IL-1 Signaling in Aging and Cancer: An Inflammaging Feedback Loop Unveiled

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Summary

In a *Science* paper, Park et al. identified IL-1α as a key driver of positive feedback in inflammaging, linking aging-associated downregulation of DNMT3A to increased IL-1α production in lung myeloid cells. This triggers emergency myelopoiesis in the bone marrow, amplifying myeloid-mediated intratumoral immunosuppression for tumor progression in aged mice.

Main text

Aging is widely recognized as one of the most significant risk factors for cancer, and these two processes share a variety of hallmarks, within which the most appreciated one is the inflammation[1]. The term "inflammaging" was coined to describe the manifestation of sterile, low-grade, chronic inflammation that develops with age. However, the precise molecular and cellular mechanisms by which inflammaging contributes to tumorigenesis remain unclear. A recent *Science* paper by Park et al. identified Interleukin(IL)-1α as a key molecule elevated during inflammaging and provided a comprehensive understanding of how IL-1α promotes cancer progression[2].

A major advancement in this study is that the connection between tumorigenesis and inflammaging was examined in a systemic manner. Using a genetically faithful non-small cell

lung cancer mouse model, the authors found that the inoculation of tumor cells triggers emergency myelopoiesis, leading to the accumulation of myeloid progenitor-like cells (MPs) and monocyte-derived macrophages (Mo-macs) in the lungs. Although the exact ontogeny of these intratumoral myeloid cells remains elusive, their accumulation is significantly more pronounced in aged mice (Figure 1). Beyond the quantitative differences, MPs from aged mice exhibited a more immature or progenitor-like transcriptome compared to their counterparts from younger mice, alongside elevated IL-1α expression.

While IL-1 family cytokines are known to promote tumor onset and progression through various mechanisms[3], Park et al. discovered novel positive feedback between bone marrow and tumor in the context of aging. They employed sophisticated experimental designs to rule out IL-1 receptor-expressing cells in the lung, the usual suspects, as the primary drivers of tumorigenesis in aged mice. Specifically, they irradiated $Il1r1^{-/-}$ and wild-type (WT) mice and reconstituted them with young or old bone marrows before tumor cell inoculation. For mice receiving young bone marrows, comparing to WT recipients, $Il1r1^{-/-}$ mice exhibited reduced tumor progression; For mice receiving old bone marrows, IL1R1 deficiency did not affect tumor burden.

This experiment conveyed a critical message: while IL-1 promotes tumorigenesis in both young and old animals, the underlying mechanisms differ subtly depending on age. IL-1 signaling in non-hematopoietic cells drives tumor progression in young mice. However, aging shifts the primary target of IL-1 to the hematopoietic lineage. This study identified aged hematopoietic stem and progenitor cells (HSPCs) as the primary cancer-promoting receptacle of IL-1 signaling. During tumorigenesis, IL-1 produced in the lung remotely shifts HSPC differentiation, favoring granulocyte-monocyte progenitors (GMPs) at the expense of lymphoid lineage production. This shift leads to an excessive supply of myeloid cells, including $Trem2^{+}$ Mo-macs, in the lungs (Figure 1). The authors further demonstrated that these Mo-macs are essential for tumor progression: genetic ablation of this population dramatically reduced tumor burden in aged mice. Although it remains uncertain from this study whether bone marrow myeloid cells or their progenitors contribute IL-1 locally, it is clear that aged myeloid cells, both in bone marrow and the tumor, produce IL-1 with an increased propensity. Elevated IL-1 levels strongly bias bone marrow hematopoiesis and supply more myeloid cells to the tumor. This positive feedback loop significantly amplifies immunosuppression within the tumor microenvironment, thereby promoting cancer progression.

How does aging predispose cells to elevated IL-1 signaling? Park et al. pinpointed the molecular mechanism to the aging-associated decline in DNMT3A expression. This decline was revealed by comparing HSC transcriptome datasets from young and aged donors and further validated using human samples from both healthy individuals and patients with non-small cell lung cancer (NSCLC). Ablation of DNMT3A expression in both human and mouse cells led to enhanced expression of IL-1α and IL-1β in Mo-macs, as well as elevated IL1R1 expression in HSCs and GMPs. This coordinated change aligns with enhanced myelopoiesis phenotype observed in aged mice, suggesting that reduced DNMT3A levels directly influence IL-1 signaling pathways. To be noticed, previous studies have shown that aging in mouse HSPCs is associated with global DNA hypermethylation and decreased 5hmC levels[4], rather than hypomethylation, which appears paradoxical given the reduced DNMT3A levels. This paradox suggests that DNMT3A is essential for maintaining a selected DNA methylation landscape in aged HSPCs, particularly for those genes involved in inflammation.

Beyond elucidating these mechanisms, Park et al. also provided valuable insights for cancer intervention. They showed that aged mice receiving young bone marrow cells experienced a significant reduction in tumor burden, which holds important implications for rejuvenating the immune system in elderly individuals. While transfusion of young blood has been shown to reprogram progenitor cells in tissues such as the liver and muscles[5], the dysfunction of bone marrow HSPCs caused by inflammaging cannot be effectively reversed[6]. Although performing transplantation with young bone marrow may currently be clinically and socio-economically unfeasible, advancements in stem cell differentiation protocols provided hope[7]. Human induced pluripotent stem cells (iPSCs) could serve as a more standardized and sustainable source for young HSPCs, offering a potential novel approach for immune system rejuvenation in cancer prevention and treatment.

Due to its critical role in inflammation, many therapeutic agents have been developed to target IL-1 signaling. Interestingly, in the CANTOS trial (NCT01327846), retrospective analysis revealed that Canakinumab, an IL-1β neutralizing antibody, reduced both the incidence and mortality of lung cancer in patients originally treated for atherosclerosis[8]. This finding provided initial evidence that targeting IL-1β signaling could serve as a strategy for cancer prevention and early intervention.

In the current study, Park et al. found that compared to anti-IL-1β treatment, IL-1α inhibition more robustly retarded lung tumor growth in aged mice, suggesting a predominant role for IL-

1α in the context of inflammaging. Bermekimab, an IL-1α-specific antibody, was tested extensively in metastatic colorectal cancer (CRC) (NCT02138422). Although its safety and efficacy profile did not win FDA approval, the Phase 3 study demonstrated clear clinical benefits, especially when patients were stratified by their pre-treatment plasma IL-1Ra levels. In CRC, circulating IL-1Ra is considered a natural IL-1 inhibitor. Clinical responses observed in patients with lower levels of plasma IL-1Ra suggest that Bermekimab may be effective against cancers that are less selected by endogenous IL-1 inhibitors, making them more susceptible to IL-1α antagonism[9].

Moreover, Park et al showed that combining antibodies against both IL-1α and IL-1β, or the small molecule IL1R antagonist Anakinra, produced additive effects in reducing tumor burden in aged lungs compared to mono-targeting strategies. Canakinumab and Anakinra are currently being tested in multiple ongoing clinical trials for solid tumors, either as monotherapies or in combination with standard-of-care chemotherapies, targeted therapies, radiotherapies, or immunotherapies[3]. Many of these trials are nearing completion, and their results are eagerly anticipated.

However, Park et al. also showed that in preclinical animal models, Anakinra treatment only provided benefits when used during the early phase of tumor development. According to their data, elevated IL-1 signaling—particularly its role in emergency myelopoiesis driven by IL-1—is only necessary during the early stages of tumor progression. Indeed, once tumors become established, other cytokines such as GM-CSF can be produced by tumor cells, driving the differentiation of immunosuppressive myeloid cells remotely[10]. Thus, IL-1 signaling is not consistently required for immunosuppression in tumors. This highlights the importance of understanding the time window of IL-1 function for effective clinical trial design. A significant contribution by Park et al. is providing critical insights that could help stratify patients, especially the elderly, for IL-1-targeted therapies at the earliest stages of cancer.

DECLARATION OF INTEREST

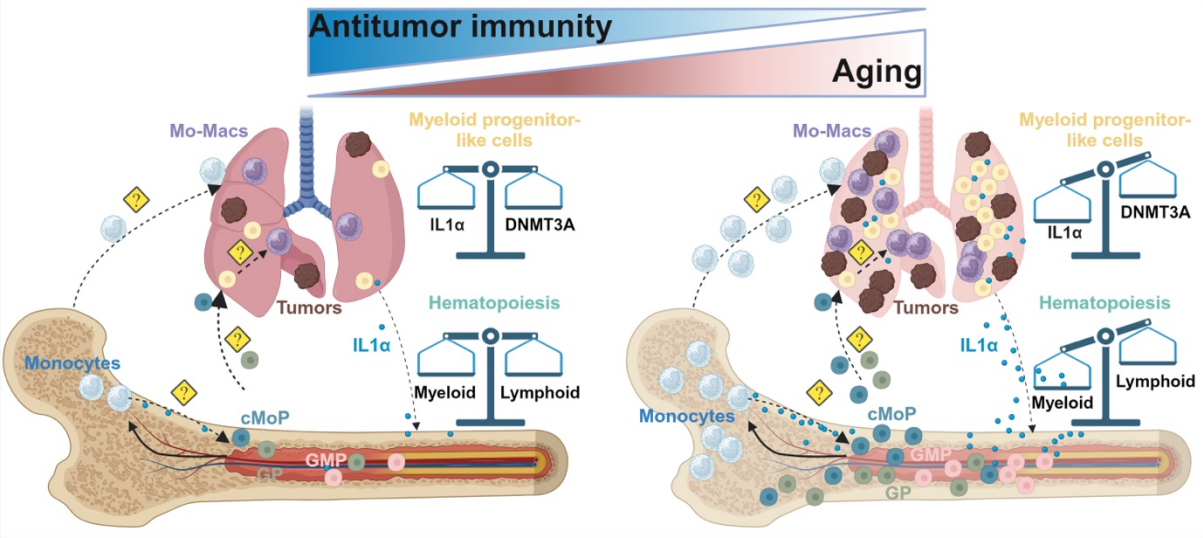
The authors declare no competing interests.

ACKNOWLEDGEMENTS

Q-J.L. is supported by core research grants provided to the IMCB and SIgN by the BMRC, A*STAR and National Research Foundation (NRF) Singapore under the NRF Investigatorship (NRFI09-0016). B.Z. is supported by the fund of the National Natural Science Foundation of China (NSFC. #81925030 and #82230095).

Figure Legend

Figure 1. IL-1α Drives an Inflammaging Feedback Loop Across Organs to Facilitate Cancer Progression.



Myeloid progenitor-like cells (MPs) are more abundant in the lung tumors of aged mice compared to young mice and secrete higher levels of IL-1α, driven by the aging-associated downregulation of DNMT3A expression. IL-1α then acts on hematopoietic stem and progenitor cells (HSPCs) in the bone marrow, inducing emergency myelopoiesis. This process increases the supply of myeloid cells, thereby amplifying immunosuppression within the lung, which ultimately leads to a greater tumor burden. The figure was created in BioRender (BioRender.com/w70v266).

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