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Inhibiting IL11: a novel approach to turning back the clock

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Abstract

The World Health Organization recognizes frailty and multimorbidity as major global health issues and underscores the need for effective interventions. Recent advances have identified interleukin-11 (IL-11), a pro-inflammatory cytokine, as a key player in modulating aging pathways (such as ERK, AMPK, mTOR and JAK–STAT3). Studies have shown that IL-11 inhibition can lead to improved health span and lifespan in animal models, with potential applications in humans. By targeting IL-11, researchers aim to mitigate age-related diseases, such as cancer, fibrosis, and multimorbidity, which pose significant healthcare challenges worldwide. IL-11 inhibition offers a promising strategy, with preclinical trials demonstrating its ability to regenerate renal cells, reduce hepatocyte death, and mitigate liver fibrosis. Further research is necessary to fully elucidate the mechanisms of IL-11 inhibition and its therapeutic potential. If successful, this approach could lead to the development of novel pharmacological interventions, promoting healthier aging and increasing human lifespan.

Keywords IL-11 inhibition, Anti-aging therapies, Cellular senescence, Chronic disease prevention, Geroprotective interventions

As we continue to navigate through the complexities of aging and ways to combat it, various options emerge claiming to reverse, halt, or slow down the aging process. Over the past three decades, numerous preclinical studies have been shown to slow aging and increase the healthy lifespan of organisms from yeast, flies, rodents to non-human primates, providing robust evidence that anti-aging interventions can delay and prevent the onset of chronic diseases in adults, potentially extending human health span and lifespan safely and effectively However, only a few genetic pathways have been identified that play a clear role in aging, making the involved genes attractive targets for anti-aging therapies [1].

Currently, various anti-aging interventions are being developed, including caloric restriction mimetics, autophagy inducers, putative cell regeneration enhancers, inhibition of DNA methyltransferase and deacetylase etc. Pro-inflammatory cytokines are one of the key drivers of age-related remodeling. Several factors fuel their release, including cellular senescence, mitochondrial dysfunction, DNA damage, and altered gut microbiota composition. Specifically, elevated levels of well-known cytokines such as IL-6, TNF-α, IL-1, IL-8, CCL2, and CXCL10 are observed in elderly individuals and are associated with conditions like cardiovascular diseases and Alzheimer's disease. Elevated IL-6 levels have also been specifically linked to frailty in age-related conditions, such as Hutchinson-Gilford progeria syndrome [2]. One new addition to the group is IL11, which has been linked with senescence via modulation of multiple aging pathways (such as ERK, AMPK, mTOR and JAK–STAT3).

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This makes IL-11 a potential target for geroprotective interventions [3, 4].

A recent preclinical trial published in Nature by Anissa A. Widjaja et al. depicted that IL-11, a pro-inflammatory and profibrotic cytokine of the IL-6 family, is progressively upregulated across tissues with age [4]. This influences an ERK–AMPK–mTORC1 axis to modulate cellular, tissue- and organismal-level aging pathologies. To explore IL11 as a potential target for anti-aging therapies the researchers conducted parallel rodent experiments to demonstrate the role of IL11 gene deletion and anti IL11 therapy in improving the health span and lifespan of mice. Deletion of the IL11 gene extended the lives of both male and female mice by 24.9% on average. In mice with genetically identical backgrounds, the mouse with the deleted IL-11 gene lived longer with reduced obesity and multimorbidity compared to its counterpart. Administration of anti-IL-11 antibodies to 75-week-old mice (equivalent to age 55 years in humans) until death increased the median lifespan of male mice by 22.5% and of female mice by 25% in addition to improvement in metabolism and muscle function. The mice in the intervention group lived for an average of 155 weeks, compared with 120 weeks in untreated mice [4]. Laboratory findings from the trial identified IL-11 as a senescence-associated secretory factor and confirmed its role in cellular aging through ERK-mTOR activation. In mouse models, IL11 blockade reduced pathogenic ERK signaling and so its notorious role in promoting fibrosis [4, 5].

The trial further revealed that inhibiting IL-11 also has a profound impact on preventing age-related diseases. Mice receiving IL-11 inhibition interventions exhibited reduced cancer incidence, diminished hallmarks of chronic inflammation such as fibrosis, and a decrease in old-age diseases. Remarkably, these findings were replicated in translational studies on human hepatocytes and fibroblasts, underscoring the potential for IL-11 inhibition to have similar outcomes in humans [4]. Researchers have also illuminated the therapeutic promise of anti-IL11 therapy, demonstrating its ability to regenerate renal cells, reduce hepatocyte death, and mitigate liver fibrosis [6–8]. Thus, the role of IL-11 inhibition in preventing and treating age-related diseases is becoming increasingly clear, offering new hope for a healthier and longer life.

Biogerontology is entering a period of rapid development with many leading health bodies, including National Health Service (NHS), and World Health Organization (WHO) acknowledging multimorbidity and frailty as the biggest global healthcare challenges of the 21st century [1]. In context of the current evidence, inhibition of IL11 has a great potential for future pharmacological interventions to slow aging. Thus, human trials need to be initiated to provide cumulative evidence into the subject. However, IL-11 deficiency and IL-11 gene deletion have shown to reduce bone mass, short stature, osteoarthritis, craniosynostosis, increase in bone-marrow adiposity and impaired glucose tolerance [9]. Careful monitoring of these adverse effects is essential in clinical trials. Moreover, additional studies are required to confirm the therapeutic potential of IL-11 inhibition in oncology and fibrotic lung disease, bridging the gap between preclinical evidence and clinical applications. Researchers might benefit more by focusing on a single age related-condition at a time to get quicker results and more specific outcomes. Based on the fact that translational studies have predominantly utilized human hepatocytes to date, focusing on liver pathologies presents a logical starting point.

Abbreviations

DNA	Deoxyribonucleic acid
IL	Interleukin
ERK	Extracellular Signal-Regulated Kinase
AMPK	AMP-Activated Protein Kinase
mTOR	Mechanistic Target of Rapamycin
JAK-STAT3	Janus Kinase-Signal Transducer and Activator of Transcription 3
mTORC1	Mechanistic Target of Rapamycin Complex 1

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OA assessed the original study and did the related literature search. MH extracted the data from all papers and both the authors formulated and reviewed the final manuscript of this informative LTE/correspondence.

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Data availability
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Declarations

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