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EDITORIAL COMMENT

Cross-Disease Communication in Cardiovascular Disease and Cancer*

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Cardiovascular disease (CVD) and cancer continue to lead the global causes of mortality, with a growing body of epidemiologic and preclinical studies supporting a bidirectional relationship between these 2 diseases. Cancer and its treatments have been shown to heighten the risk of CVD in cancer survivors.[1,2] Additionally, studies are emerging that suggest a reciprocal relationship wherein cardiovascular events can accelerate tumor growth or cancer progression in animal models and humans. In this issue of *JACC: CardioOncology*, Tani et al[3] identify the cardiac release of nerve growth factor (NGF) and its signaling via the tropomyosin receptor kinase A (TRKA) pathway as regulators of tumor cell proliferation after myocardial infarction (MI).

Historically, the field of cardio-oncology has focused on understanding how cancer, particularly its treatments, heighten the risk of developing CVD.[4] However, as cardio-oncology continues to evolve and integrate itself into standard cancer patient care, the following pivotal question has surfaced: Can underlying CVD or incident cardiovascular events influence cancer-specific outcomes? Numerous studies have established that CVD can influence systemic immune responses and metabolism, thereby exacerbating comorbid conditions characterized by chronic inflammation, such as atherosclerosis and diabetes.[5,6] That said, how such systemic dysregulations influence cancer pathogenesis is only beginning to be understood.[7] Cancer and CVD share a multitude of common risk factors, including obesity, hyperlipidemia, and inflammation.[8] Furthermore, several epidemiologic studies have shown associations between CVD and cancer incidence,[9-12] linking a cardiovascular event before and/or after cancer diagnosis with worsened cancer outcomes. There have also been a handful of functional studies in recent years showing that cardiovascular pathologies, including MI, post-MI heart failure, and pressure overload cardiac hypertrophy, can accelerate primary tumor burden in mice.[13-15] Both cardiac-derived factors[13,15,16] and immune-related mechanisms[14] have been proposed to participate, yet much remains unknown about the mechanisms underlying CVD-induced tumor growth.

Tani et al[3] now demonstrate that heart failure hastens the growth of mammary tumors orthotopically implanted 2 weeks post-MI in BALB/c mice. Immunohistochemical and RNA sequencing analysis of mouse 4T1 mammary tumors 5 weeks after ligation of the left anterior descending coronary artery revealed an increase in Ki67^{+} proliferating cells and a transcriptomic profile suggestive of cell cycle and activation of the phosphoinositide 3-kinase (PI3K)-AKT/protein kinase B pathway,[3] which has been previously linked to breast tumor progression.[17] Interrogation of 2 known ligands of the PI3K-AKT pathway, NGF and brain-derived neurotrophic factor, identified an up-regulation of NGF in the infarcted myocardium 3 days after MI and a sustained increase in NGF in circulation out to 5 weeks post-MI. NGF, known for its high binding affinity with TRKA, activates target gene expression crucial for neuronal survival and development.[18] Tani et al[3] observed increased phosphorylation of tumoral TRKA, AKT,

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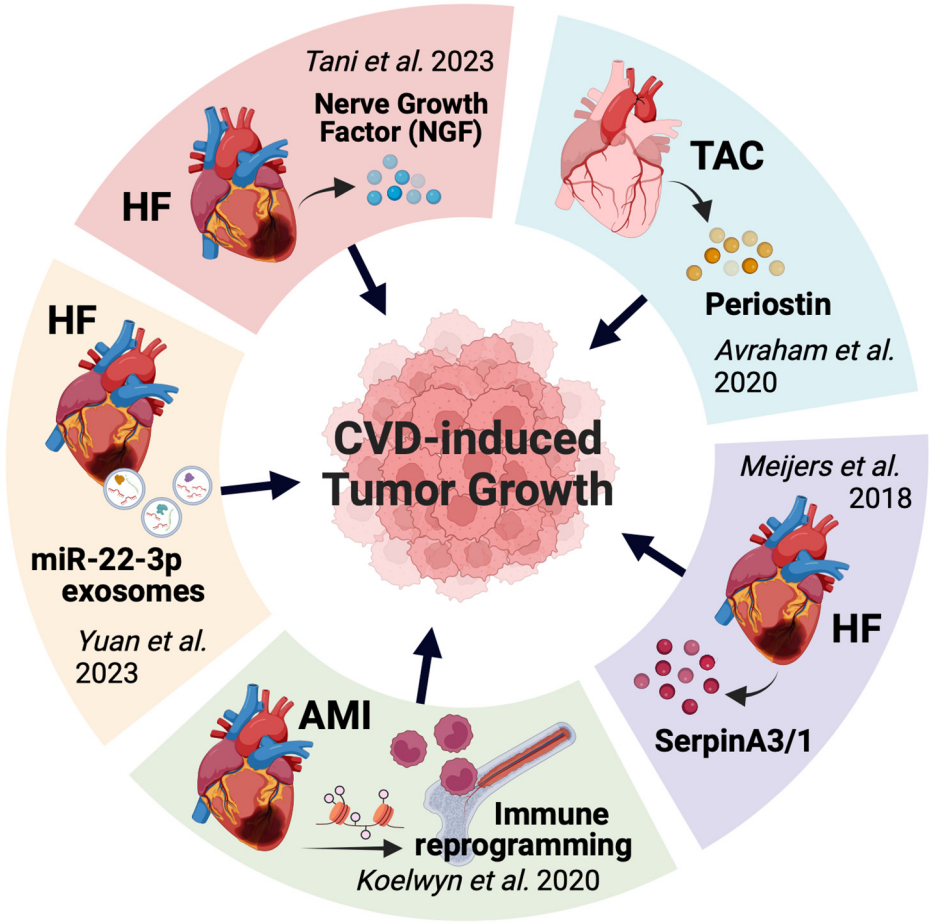
FIGURE 1 Mechanisms of Detrimental Cross-Talk Between CVD and Cancer



Preclinical studies have identified several mechanisms that may underlie the stimulatory effects of acute myocardial infarction (AMI), post-MI heart failure (HF), and transverse aortic constriction (TAC)-induced cardiac hypertrophy on tumor growth. These include cardiac release of nerve growth factor (NGF),[3] periostin,[15] serpinA3,[13] and exosomes carrying miR-22-3p,[16] as well as epigenetic reprogramming of innate immune progenitor cells in the bone marrow.[14] Biorender was used to generate this figure. CVD = cardiovascular disease.

and extracellular signal-regulated kinase after MI, implicating the NGF-TRKA axis in MI-stimulated tumor growth.

In the infarcted heart, NGF elaborated by cardiomyocytes is reported to prevent pathological ventricular remodeling. Interestingly, NGF has also been found to be expressed in breast cancer tissue, and studies have demonstrated that it contributes to tumor cell growth and survival as well as invasion and metastasis.[19] Thus, although cardioprotective, increased circulating NGF levels may stimulate the growth of coincident tumors. Indeed, Tani et al[3] showed that exposure of 4T1 tumor cells to exogenous NGF in vitro increased phosphorylation of AKT and extracellular signal-regulated kinase as well as cell proliferation. Notably, silencing of TRKA using small interfering RNA or pharmacologic inhibition attenuated NGF-induced AKT phosphorylation and tumor cell proliferation. To determine whether TRKA inhibition could suppress MI-induced tumor growth, Tani et al[3] treated mice with GW441756, a potent and selective TRKA inhibitor, twice weekly for 3 weeks after 4T1 tumor implantation. They observed a marked decrease in tumoral AKT phosphorylation and cell proliferation in the absence of changes in the tumor immune microenvironment or expression of inflammatory cytokines.[3] Importantly, post-MI TRKA inhibition showed no adverse effects on left ventricular function or infarct size in the treated mice, suggesting that targeting TRKA signaling may be a

promising approach to treat heart failure patients with coincident breast cancer. Indeed, 2 tropomyosin receptor kinase (TRK) inhibitors, larotrectinib and entrectinib, are Food and Drug Administration approved for the treatment of cancers with chromosomal rearrangements of *NTRK* resulting in *TRK*-fusion proteins and have shown durable antitumor activity in patients with TRK fusion-positive cancer regardless of tumor type.[20] Further preclinical studies of TRK inhibition in heart failure-induced tumor growth are warranted and should consider different cancer types and mouse models and strains.

The identification of NGF-TRKA signaling as a contributor to MI-accelerated tumor growth adds to our growing understanding of the mechanistic cross-talk between heart failure and cancer. Mounting experimental evidence suggests that a number of systemic changes, as well as factors secreted from the failing heart, contribute to accelerated growth of multiple tumor types (**Figure 1**). A study by Meijers et al[13] first shed light on this causal relationship in a mouse model of precancerous colon adenomas in which post-MI heart failure was found to increase tumor growth independent of hemodynamic changes. From a screen of proteins secreted by the failing heart, the authors identified alpha-1-antichymotrypsin/serine proteinase inhibitor A3 as a regulator of tumor proliferation via phosphorylation of AKT and rpS6.[13] A subsequent study by Avraham and colleagues[15] showed that plasma from mice subjected to transverse aortic constriction, a model of pressure overload-induced cardiac hypertrophy, increased proliferation of breast and lung cancer cell lines and identified periostin as a circulating factor released during cardiac remodeling that accelerated tumor growth. Post-MI exosome release has also been reported to facilitate tumor growth by delivering microRNA cargo that can inhibit cell death mechanisms.[16] An alternative mechanism was identified by Koelwyn et al[14] through which MI accelerates breast cancer growth via innate immune cell reprogramming.

Although the study by Tani et al[3] provides independent corroborative evidence that MI-induced heart failure can accelerate breast cancer, a number of differences between the various studies indicate that further investigation is needed to better understand this relationship. First, unlike the study by Meijers et al,[13] Tani et al[3] noted no correlation between accelerated tumor growth and metrics of cardiac remodeling, such as left ventricular ejection fraction or myocardial fibrosis. Furthermore, although Koelwyn et al[14] reported changes in the immune cell composition of mammary tumors post-MI in 2 independent mouse breast cancer models (E0771 and MMTV-PyMT), Tani et al[3] observed no differences in the tumoral immune landscape of 4T1 mammary tumors post-MI. The different mouse strains (BALB/c vs C57BL/6) used as well as the potential variation in antigen presentation among the different tumor lines studied likely contribute to these discrepant findings; thus, further studies investigating common mechanisms underlying heart failure-induced oncogenesis are warranted. Finally, there is a lack of consensus among the various studies of the effects of MI and heart failure on tumor metastasis, with some studies supporting increased metastatic outgrowth of tumors post-MI[14,15] and others reporting no change.[3] Because metastatic disease accounts for approximately 90% of cancer-related deaths,[21] clarification of the relationship between post-MI heart failure and tumor metastasis will be critically important. Nonetheless, the aforementioned studies taken together strongly support detrimental cross-disease communication between MI-induced heart failure and cancer and the importance of understanding the mechanistic underpinning of "reverse cardio-oncology."

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