



## Tumor-driven organ aging and pre-metastatic niche formation

Haipeng Li<sup>#</sup>, Qing Xu<sup>#</sup>

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Aging and cancer are intimately connected biological processes. Advancing age is accompanied by cellular senescence, chronic inflammation, extracellular matrix (ECM) remodeling, immune dysfunction, and metabolic alterations that collectively generate tissue environments permissive to tumor initiation and progression. Senescent stromal cells are particularly important components of this relationship because their senescence-associated secretory phenotype (SASP) can promote inflammation, matrix remodeling, and malignant-cell fitness<sup>[1,2]</sup>. Consequently, an aging host provides an increasingly favorable microenvironment for the growth and spread of malignant cells.

Although aging is commonly considered an upstream determinant of cancer, evidence also links malignancy to accelerated aging and functional deterioration. Siddique *et al.* reported accelerated functional decline among older cancer survivors<sup>[3]</sup>, while Han *et al.* identified an association between cancer history and phenotypic age acceleration<sup>[4]</sup>. These observational findings cannot isolate the effects of the tumor from those of treatment, comorbidities, and shared risk factors. Providing complementary experimental evidence, Hesterberg *et al.* showed that B-cell lymphoma induces aging-associated changes in T cells and other tissues<sup>[5]</sup>. The remaining question is how specific tumor-derived signals remodel distant organs and whether these changes contribute to metastatic colonization.

A recent study by Liu *et al.* published in *Nature Aging* provides compelling evidence for such a reciprocal relationship. The authors demonstrate that extracellular vesicles (EVs) derived from triple-negative breast cancer cells accumulate in the lung and induce a striking aging-associated phenotype. Mice exposed to tumor-derived EVs exhibited increased Senescence-Associated  $\beta$ -Galactosidase activity and p21 expression, shortened telomeres, enhanced  $\alpha$ -smooth muscle actin expression, collagen deposition, and enrichment of aging-associated transcriptional programs. Suppressing EV secretion through RAB27A depletion substantially attenuated these changes, supporting a causal role for tumor-derived vesicular communication in



Cardiology Division, Department of Medicine, the University of Hong Kong, Hong Kong 999077, China.

<sup>#</sup>These authors contributed equally to this work.

**Correspondence to:** Dr. Haipeng Li, Cardiology Division, Department of Medicine, the University of Hong Kong, Hong Kong 999077, China. E-mail: L1522329018@163.com

remote lung aging<sup>[6]</sup>. Together, these findings suggest that tumors do not merely encounter an aging host environment and support the possibility that tumor-derived signals induce aging-associated remodeling in distant tissues.

The study further identifies Dimethylarginine Dimethylaminohydrolase 1 (DDAH1) as a critical molecular cargo responsible for this phenotype. DDAH1 was enriched in breast cancer-derived EVs and accumulated within pulmonary fibroblasts. Gain- and loss-of-function experiments supported a functional role for EV-associated DDAH1 in promoting lung fibroblast senescence and fibrotic remodeling in the models examined. Single-cell RNA sequencing further revealed an expansion of senescent-like fibroblast populations and increased aging- and fibrosis-related transcriptional programs in tumor-bearing lungs, whereas tumor-specific DDAH1 deletion diminished these phenotypes. Importantly, deletion of tumor-derived DDAH1 was accompanied by reduced pulmonary metastasis, connecting remote tissue aging with metastatic progression rather than treating it as a passive by-product of malignancy.

Mechanistically, Liu *et al.* uncover an unexpected link between tumor metabolism, protein citrullination, and stromal aging. DDAH1 catalyzes the metabolism of asymmetric dimethylarginine to generate citrulline<sup>[6]</sup>. Increased DDAH1 activity consequently results in pulmonary citrulline accumulation, which is sufficient to induce senescence-associated and fibrotic phenotypes. The authors demonstrate that citrulline occupies the functional pocket of peptidyl arginine deiminase 4 (PAD4), thereby interfering with PAD4-mediated citrullination of Transforming Growth Factor Beta 1 (TGF- $\beta$ 1). Reduced TGF- $\beta$ 1 citrullination stabilizes its signaling activity and enhances downstream Smad3 activation in pulmonary fibroblasts. Importantly, genetic loss of PAD4 largely abolished the capacity of citrulline or DDAH1-enriched EVs to induce the aging phenotype, establishing a DDAH1-citrulline-PAD4-TGF- $\beta$ 1/Smad3 axis linking tumor-derived metabolic signals with fibroblast senescence and fibrosis.

These metabolic and stromal effects should also be considered in the context of the genetic alterations underlying cancer. Gene mutations and changes in chromosome number or structure contribute to tumor heterogeneity and evolution. For example, chromosomal instability can promote metastasis through activation of cytosolic DNA sensing pathways. An important question is whether the genetic background of a tumor also influences its capacity to induce senescence in distant tissues. In the context of the findings by Liu *et al.*<sup>[6]</sup>, future studies could examine whether specific genomic alterations affect DDAH1 expression or its packaging into EVs. Such studies would help connect tumor-intrinsic genetic changes with the metabolic signals that remodel distant organ microenvironments.

The conceptual significance of these findings may extend beyond DDAH1 itself. Primary tumors can prepare distant organ microenvironments for subsequent metastatic colonization. For example, Hoshino *et al.* demonstrated that tumor-derived exosomes exhibit organ-specific uptake and contribute to pre-metastatic niche formation<sup>[7]</sup>. Growing evidence indicates that senescent stromal cells are not passive markers of tissue aging but active architects of tumor-permissive niches. In aged bladder tissue, for example, p16-high senescent fibroblasts acquire inflammatory cancer-associated fibroblast features and promote tumor growth through C-X-C motif chemokine ligand 12 secretion, while their elimination suppresses tumor progression<sup>[8]</sup>. These observations establish that physiological aging can generate stromal environments favorable to malignancy. The study by Liu *et al.* extends this paradigm in an important direction: rather than merely exploiting a pre-existing aged microenvironment, tumor cells may actively accelerate aging-like remodeling in distant organs before metastatic colonization<sup>[6]</sup>.

Evidence from aging liver tissue suggests that EV-mediated communication may operate in both directions. Li *et al.* showed that EVs from senescent hepatocytes enhance tumor invasiveness and metastasis in mice through their microRNA (miRNA) cargo. Treatment with the senolytic combination dasatinib and

quercetin, inhibition of P2RX7 (purinergic receptor P2X, ligand-gated ion channel, 7), or silencing of EV-associated miRNAs reduced metastasis in aged mice<sup>[9]</sup>. Together with the findings of Liu *et al.*, these results suggest that senescent host cells can promote malignant behavior, while tumor-derived signals can induce senescence-associated changes in distant tissues. We hypothesize that these processes could form a self-reinforcing cycle; however, such a cycle has not been directly demonstrated within a single experimental system<sup>[6]</sup>.

Several additional questions emerge. First, how organ-specific is tumor-driven aging? The lung is a major metastatic destination for breast cancer and efficiently captures circulating tumor-derived EVs. It remains unclear whether DDAH1-containing EVs similarly affect the liver, bone, brain, cardiovascular system, or other tissues, or whether distinct EV cargoes drive tissue-specific aging programs at different metastatic sites. Mapping circulating tumor-derived signals against organ-specific aging responses could reveal whether systemic malignancy produces a mosaic of accelerated aging phenotypes rather than a uniform whole-body aging process.

Second, the timing and persistence of tumor-induced stromal changes require further investigation. The current findings strongly associate DDAH1-induced pulmonary aging with increased metastasis, but it will be important to determine the precise window during which senescent remodeling becomes permissive for disseminated tumor cells. Does a transient period of tumor-derived signaling establish a durable “aging memory” within distant tissue? Conversely, can removal of the primary tumor reverse this phenotype, or does the senescent and fibrotic niche persist independently after tumor-derived EV exposure ceases? Longitudinal studies following primary-tumor removal or withdrawal of DDAH1-containing EVs could determine whether pulmonary remodeling resolves, persists, or continues to facilitate metastatic colonization.

Third, tumor-induced fibroblast senescence may initiate a broader process of multicellular remodeling. Acosta *et al.* demonstrated that SASP components can transmit senescence through paracrine signaling, providing a mechanistic basis for amplification beyond the initially affected cells<sup>[10]</sup>. Senescent fibroblasts can profoundly influence macrophages, neutrophils, lymphocytes, endothelial cells, and neighboring stromal populations through SASP factors and ECM remodeling. Fibroblast senescence is unlikely to remain a fibroblast-restricted phenomenon. Senescent stromal cells can remodel extracellular matrix architecture and profoundly influence neighboring immune populations. In pancreatic cancer, senescent cancer-associated fibroblasts have been shown to restrict CD8<sup>+</sup> T-cell activation and impair responsiveness to immunotherapy, while age-associated fibroblast and extracellular-matrix remodeling has been linked to immune exclusion and metastatic behavior<sup>[11]</sup>. These observations suggest that tumor-induced fibroblast senescence may represent an initiating event in a broader multicellular reprogramming process rather than an isolated stromal phenotype. The resulting niche may therefore represent a multicellular aging ecosystem rather than a fibroblast-restricted phenotype.

Pulmonary fibrosis, cellular senescence, and inflammation may reinforce one another within this microenvironment. Senescent fibroblasts could sustain inflammatory and profibrotic signaling through the SASP; persistent inflammatory stress could promote additional senescence, while ECM accumulation and altered tissue mechanics could maintain fibroblast activation and impair repair. The DDAH1-citrulline-PAD4-TGF- $\beta$ 1/Smad3 pathway described by Liu *et al.* provides a potential entry point into this proposed feedback network<sup>[6]</sup>. However, the coexistence of senescence markers and collagen deposition does not by itself establish the direction of these interactions. Temporally controlled, cell-type-specific interventions would help determine whether fibroblast senescence initiates remodeling, maintains an established niche, or has different roles at different stages.

More broadly, the work raises the possibility that senotherapeutic strategies could intersect with metastasis prevention. Senolytics that eliminate persistent senescent stromal cells or senomorphics that suppress detrimental SASP programs could theoretically make distant tissues less hospitable to disseminated cancer cells. Yet senescence is heterogeneous and context-dependent, and indiscriminate elimination of senescent cells may interfere with wound healing, tissue repair, or tumor-suppressive responses. The therapeutic goal may therefore not be to eliminate senescence globally, but to identify and selectively disrupt tumor-educated senescent states that facilitate metastatic colonization.

The study by Liu *et al.* thus expands the relationship between cancer and aging from a predominantly one-directional paradigm into a reciprocal process<sup>[6]</sup>. Aging can create environments that support cancer, but cancer may in turn accelerate aging in distant tissues and exploit the resulting microenvironment for its own dissemination. The DDAH1-citrulline-PAD4-TGF- $\beta$ 1 axis provides a mechanistic example of how such communication can occur and establishes fibroblast senescence as an actionable component of the metastatic niche. Future studies defining the persistence, organ specificity, multicellular propagation, and clinical relevance of tumor-induced aging will determine how broadly this paradigm applies. Ultimately, preventing metastasis may require not only targeting the migrating seed, but also preventing the tumor from prematurely aging the distant soil in which that seed is destined to grow.

## DECLARATIONS

### Authors' contributions

Conceptualization, visualization, writing - original draft: Li H

Methodology, supervision: Xu Q

Investigation, writing - review & editing: Li H, Xu Q

### Availability of data and materials

Not applicable.

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### Consent for publication

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