potential benefits and risks of immune enhancement in the absence of disease. Parallel debates in the field of gene editing and anti-aging pharmacology provide useful precedents, highlighting the need for transparency, community engagement, and safeguards against overpromising outcomes [2–4].

Equitable access represents another challenge. Advanced NK interventions—such as engineered or iPSC-derived NK therapies—are resource-intensive and likely to be accessible only to wealthy populations in early phases. This could exacerbate existing health inequities, where longevity-enhancing therapies become privileges of the few rather than tools for public health [4, 111, 112]. Addressing this requires a tiered approach, in which accessible strategies such as lifestyle interventions, nutritional optimization, microbiome-targeted therapies, and checkpoint blockade are scaled broadly, while advanced cellular products are reserved for high-need subgroups. Policymakers and healthcare systems must anticipate these disparities and design frameworks to ensure equitable deployment, potentially through public–private partnerships, insurance models, or tiered pricing mechanisms. The ethical principle of justice demands that longevity medicine not deepen divides between populations but rather contribute to collective healthspan extension.

Another consideration is the potential for NK-based longevity therapies to redefine concepts of aging and health. If routine NK profiling and rejuvenation become part of standard preventive care, biological age could become a measurable and actionable metric akin to blood pressure or cholesterol levels. This would shift cultural narratives around aging from inevitability to modifiable risk factor. While empowering, such a shift also risks medicalizing normal aging, potentially pathologizing natural variations in immune function [3, 4]. Safeguards must therefore ensure that longevity medicine complements rather than undermines holistic views of aging, respecting quality of life, dignity, and autonomy.

Future research directions will be shaped by technological advances. Precision NK medicine will likely incorporate multi-omic profiling, artificial intelligence, and systems immunology to stratify individuals by immune age and design personalized interventions [111, 112]. Organoid and humanized mouse models will provide platforms to test NK-based senotherapies in tissue-specific contexts, while advances in single-cell epigenomics

will uncover mechanisms of NK exhaustion and rejuvenation [13–15]. The field may also move toward synthetic biology approaches, in which NK cells are engineered with tunable receptors, safety switches, and metabolic enhancements tailored for aging tissues [108–110]. These developments hold promise but also require regulatory frameworks to ensure safety, reversibility, and accountability in their application.

Finally, NK-centered longevity medicine must be embedded within a broader societal discourse on the

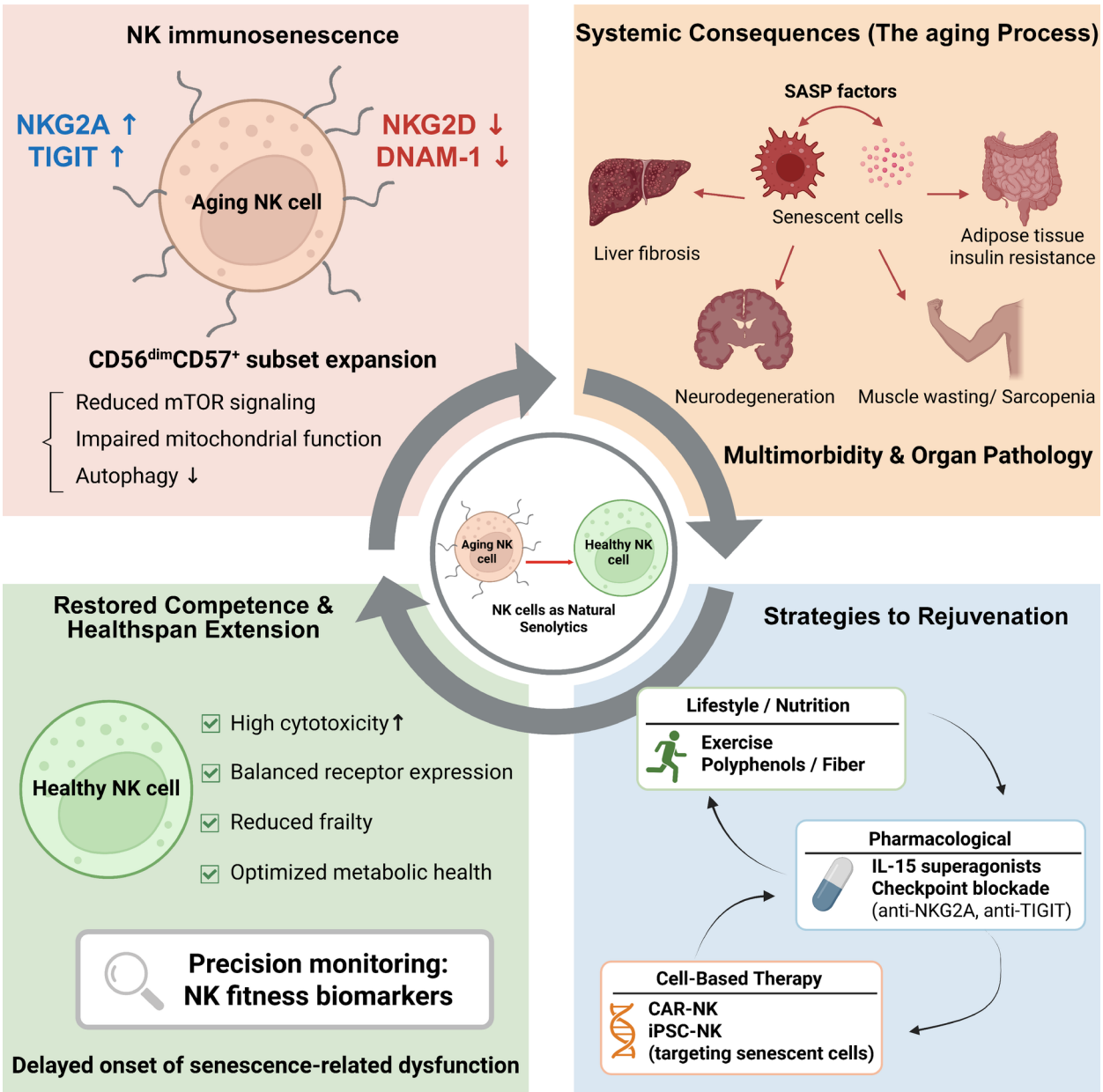


Fig. 5 NK cell immunosenescence, systemic effects, and re-energization strategies resulting in improved functionality. A four-phase model based on natural killer (NK) cells is described in this overview. **a** Immunosenescence: In aged NK cells, inhibitory receptors, for instance NKG2A and TIGIT, increase and activating receptors like NKG2D and DNAM-1 decrease. The $CD56^{dim}CD57^{+}$ subset becomes predominant. Furthermore, mTOR signaling decreases, mitochondrial function deteriorates, and autophagy reduces. **b** Systemic impact: The senescent cells and SASP factors lead to a range of diseases and organ damage, such as liver fibrosis, insulin resistance in adipose tissue, neurodegenerative diseases, and muscle wasting or sarcopenia. **c** Rejuvenation strategies: NK cell function could be restored via lifestyle interventions (e.g., exercise, polyphenols and fiber intake), pharmacological strategies (including IL-15 superagonists, checkpoint blockade utilizing anti-NKG2A and anti-TIGIT), and cell therapies (e.g., CAR-NK and iPSC-NK that specifically act toward senescent cells). **d** Restored functionality and healthspan extension: After treatment, NK cells are both highly cytotoxic and have more balanced receptor expression

goals of life extension. Extending healthspan has profound implications for demographics, healthcare systems, intergenerational equity, and resource allocation. Ethical questions arise: who decides which interventions are prioritized, who gains access first, and how should societies adapt if large populations live longer, healthier lives? These debates echo those surrounding vaccines, organ transplantation, and emerging gene-editing technologies, reminding us that biomedical innovation always operates within social and cultural contexts. Interdisciplinary collaboration—spanning geroscience, immunology, ethics, sociology, and policy—will be critical to ensure that NK-based longevity medicine evolves responsibly.

Together, NK-centered longevity medicine stands at the intersection of cutting-edge immunology and pressing societal questions. Its promise lies in harnessing NK biology to extend healthspan and reduce the burden of multimorbidity, but its realization depends on navigating complex ethical terrain. Balancing innovation with safety, ensuring equitable access, avoiding over-medicalization, and engaging in transparent societal dialogue will be essential. By proactively addressing these challenges, the field can chart a course in which NK-based interventions become not only powerful biomedical tools but also ethically grounded contributions to a healthier aging society.

Conclusion

Natural killer cells undergo profound functional and phenotypic remodeling with age, reflecting broader changes in immune competence, tissue homeostasis, and systemic inflammatory balance. Rather than acting as a singular driver of aging, NK cells should be viewed as key immune effectors whose functional integrity disproportionately influences senescence surveillance, immunometabolic regulation, and resilience against age-associated pathologies. Their age-related decline compromises the clearance of senescent and stressed cells, amplifies inflammatory signaling, and contributes to the progression of multimorbidity across multiple organ systems. This review synthesizes evidence across immunology, geroscience, and regenerative biology to situate NK cells within the emerging paradigm of longevity medicine. By integrating NK immunosenescence with hallmarks of aging, tissue-specific dysfunction, and translational intervention strategies, we propose that NK cells represent a mechanistically grounded and clinically tractable component of immune aging, rather than a newly discovered determinant. Importantly, NK-related phenotypic and functional metrics may serve as complementary biomarkers of immune aging, particularly in contexts where senescence burden, infection susceptibility, or cancer risk dominate healthspan trajectories. However, their specificity and independent prognostic value relative to established aging biomarkers remain to be rigorously validated in longitudinal human studies. Until such validation is achieved, NK-based biomarkers should be interpreted as mechanistically informative components of integrated immune-aging assessments, rather than as definitive or stand-alone measures of biological age. Therapeutic strategies aimed at preserving or restoring NK competence span a broad spectrum, from lifestyle optimization and nutritional modulation to cytokine-based therapies and immune checkpoint inhibition. Advanced cellular approaches, including cytokine-induced memory-like NK cells, iPSC-derived NK cells, and CAR-NK platforms, offer promising future directions but remain largely investigational outside oncology settings. Their application in preventive or longevity medicine will require careful evaluation of long-term safety, reversibility, and ethical considerations, particularly in otherwise healthy aging populations. Looking forward, progress in NK-centered longevity medicine will depend on the integration of multi-omic profiling, systems immunology, and adaptive clinical trial designs to define when, where, and for whom NK-targeted interventions are most beneficial. Comparative studies across immune compartments, rigorous biomarker validation, and context-specific assessment of risk–benefit ratios will be essential. By embedding NK biology within a systems-level view of aging, this framework supports the rational incorporation of NK cells into precision strategies aimed at extending healthspan, while avoiding overstatement of their role as a singular regulator of human aging (Fig. 5).

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Authors' contributions
Correspondence should be sent to Oscar K. Lee, MD, PhD Department of Biotechnology Medicine MacKay Memorial Hospital Taipei, Taiwan E-mail: oscarlee9203@gmail.com *These authors contributed equally to this work.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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References

1. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2023;186:1–21.
2. Kennedy BK, et al. Geroscience: linking aging to chronic disease. Cell. 2014;159:709–13.
3. Zhavoronkov A, Bischof E, Lee KF. Artificial intelligence in longevity medicine. Nat Aging. 2021;1:5–7.
4. Partridge L, Deelen J, Slagboom PE. Facing up to the global challenges of ageing. Nature. 2018;561:45–56.
5. Vivier E, et al. Innate lymphoid cells: 10 years on. Cell. 2018;174:1054–66.
6. Long EO, Kim HS, Liu D, Peterson ME, Rajagopalan S. Controlling natural killer cell responses: integration of signals for activation and inhibition. Annu Rev Immunol. 2013;31:227–58.
7. Lanier LL. NKG2D receptor and its ligands in host defense. Cancer Immunol Res. 2015;3:575–82.
8. Solana R, et al. Innate immunosenescence: effect of aging on cells and receptors of the innate immune system in humans. Semin Immunol. 2012;24:331–41.
9. Strauss-Albee DM, Blish CA. Human NK cell diversity in viral infection: ramifications of ramification. Front Immunol. 2016;7:66.
10. Chidrawar SM, et al. Cytomegalovirus-seropositivity has a profound influence on the magnitude of major lymphoid subsets within healthy individuals. Clin Exp Immunol. 2009;155:423–32.
11. Björkström NK, Strunz B, Ljunggren HG. Natural killer cells in antiviral immunity. Nat Rev Immunol. 2022;22:112–23.
12. Krizhanovsky V, et al. Senescence of activated stellate cells limits liver fibrosis. Cell. 2008;134:657–67.
13. Iannello A, Raulet DH. Immunosurveillance of senescent cancer cells by natural killer cells. Oncoimmunology. 2014;284:63–75.
14. Pereira BI. et al. Senescent cells evade immune clearance via HLA-E-mediated NK and CD8+ T cell inhibition. Nat Commun. 2019;10:2387.
15. Sagiv A, Krizhanovsky V. Immunosurveillance of senescent cells: the bright side of the senescence program. Biogerontology. 2013;14:617–28.
16. Gorgoulis VG, et al. Cellular senescence: defining a path forward. Cell. 2019;179:813–27.
17. Huang W, Hickson LJ, Eirin A, Kirkland JL, Lerman LO. Cellular senescence: the good, the bad and the unknown. Nat Rev Nephrol. 2022;18:611–27.
18. Childs BG, Durik M, Baker DJ, van Deursen JM. Cellular senescence in aging and disease. Nat Med. 2015;21:1424–35.
19. Baker DJ, et al. Clearance of p16Ink4a-positive senescent cells delays age-associated disorders. Nature. 2011;479:232–6.
20. Baker DJ, et al. Naturally occurring p16Ink4a-positive cells shorten healthy lifespan. Nature. 2016;530:184–9.
21. Xu M, et al. Senolytics improve physical function and increase lifespan in old age. Nat Med. 2018;24:1246–56.
22. Justice JN, et al. Senolytics in idiopathic pulmonary fibrosis: pilot study. EBioMedicine. 2019;40:554–63.
23. Hickson LJ, et al. Senolytics decrease senescent cells in humans: preliminary report from a clinical trial. EBioMedicine. 2019;47:446–56.
24. Baar MP, et al. Targeted apoptosis of senescent cells restores tissue homeostasis. Cell. 2017;169:132–47.
25. Lee BC, et al. Adipose natural killer cells regulate adipose tissue macrophages. Cell Metab. 2016;23:685–98.
26. Wensveen FM, et al. NK cells link obesity-induced adipose stress to inflammation. Nat Immunol. 2015;16:376–85.
27. Gao Y, et al. Tumor immunoevasion by the conversion of effector NK cells into type 1 innate lymphoid cells. Nat Immunol. 2017;18:1004–15.
28. Bou Ghanem EN. et al. Immune senescence, immunosenescence and aging. Front Aging. 2022;3:900028.
29. Ovadya Y, Krizhanovsky V. Senescent cells: SASPected drivers of age-related pathologies. Biogerontology. 2014;15:627–42.
30. Han X, Zhang T, Liu H, Mi Y, Gou X. Astrocyte senescence and Alzheimer's disease: a review. Front Aging Neurosci. 2020;12:148.
31. Irwin M, et al. Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. FASEB J. 1996;10:643–53.
32. Fiuza-Luces C, Valenzuela PL, Gálvez BG, et al. The effect of physical exercise on anticancer immunity. Nat Rev Immunol. 2024;24:282–93.
33. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019;8:201–17.
34. DeBolt CA, Yu H, Riis V, Ncube L, Horowitz A, Elovitz MA. Revealing the complexity of immunobiological shifts from non-pregnant to pregnant state. Am J Reprod Immunol. 2025;94:e70166.
35. Conlon KC, et al. Redistribution, hyperproliferation, activation of natural killer cells and CD8 T cells, and cytokine production during first-in-human clinical trial of recombinant human interleukin-15. J Clin Oncol. 2015;33:74–82.
36. Romee R. et al. Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. Sci Transl Med. 2016;8:357ra123.
37. Wrangle JM, et al. ALT-803, an IL-15 superagonist, in combination with nivolumab in patients with metastatic non-small cell lung cancer. Lancet Oncol. 2018;19:694–704.
38. Waldmann TA, Tagaya Y. The multifaceted regulation of interleukin-15 expression and the role of this cytokine in NK cell differentiation and host response to intracellular pathogens. Annu Rev Immunol. 1999;19:19–49.
39. André P, et al. Anti-NKG2A mAb is a checkpoint inhibitor that promotes anti-tumor immunity. Cell. 2018;175:1731–43.
40. van Hall T, et al. Monalizumab: inhibiting the novel immune checkpoint NKG2A. J Immunother Cancer. 2019;7:263.
41. Zhang Q, et al. Blockade of the checkpoint receptor TIGIT prevents NK cell exhaustion and elicits potent anti-tumor immunity. Nat Immunol. 2018;19:723–32.
42. Johnston RJ, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. Cancer Cell. 2014;26:923–37.
43. Ndhlovu LC, et al. Tim-3 marks human natural killer cell maturation and suppresses cell-mediated cytotoxicity. Blood. 2012;119:3734–43.
44. Liu E, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. N Engl J Med. 2020;382:545–53.
45. Rezvani K, Rouce R, Liu E, Shpall E. Engineering natural killer cells for cancer immunotherapy. Mol Ther. 2017;25:1769–81.
46. Deng X, Terunuma H. Adoptive NK cell therapy: a potential revolutionary approach in longevity therapeutics. Immun Ageing. 2024;21:43.
47. Bednarski JJ, Zimmerman C, Berrien-Elliott MM, Foltz JA, Becker-Hapak M, Neal CC, et al. Donor memory-like NK cells persist and induce remissions in pediatric patients with relapsed AML after transplant. Blood. 2022;139(11):1670–83.
48. Shapiro RM, et al. Expansion, persistence, and efficacy of donor memory-like NK cells infused for posttransplant relapse. J Clin Invest. 2022;132:e154334.
49. Ruggeri L, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science. 2002;295:2097–100.
50. Merino A, Maakaron J, Bachanova V. Advances in NK cell therapy for hematologic malignancies: NK source, persistence and tumor targeting. Blood Rev. 2023;60:101073.
51. Knorr DA, Bachanova V, Verneris MR, Miller JS. Clinical utility of natural killer cells in cancer therapy and transplantation. Semin Immunol. 2014;26:161–72.
52. Li Y, Hermanson DL, Moriarity BS, Kaufman DS. Human iPSC-derived natural killer cells engineered with chimeric antigen receptors enhance anti-tumor activity. Cell Stem Cell. 2018;23:181-92.e5.
53. Pan K, et al. CAR race to cancer immunotherapy: from CAR T, CAR NK to CAR macrophage therapy. J Exp Clin Cancer Res. 2022;41:119.
54. Kikuchi T, Takeuchi I, Yamaguchi H. Scalable production process development for NK cells targeting large-scale expansion. Regen Ther. 2025;30:535–43.
55. Amor C, et al. Senolytic CAR T cells reverse senescence-associated pathologies. Nature. 2020;583:127–32.
56. Sagiv A, et al. NKG2D ligands mediate immunosurveillance of senescent cells. Aging (Albany NY). 2016;8:328–44.
57. Coppé JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol. 2010;5:99–118.
58. van Deursen JM. The role of senescent cells in ageing. Nature. 2014;509:439–46.
59. Tchkonia T, et al. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. J Clin Invest. 2013;123:966–72.
60. Zhu Y, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell. 2015;14:644–58.

61. Palmer AK. et al. Targeting senescent cells alleviates obesity-induced metabolic dysfunction. Aging Cell. 2019;18:e12950.
62. Farr JN, et al. Targeting cellular senescence prevents age-related bone loss in mice. Nat Med. 2017;23:1072–9.
63. He S, Sharpless NE. Senescence in health and disease. Cell. 2017;169:1000–11.
64. Davalos AR, et al. p53-dependent release of Alarmin HMGB1 is a central mediator of senescent phenotypes. J Cell Biol. 2013;201:613–29.
65. Freund A, Orjalo AV, Desprez PY, Campisi J. Inflammatory networks during cellular senescence: causes and consequences. Trends Mol Med. 2010;16:238–46.
66. Franceschi C, et al. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018;14:576–90.
67. Calder PC, et al. Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition. Ageing Res Rev. 2017;40:95–119.
68. Fulop T, Larbi A, Pawelec G, et al. Immunology of aging: the birth of inflammaging. Clin Rev Allergy Immunol. 2023;64:109–22.
69. Naylor K, et al. The influence of age on T cell generation and TCR diversity. J Immunol. 2005;174:7446–52.
70. Field AE, et al. DNA methylation clocks in aging: categories, causes, and consequences. Mol Cell. 2018;71:882–95.
71. Campisi J, et al. From discoveries in ageing research to therapeutics for healthy ageing. Nat Med. 2019;571:183–92.
72. Lu JK, et al. Digital biomarkers of ageing for monitoring physiological systems in community-dwelling adults. Lancet Healthy Longev. 2025;6:100725.
73. López-Otín C, et al. Hallmarks of aging: an expanding universe. Cell. 2023;186:243–78.
74. Hammer Q, Romagnani C, Dunbar PR. Natural killer cell specificity for viral infections. Nat Immunol. 2018;19:800–8.
75. Sun JC, Beilke JN, Lanier LL. Adaptive NK cell responses. Nature. 2009;457:557–61.
76. O'Leary JG, Goodarzi M, Drayton DL, von Andrian UH. T cell–dependent recruitment of NK cells. Nat Immunol. 2006;7:507–16.
77. Bryceson YT, March ME, Ljunggren HG, Long EO. Synergy among receptors on resting NK cells for the activation of natural cytotoxicity and cytokine secretion. Blood. 2006;107:159–66.
78. Chen S, Zhu H, Jounaidi Y. Comprehensive snapshots of natural killer cells functions, signaling, molecular mechanisms and clinical utilization. Signal Transduct Target Ther. 2024;9:302.
79. Orange JS. Formation and function of the lytic NK synapse. Nat Rev Immunol. 2008;8:713–25.
80. Cerwenka A, Lanier LL. Natural killer cell memory in infection, inflammation and cancer. Nat Rev Immunol. 2016;16:112–23.
81. Raulet DH, et al. Regulation of ligands for the NKG2D activating receptor. Annu Rev Immunol. 2013;31:413–31.
82. Guerra N, et al. NKG2D-deficient mice and tumor surveillance. Immunity. 2008;28:571–80.
83. Hickman HD, et al. Direct priming of antiviral CD8+ T cells in the peripheral interfollicular region of lymph nodes. Nat Immunol. 2008;9:155–65.
84. Chan CJ, Smyth MJ, Martinet L. Molecular mechanisms of natural killer cell activation in response to cellular stress. Cell Death Differ. 2014;21:5–14.
85. Peng H, Tian Z. Natural killer cell memory: progress and implications. Front Immunol. 2017;8:1143.
86. Björkström NK, et al. Expression patterns of NKG2A, KIR, and CD57 define a process of CD56dim NK-cell differentiation uncoupled from NK-cell education. Blood. 2010;116:3853–64.
87. Schlums H, et al. Cytomegalovirus infection drives adaptive epigenetic diversification of NK cells. Immunity. 2015;42:443–56.
88. Cichocki F, et al. CD56dimCD57+NKG2C+ NK cell expansion is associated with reduced leukemia relapse after reduced intensity HCT. Leukemia. 2016;30:456–63.
89. Romee R, et al. Cytokine activation induces human memory-like NK cells. Blood. 2012;120:4751–60.
90. Reeves RK, et al. CD16- natural killer cells: enrichment in mucosal and secondary lymphoid tissues and altered function during chronic SIV infection. Blood. 2010;115:4439–46.
91. Scully E, Alter G. NK cells in HIV disease. Curr HIV AIDS Rep. 2016;13:85–94.
92. Vivier E, et al. Functions of NK cells. Nat Immunol. 2008;9:503–10.
93. Guillerey C, Huntington ND, Smyth MJ. Targeting natural killer cells in cancer immunotherapy. Nat Immunol. 2016;17:1025–36.
94. Marcus A, et al. Tumor-derived cGAMP triggers a STING-mediated interferon response in non-tumor cells to activate the NK cell response. Immunity. 2018;49:754–63.
95. Pawelec G. Immunosenescence and cancer. Biogerontology. 2017;18:717–21.
96. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol. 2015;15:486–99.
97. Selathurai A, Deswaerte V, Kanellakis P, et al. Natural killer (NK) cells augment atherosclerosis by cytotoxic-dependent mechanisms. Cardiovasc Res. 2014;102:128–37.
98. Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: depression fans the flames and feasts on the heat. Am J Psychiatry. 2015;172:1075–91.
99. Besedovsky L, Lange T, Born J. Sleep and immune function. Pflugers Arch. 2012;463:121–37.
100. Xie G, et al. CAR-NK cells: a promising cellular immunotherapy for cancer. EBioMedicine. 2020;59:102975.
101. Liu E, et al. Cord blood NK cells engineered to express IL-15 and a CD19-targeted CAR show long-term persistence and potent antitumor activity. Leukemia. 2018;32:520–31.
102. Daher M, Melo Garcia L, Li Y, Rezvani K. CAR-NK cells: the next wave of cellular therapy for cancer. Clin Transl Immunol. 2021;10:e1274.
103. Shimasaki N, Jain A, Campana D. NK cells for cancer immunotherapy. Nat Rev Drug Discov. 2020;19:200–18.
104. Daher M, Rezvani K. Next generation natural killer cells for cancer immunotherapy: the promise of genetic engineering. Curr Opin Immunol. 2018;51:146–53.
105. Pfefferle A, Huntington ND. Deciphering natural killer cell homeostasis. Front Immunol. 2020;11:812.
106. Berrien-Elliott MM, Cashen AF, Cubitt CC, Neal CC, Wong P, Wagner JA, et al. Multidimensional analyses of donor memory-like NK cells reveal new associations with response after adoptive immunotherapy for leukemia. Cancer Discov. 2020;10(12):1854–71.
107. Basar R, Daher M, Rezvani K. Next-generation cell therapies: the emerging role of CAR-NK cells. Blood Adv. 2020;4:5868–76.
108. Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing. Nat Rev Mol Cell Biol. 2021;22:75–95.
109. Faget DV, Ren Q, Stewart SA. Unmasking senescence: context-dependent effects of SASP in cancer. Nat Rev Cancer. 2019;19:439–53.
110. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. 2017;168:960–76.
111. Strunz B, Hengst J, Deterding K, et al. Chronic hepatitis C virus infection irreversibly impacts human natural killer cell repertoire diversity. Nat Commun. 2018;9:2275.
112. Page A, Chuvin N, Valladeau-Guilemond J, Depil S. Development of NK cell-based cancer immunotherapies through receptor engineering. Cell Mol Immunol. 2024;21:315–31.

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