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Peripheral Ischemia Fuels Breast Cancer Via Myeloid-Skewed Hematopoiesis

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Adult cancer survivors exhibit higher rates of myocardial infarction, heart failure, and stroke than the general population,[1] while patients with pre-existing cardiovascular disease are disproportionately likely to develop new or metastatic cancers over time.[2] However, the mechanistic details of this harmful reciprocity remain unresolved. Peripheral ischemia, long recognized as a driver of cardiovascular morbidity, is now shown to influence tumor biology directly. Chronic reductions in perfusion expose skeletal muscle to repeated cycles of hypoxia-reperfusion, triggering a cytokine storm and danger-associated molecular patterns that flood into the circulation and seed the bone marrow.[3] That type of systemic inflammatory insults can imprint long-lived adaptations in bone marrow hematopoietic stem and progenitor cells (HSPCs) through epigenetic remodeling that endows their myeloid progeny with "trained" innate immune memory.[4] Such imprinting sustains chronic myeloid bias and low-grade inflammation, phenomena believed to heighten susceptibility to a broad spectrum of age-related disorders,[5] including malignant transformation and cancer progression.

In this issue of *JACC: CardioOncology*, Newman et al[6] present murine data showing that hind limb ischemia, a surrogate for peripheral artery disease (PAD), accelerates mammary tumor growth by epigenetically rewiring bone marrow progenitors toward an inflammatory, myeloid-biased state (age-mimicking low-grade inflammation generated by myeloid-skewed hematopoiesis or "inflammaging").[6] In the study hind limb ischemia in mice doubled the growth of orthotopic breast tumors regardless of whether the vascular insult preceded or followed tumor implantation. Tumor acceleration coincided with sustained expansion of circulating Ly6C^{hi} monocytes and neutrophils, enrichment of immunosuppressive myeloid cells and regulatory T lymphocytes within the tumor microenvironment, and a marked shift of bone marrow hematopoiesis away from balanced output toward a myeloid bias reminiscent of age-related "inflammaging." Single-cell RNA and ATAC profiling located the epicenter of this shift in NLRP3-positive monocyte-dendritic progenitors, which acquired permissive chromatin at inflammatory and aging loci (eg, Il1b, Thbs1, Neo1) and lost accessibility at CEBP family sites that ordinarily support granulopoiesis. Strikingly, transplantation of HSPCs harvested 3 weeks after ischemia transferred the myeloid-skewed program and the capacity to accelerate tumor growth to naïve recipients, suggesting durable epigenetic reprogramming rather than transient mobilization. There, HSPCs abandon balanced lymphomyelopoiesis in favor of emergency myelopoiesis, releasing monocytes and neutrophils primed for inflammatory crosstalk with nascent tumors. These results broaden the "reverse cardio-oncology" framework by showing that a vascular insult itself, independently of chemotherapy or radiation, could directly reprogram tumor behavior. These insights align with epidemiological data associating PAD with higher cancer incidence and with clinical observations that blockade of interleukin (IL)-1β lowers both cardiovascular and cancer-related mortality.[7,8]

Despite its mechanistic depth, the study has limitations that must be addressed before its findings can be directly extrapolated to clinical care. The model employs acute femoral artery ligation in young

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female mice, whereas human peripheral artery disease is typically chronic, multifocal, and accompanied by comorbidities such as diabetes, renal insufficiency, and advanced age that themselves modify immunity. Only one tumor type and one sex were studied, leaving open the question of generalizability across malignancies and host backgrounds. Mechanistic attribution to the IL-1/NLRP3 axis remains correlative; the study did not include pharmacologic or genetic interruption of inflammasome signaling, nor did it explore alternative mediators such as sympathetic drive, β-adrenergic signaling, or microbiome shifts that have been implicated in other cardio-oncologic models.[9] Future work should model chronic ischemia, incorporate both sexes and additional tumor types, and test whether reversing the myeloid bias, through cytokine inhibition, β-blockade, or epigenetic modifiers, can decelerate tumor growth without impairing limb repair. Finally, the observation period ended before overt metastasis, so the impact of ischemia on dissemination and long-term survival is unknown.

Despite these caveats, the findings carry practical implications. They suggest that patients with PAD, whether overtly symptomatic or clinically silent, might benefit from intensified oncologic surveillance. They also provide scientific premise for trials designed to evaluate drugs capable of blocking the inflammasome or IL-1 in the PAD population, using a combined endpoint that includes both cardiovascular and cancer outcomes. Exercise rehabilitation and revascularization, long-standing pillars of PAD care, should be evaluated for their capacity to normalize hematopoietic output and restore lymphoid competence. Finally, exploration of epigenetic reversibility of hematopoietic programming using demethylating agents, histone deacetylase inhibitors, or targeted CRISPR (clustered regularly interspaced short palindromic repeats) epigenome editing to restore balanced lymphomyelopoiesis. Together, these lines of inquiry will turn a mechanistic mouse observation into actionable cardio-oncologic therapy and prevention.

Newman et al remind us that the vascular bed is not a passive bystander in cancer, but rather is an active participant whose insults reverberate through the immune system and into the tumor. Their study alerts the cardio-oncology community to look beyond cancer therapy cardiotoxicity and toward the vascular injuries that patients bring with them to the clinic. Addressing those injuries could open a new avenue for controlling tumor growth in patients with PAD.

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REFERENCES

1. Florido R, Daya NR, Ndumele CE, et al. Cardiovascular disease risk among cancer survivors: the Atherosclerosis Risk In Communities (ARIC) Study. *J Am Coll Cardiol*. 2022;80(1):22–32.

2. Bell CF, Lei X, Haas A, et al. Risk of cancer after diagnosis of cardiovascular disease. *JACC CardioOncol*. 2023;5(4):431–440.

3. Coppin E, Zhang X, Ohayon L, et al. Peripheral ischemia imprints epigenetic changes in hematopoietic stem cells to propagate inflammation and atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2023;43(6):889–906.

4. Netea MG, Dominguez-Andres J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol*. 2020;20(6):375–388.

5. Ross JB, Myers LM, Noh JJ, et al. Depleting myeloid-biased haematopoietic stem cells rejuvenates aged immunity. *Nature*. 2024;628(8006):162–170. https://doi.org/10.1038/s41586-024-07238-x

6. Newman AAC, Barcia Durán JG, Von Itter R, et al. Ischemic injury drives nascent tumor growth via accelerated hematopoietic aging. *JACC CardioOncol*. 2025;7(5):559–577.

7. Koelwyn GJ, Newman AAC, Afonso MS, et al. Myocardial infarction accelerates breast cancer via innate immune reprogramming. *Nat Med*. 2020;26(9):1452–1458.

8. Ridker PM, MacFadyen JG, Thuren T, et al. Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;390(10105):1833–1842.

9. Avraham S, Abu-Sharki S, Shofti R, et al. Early cardiac remodeling promotes tumor growth and metastasis. *Circulation*. 2020;142(7):670–683.

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