Targeting IL-11: A New Approach to Curing Cancer, Slowing Aging and Promoting Longevity

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ABSTRACT

Interleukin-11 (IL-11) is a cytokine that bridges inflammation, cancer, and aging-related processes. Initially identified for its role in hematopoiesis, recent research highlights its involvement in tumor progression and chronic inflammation. IL-11 signaling, through its receptor IL-11Rα, is strongly linked to aggressive cancers such as gastric and colorectal malignancies, where it promotes tumor proliferation and immune evasion. Simultaneously, IL-11 is implicated in cellular senescence and systemic inflammation, driving age-related conditions including fibrosis, metabolic dysfunction, and multimorbidity.

Preclinical studies demonstrate the transformative potential of IL-11 inhibition. In animal models, blocking IL-11 significantly reduces tumor growth, improves tissue regeneration, and extends lifespan by mitigating inflammatory and aging-related pathologies. Anti-IL-11 therapies, including monoclonal antibodies and IL-11 receptor antagonists, show promise in reversing fibrosis, enhancing metabolic health, and reducing cancer incidence. These findings suggest that IL-11-targeted treatments could address diverse conditions, from inflammation-driven cancers to chronic age-related diseases.

Despite this promise, challenges remain. Individual variability in IL-11's role across diseases and tissues complicates therapeutic applications, and the long-term effects of IL-11 inhibition are not fully understood. However, with continued research and clinical validation, IL-11-targeted therapies have the potential to improve health outcomes, extend health span, and redefine approaches to cancer and aging.

Keywords: IL-11 signaling, Cancer therapy, Cellular senescence, Chronic inflammation, Anti-aging therapies

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Introduction

Recent advances in our understanding of tumor biology, aging, and longevity underscore the critical role of the immune system in the regulation of both healthy and malignant cell dynamics. The concept of immunosurveillance, which postulates the immune system's capacity to detect and eliminate cancer cells, has evolved into a broader framework known as immunoediting. This process encompasses the bidirectional influence between the immune system and cancer cells, leading to cancer's eventual emergence and progression.[1] Additionally, the aging population presents multifaceted challenges, emphasizing the need to address the physical decline associated with aging through effective interventions. This could potentially offer significant societal and economic benefits.

Central to the regulation of lifespan across various species are pathways like ERK, STK11 (LKB1), AMPK, mTORC1, and the IGF1–insulin modules (Figure 1).[2–4] Particularly in aged organisms, the interplay between AMPK and mTORC1 is crucial for maintaining metabolic health, impacting processes such as inflammation, mitochondrial function, and cellular senescence.[5,6] The role of chronic sterile inflammation is now recognized as a central hallmark of aging, closely associated with aging pathologies. Aging is linked with a decline in the adaptive immune system, marked by immunosenescence and thymic involution, and an aberrant activation of innate immune responses, including the interleukin-6 pathway.[7,8] This inflammatory state is further potentiated by key signaling molecules such as NF-κB and JAK–STAT3, which are implicated in aging and can be modulated to alleviate age-related dysfunction.[9] The concept is based on studies demonstrating that interleukin-11 (IL-11) can activate ERK-mTORC1 and/or JAK-STAT3,[10] the discovery that IL-11 is increased in older people,[11] and the fact that IL-11 is increasingly acknowledged to play a role in senescence, a characteristic of aging.[12]

Cytokines, especially interleukins, play pivotal roles within the tumor microenvironment, influencing cancer development through their complex interactions with both immune and non-immune cells.[13] Chronic inflammation is a recognized driver of carcinogenesis across several cancer types. Among the interleukins, IL-11 has garnered attention for its diverse functions beyond its initial identification as a hematopoietic factor. Produced by stromal cells from the bone marrow, IL-11 has been implicated in processes ranging from adipogenesis and osteoclastogenesis to neurogenesis and platelet maturation.[14] However, in the context of cancer, IL-11 signaling can transform from a homeostatic mechanism into a promoter of tumor growth and metastasis. This review aims to explore the multifaceted roles of IL-11 in cancer, aging, and longevity, highlighting its potential as a therapeutic target in these intertwined biological processes.

IL-11: Fighting Cancer and Slowing Aging

IL-11 exerts its effects by binding to its transmembrane co-receptor IL-11Rα (Figure 2). This interaction activates downstream signaling pathways that link IL-11 to inflammation and malignancy. Recent studies have identified overexpression of IL-11Rα in cancers such as lung, colorectal, gastric, breast, and prostate cancers, and osteosarcoma, suggesting that IL-11 signaling plays a critical role in oncogenesis.[15] Despite its widespread presence across various cell types, including osteoblasts, fibroblasts, hepatocytes, and epithelial cells, the main source of IL-11 secretion remains unclear.

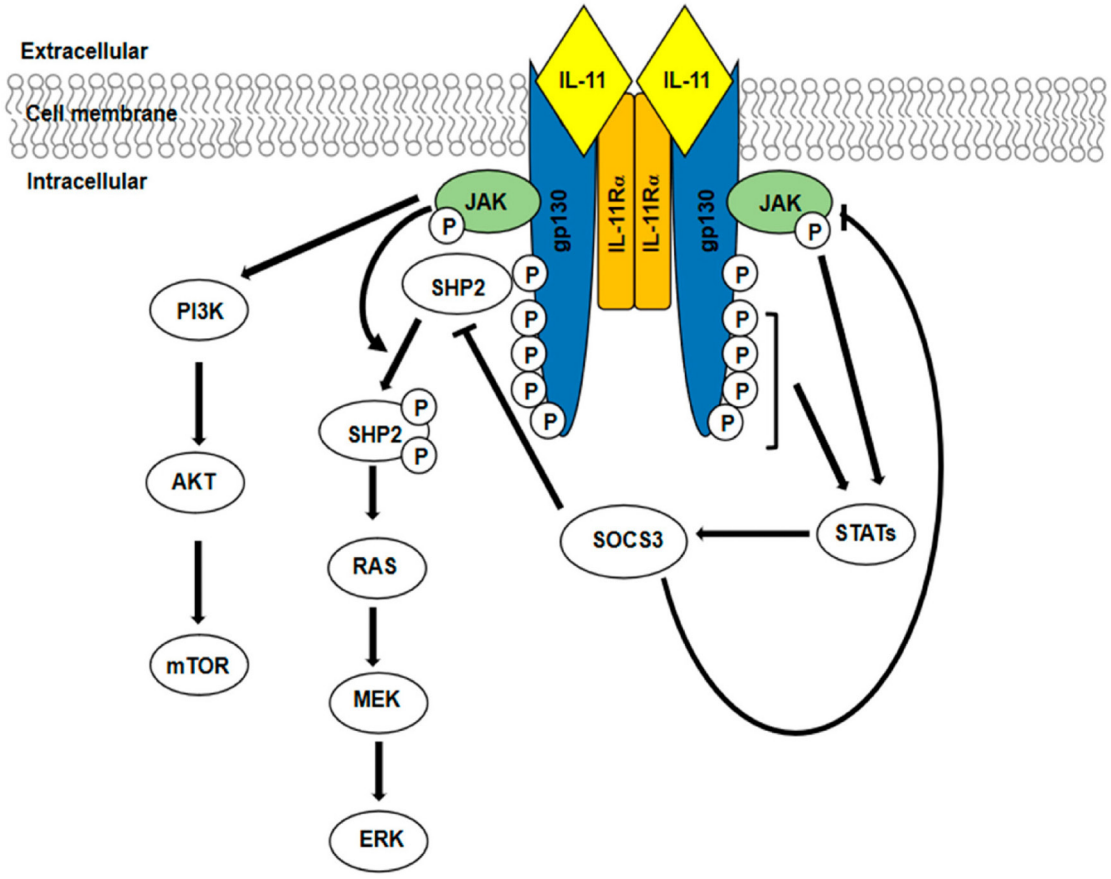

Fig 1 | IL-11 signaling pathways

Credit: https://doi.org/10.3390/biomedicines9060659

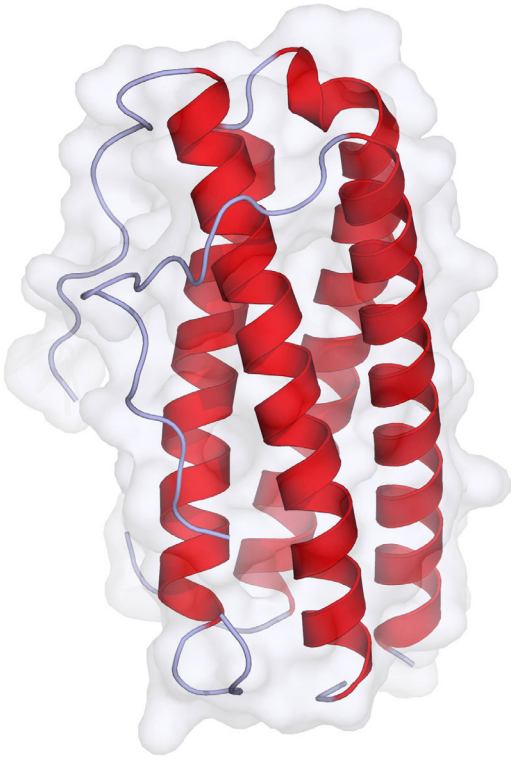

Fig 2 | Interleukin-11

In healthy individuals, IL-11 mRNA is present at low levels throughout the body,[16] and IL-11 protein is rarely detectable in the serum. However, in inflammatory diseases and cancers, IL-11 levels become readily measurable, indicating that inflammation acts as a pathological trigger for IL-11 expression.[17] Multiple studies have confirmed the involvement of IL-11 in gastric, colorectal, pancreatic, prostate, breast, ovarian, endometrial, and bone cancers.[18–20] Specifically, IL-11Rα expression in gastric and colorectal cancers correlates with tumor grade and invasiveness. For instance, Nakayama et al.[18] analyzed 73 cases of gastric adenocarcinoma and found that 72.6% stained positive for IL-11, while 64.4% stained positive for IL-11Rα. These findings were supported by evidence of IL-11 and IL-11Rα expression in gastric cancer cell lines such as MKN-1, MKN-28, NUGC-3, and SCH derived from the metastatic location of the lymph nodes.[18]

Similar patterns were observed in colorectal carcinoma and colorectal adenoma, as confirmed by Yamazumi et al.[22] and Yoshizaki et al.[21] These studies suggest that IL-11 may regulate tumor progression through an autocrine loop, particularly in cancers of the megakaryocytic lineage.[21,22] Kobayashi et al.[23] demonstrated that IL-11 stimulates the growth of megakaryoblastic cells, while IL-11 antisense oligonucleotides inhibit this growth. This suggests that

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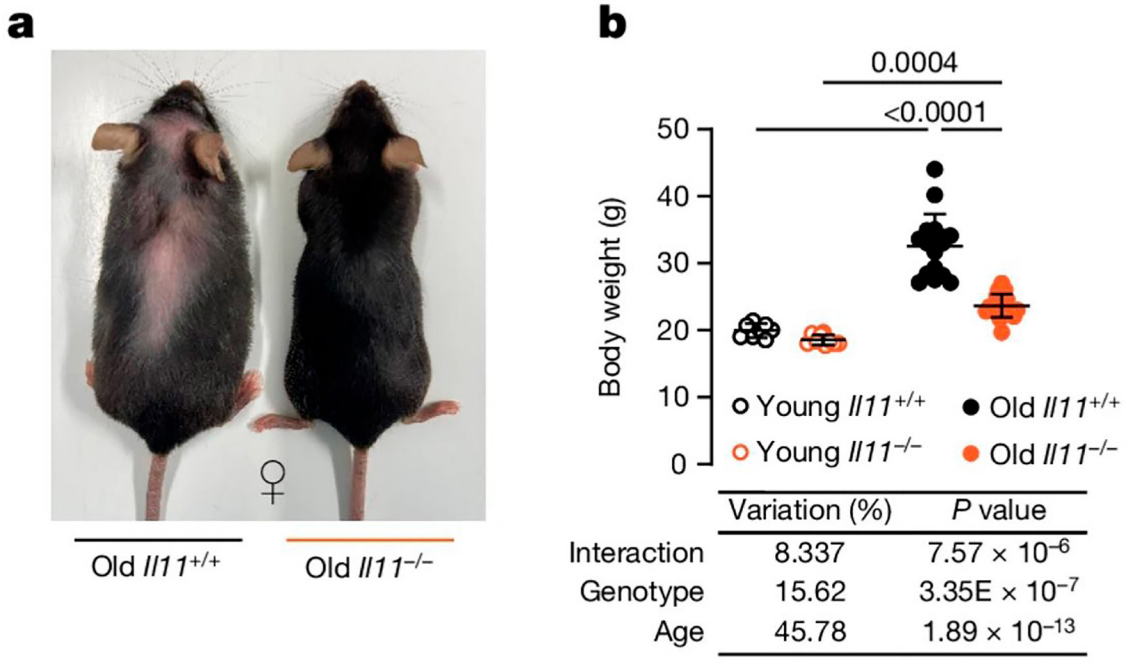

Fig 3 | Removal of interleukin-11 improves health and extends mouse lifespan by up to 24%

Credit: https://doi.org/10.1038/s41586-024-07701-9

IL-11 acts as an autocrine growth factor. Notably, autocrine signaling involving the IL-6/soluble IL-6Rα complex has been implicated in endothelial activation and chronic inflammation, mechanisms that may also apply to IL-11.[23]

The therapeutic targeting of IL-11 signaling is gaining attention due to its restricted, low-level expression in normal tissues, which minimizes potential off-target effects. Preclinical models have highlighted the efficacy of IL-11 antagonists, such as IL-11-Mutein, which binds IL-11Rα with 20 times the affinity of native IL-11.[24] Administration of IL-11-Mutein in mice has demonstrated significant therapeutic effects, including reduced tumor proliferation and enhanced apoptosis in gastric and colorectal cancer models. In gastric carcinoma, IL-11-Mutein reduced the number of cancer-associated inflammatory cells, while in colorectal cancer, it reduced tumor size and multiplicity.[25] These findings support the potential of IL-11 antagonists as cancer therapeutics.

In addition to its role in cancer, IL-11 contributes to aging-related pathologies through its involvement in chronic inflammation. Pro-inflammatory cytokines, including IL-11, are important drivers of tissue remodeling in aging. Factors such as cellular senescence, mitochondrial dysfunction, DNA damage, and altered gut microbiota composition fuel the release of cytokines like IL-11, IL-6, TNF-α, IL-1, IL-8, CCL2, and CXCL10. Elevated IL-11 levels are linked to cardiovascular diseases, Alzheimer's disease, and frailty in conditions such as Hutchinson-Gilford progeria syndrome.[26] IL-11 has been identified as a senescence-associated secretory factor that modulates aging pathways including ERK, AMPK, mTOR, and JAK–STAT3, positioning it as a promising target for anti-aging therapies.[27]

A preclinical trial by Anissa A. Widjaja et al. demonstrated that IL-11 is progressively upregulated across tissues with age, influencing the ERK–AMPK–mTORC1 axis and contributing to cellular and organismal aging.[28] Gene deletion experiments in mice revealed that IL-11 knockout extended lifespan by an average of 24.9% in both males and females. These mice exhibited reduced obesity, decreased multimorbidity, and preserved metabolic health compared to their wild-type counterparts. Anti-IL-11 antibody therapy administered to 75-week-old mice (approximately 55 human years) until death increased median lifespan by 22.5% in males and 25% in females (Figure 3). Treated mice also showed improved muscle function, metabolic health, and reduced markers of chronic inflammation and fibrosis.[28]

The researchers further examined the relationship between IL-11 upregulation and aging-related signaling pathways in aged mice. IL-11 expression was progressively elevated in the liver, visceral gonadal white adipose tissue (vWAT), and skeletal muscle.[28] These tissues exhibited increased activation of molecular pathways involved in cell growth and stress responses (ERK–p90RSK), reduced activity in pathways that regulate energy balance (LKB1–AMPK), and overactivation of cell growth pathways (mTOR–p70S6K).[28] In simpler terms, these changes signify an imbalance in the signals that control cellular health, leading to inflammation, reduced adaptability to energy stress, and unhealthy cell growth—all hallmarks of aging. To study IL-11's specific expression, the researchers used IL-11- Enhanced Green Fluorescent

Protein (EGFP) reporter mice. These genetically engineered mice have an EGFP tag attached to the IL-11 gene, allowing visualization of IL-11 expression by detecting the green fluorescence emitted under specific light conditions. Immunohistochemical analysis of these mice revealed IL-11 expression in a wide range of cell types, including hepatocytes, adipocytes, myocytes, stromal cells, epithelial cells, and endothelial cells, across multiple tissues.[28] This widespread expression pattern underscores IL-11's systemic impact on aging processes.

Comparative analyses between wild-type and IL-1ra1−/− mice revealed significant differences in aging markers. IL11ra1−/− mice are genetically modified in which the IL-11 receptor alpha-1 gene (IL11ra1) has been completely deleted or "knocked out." This means these mice lack the IL-11Rα protein, which is the receptor that IL-11 binds to activate its signaling pathways. Old IL11ra1−/− mice exhibited lower body weights, reduced fat mass, increased lean mass, improved liver function, and reduced expression of pro-inflammatory and fatty acid synthesis genes.[28] Serum alanine transaminase and aspartate aminotransferase levels were lower in IL11ra1−/− mice, indicating less hepatocyte damage.[28] Additionally, IL11ra1−/− mice demonstrated preserved telomere lengths and mitochondrial DNA copy numbers, biomarkers of biological age.[28,29] These data show that IL11ra1 deletion promotes healthy aging by reducing inflammation, maintaining cellular integrity, and lowering hepatocyte damage markers.

Anti-IL-11 therapy also reversed the hallmarks of aging in treated mice. Fibrosis, a canonical feature of aging, was significantly reduced in aged tissues such as vWAT, skeletal muscle, and liver.[28,30] ERK–mTOR activity, as well as expression of senescence markers p16 and p21, was decreased in treated mice.[31] In metabolic studies, treated mice showed improved respiratory exchange ratios and reduced age-associated metabolic inflexibility.[28] Importantly, mice receiving anti-IL-11 therapy exhibited lower cancer incidence compared to controls, suggesting that IL-11 inhibition may simultaneously mitigate aging and cancer risk.[28]

These findings were corroborated in lifespan studies. Male and female IL11−/− mice demonstrated significantly extended lifespans compared to wild-type controls. Similarly, aged mice treated with anti-IL-11 antibodies lived longer and healthier. Gross autopsy data revealed fewer macroscopic tumors in both Il11−/− and treated mice, further supporting the dual role of IL-11 in aging and cancer.[28]

Potential Therapies

The inhibition of IL-11 signaling presents an opportunity for improving health outcomes across two of the most challenging areas of medicine: cancer and aging-related conditions. By targeting the pathways associated with IL-11, researchers and clinicians could create therapies for inflammatory cancers, reduce the burden of age-related diseases, and potentially enhance longevity and quality of life.

In oncology, IL-11-targeted therapies could address cancers characterized by inflammation-driven growth, such as gastric, colorectal, and breast cancers. With IL-11's overexpression tightly linked to tumor aggression and invasiveness, blocking its signaling pathway could prevent tumors from thriving in the pro-inflammatory microenvironment. Patients with high-risk or advanced cancers could receive an IL-11 antagonist like IL-11-Mutein as an adjunct to chemotherapy or immunotherapy. This therapy could not only shrink tumors but also reduce the inflammatory response that promotes cancer recurrence, potentially improving survival rates and reducing long-term treatment side effects.

Beyond cancer treatment, the practical implications of IL-11 inhibition in aging-related disorders are also intriguing. Chronic inflammation, often referred to as "inflammaging," is a hallmark of many conditions that compromise health span in older adults, including cardiovascular disease, liver fibrosis, arthritis, and metabolic syndrome. Anti-IL-11 therapies could interrupt this cycle of inflammation, providing relief from persistent symptoms and slowing disease progression.

One particularly interesting application is the potential use of IL-11 inhibitors in preventative medicine. Regular low-dose administration of IL-11-targeted treatments could be considered for populations at higher risk of chronic inflammatory diseases, such as those with genetic predispositions or a history of inflammatory disorders. For example, individuals with early markers of cardiovascular disease could benefit from reduced arterial inflammation, lowering their risk of heart attacks or strokes.

The role of IL-11 in extending lifespan opens up even more futuristic possibilities. The results from preclinical models, where anti-IL-11 therapies increased lifespan by 20%–25%, suggest that targeted inhibition of this cytokine could someday be part of personalized anti-aging interventions.

Looking ahead, IL-11 inhibitors could also have applications in treating metabolic conditions like obesity and diabetes. In aged mice, IL-11 inhibition was associated with better metabolic profiles, including improved fat distribution and glucose regulation. These findings could translate into new treatments for individuals struggling with metabolic dysfunction, particularly those whose conditions are complicated by systemic inflammation.

Overall, the potential implications of IL-11 inhibition on health, illness management, and perhaps prevention are significant and notable. This approach could redefine how we treat inflammation-driven conditions, offering solutions that extend beyond symptom relief to fundamentally alter the trajectory of diseases and aging processes.

Limitations

While IL-11-targeted therapies hold significant promise, several limitations and challenges must be addressed. A primary limitation lies in the complexity of IL-11's functions in the body. IL-11 is not solely a

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driver of inflammation and disease; it also plays roles in normal tissue repair and homeostasis. For example, IL-11 contributes to platelet production and bone remodeling. Blocking IL-11 signaling on a systemic level might interfere with these essential physiological processes, leading to unintended consequences, such as impaired wound healing, altered bone health, or immune dysfunction.

Another significant challenge is the variability of IL-11 expression across individuals and conditions. IL-11's role in cancer and aging appears to depend on specific contexts, such as the type of tissue, the presence of chronic inflammation, or the stage of disease. For example, while IL-11 overexpression is linked to aggressive cancers like gastric and colorectal tumors, it may not be as relevant in cancers with different inflammatory profiles.

The limited understanding of IL-11's regulatory mechanisms is also a challenge. While preclinical studies have identified its association with specific pathways like ERK and mTOR, the broader network of interactions involving IL-11 remains unclear.

From a practical standpoint, there are significant hurdles to translating the success of IL-11 inhibition in animal models to human patients. While mice studies have demonstrated remarkable improvements in lifespan and health span with IL-11 inhibition, human physiology is more complex and diverse.

Conclusion

IL-11 is closely linked to cancer progression and aging, acting as a key driver of inflammation and cellular dysfunction. Targeting IL-11 signaling has shown strong potential in reducing tumor growth, reversing aging-related changes, and improving health span in preclinical models. These findings indicate that IL-11 inhibitors could provide effective treatments for cancers driven by inflammation and chronic diseases associated with aging.

However, challenges such as long-term safety and differences in individual responses remain. Further research, especially in human trials, is essential to address these issues and validate IL-11 inhibition as a therapeutic approach. If successfully developed, IL-11-based therapies could significantly improve the quality of life and outcomes in cancer and aging-related conditions.

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