From Studying Heart Disease and Cancer Simultaneously to Reverse Cardio-Oncology

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ON MY MIND

From Studying Heart Disease and Cancer Simultaneously to Reverse Cardio-Oncology

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Clinical observations have shown that cancer is an important contributor to noncardiac mortality in patients with heart failure (HF), and that patients with HF are at increased risk for developing cancer. These correlations can be explained in part by the many shared risk factors that underlie both diseases, including aging, obesity, and smoking,[1] but the mounting experimental evidence for a causal relation between HF and cancer should prompt the scientific and clinical community to reconsider the relationship of these 2 diseases. HF and cancer are associated with systemic manifestations, and it is becoming increasingly apparent that an important cross talk exists. We have termed this phenomenon "reverse cardio-oncology"[1] (Figure).

Several preclinical studies have now shown that the failing heart itself and systemic changes in response to HF may directly affect tumor growth in various ways, independent of shared risk factors.[2–4] Meijers et al[2] first reported this causal relation by showing that intestinal polyp growth in tumor-prone *Apc*^{Min} mice was increased when HF was provoked by myocardial infarction. Corroborative evidence that myocardial infarction–induced HF can accelerate tumor growth was provided in a recent study by Koelwyn et al,[3] who showed in 2 independent mouse breast cancer models that tumor growth was significantly increased in mice subjected to myocardial infarction. Last, Avraham et al[4] recently further validated this concept, showing that tumor growth was also stimulated in mice subjected to transverse aortic constriction, leading to pressure overload–induced cardiac hypertrophy, which resulted in increased tumor growth in mouse xenograft models for breast cancer and lung cancer.

Because HF treatments have improved over the past years, more patients will die of noncardiac causes, among which cancer is an important contributor. Therefore, we should explore further the cross talk between HF and cancer. First, it is imperative to map the clinical scope of the problem. To date, limited clinical data are available on the HF-cancer connection. More precise clinical transdisciplinary phenotyping will be needed to obtain a better understanding of which cancer types are commonly affected by HF, and to distinguish differences in HF subtypes. In addition, specific screening protocols should be developed to detect cancer in patients with HF, allowing early and timely diagnosis and potentially increasing survival. Second, we need to conduct more basic studies to define the mechanisms of this cross talk. The evidence published so far points to 2 major potential mechanisms involved in the HF-induced tumor growth: (1) secreted factors and (2) immune cell reprogramming, but underlying mechanisms remain to be studied.

On one hand, Meijers et al presented evidence that secreted circulating factors play a role in HF-induced tumor growth by showing that HF induced tumor growth independent of hemodynamic changes.[2,4] Several promising circulating proteins were identified, of which SerpinA3 showed proliferative effects in vitro.[2] Avraham et al[4] then showed that treatment with plasma from transverse aortic constriction-operated mice led to increased proliferation of multiple cancer cell lines. They identified periostin as a promising circulating factor and showed that periostin-depleted plasma no longer led to proliferation. These data collectively support the hypothesis of HF-induced circulating factors promoting tumor growth. Secreted factors could be of clinical relevance as bio-

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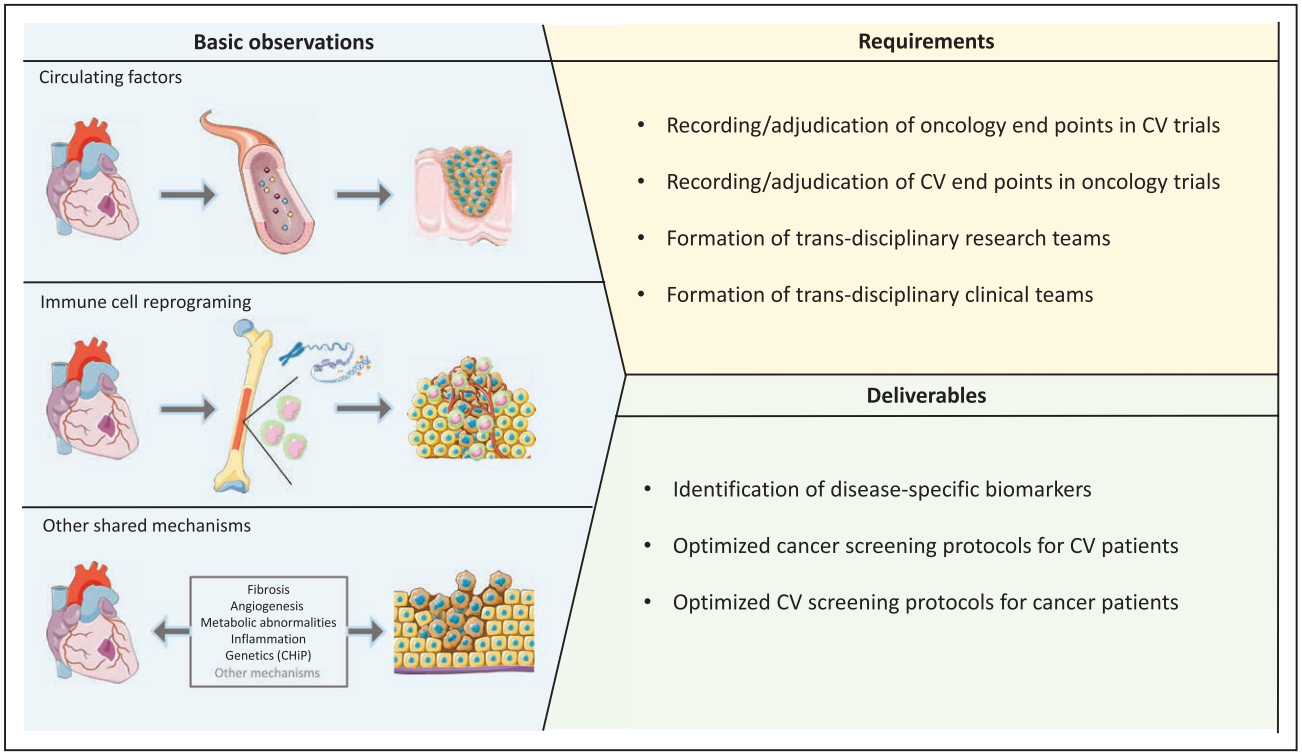

Figure. Reverse cardio-oncology: the effect of heart disease on tumor growth.
Accumulating evidence is suggesting that a bidirectional relation between heart failure (HF) and cancer exists. Several preclinical studies have shown that the failing heart can stimulate tumor growth directly, independent of shared risk factors. Mechanisms have been identified that could underlie HF-induced tumor growth, including secreted circulating factors and HF-induced immune cell reprogramming. In addition, HF and cancer are characterized by several shared mechanisms that are likely to also play a role in the HF-induced tumor growth. These studies are revealing that complex cross talk between HF and cancer exists. We therefore call for more focus on the field of reverse cardio-oncology. It is imperative to study how the preclinical findings translate to humans, so that early screening protocols for cancer in patients with HF can be set up. In addition, it is essential to further unravel the underlying mechanisms involved, which can help identify potential biomarkers or targets for therapeutics. CHIP indicates clonal hematopoiesis of indeterminate potential; and CV, cardiovascular.

markers for increased cancer risk, or as biotargets for therapeutic strategies. Therefore, identifying the key players and the underlying mechanisms has high priority.

On the other hand, Koelwyn et al[3] presented compelling evidence that HF accelerates breast cancer growth through immune cell reprogramming. They showed that increased tumor growth was accompanied by an epigenetically induced increase in monocytic myeloid–derived suppressor cells in the tumor tissue. Selective depletion of CCR2^{+} monocytes resulted in less tumor growth in mice with HF, nearly comparable to control levels, indicating the importance of the monocytic myeloid–derived suppressor cells in HF-induced tumor growth. CCL2 overexpression has been shown to stimulate tumor growth in several types of cancer and the CCL2/CCR2 axis has attracted interest as a therapeutic target for cancer in the past years, leading to the discovery of several CCR2 inhibitors that are currently evaluated in clinical trials.[5] Combination of such treatments with HF therapies could be an interesting strategy addressing both diseases simultaneously. Furthermore, the CCL2/CCR2 axis also has been associated with atherosclerosis and metabolic disease, suggesting that HF may not only trigger tumor growth but also systemic dysfunction through interorgan communication.

Avraham et al[4] presented contradictory results about the role of the immune system in HF-induced tumor growth; in their hands, HF did not lead to changes in tumor and blood immune cell populations. In addition, transverse aortic constriction–operated NOD/SCID mice showed a similar increase in tumor growth as transverse aortic constriction–operated C57BL/6 mice.[4] This underscores the complexity of this bidirectional interplay between HF and cancer and emphasizes the need to further study the precise cells, proteins, and dynamics involved in the underlying mechanisms. Besides secreted factors and the immune system, several other mechanisms are involved in the pathogenesis of both diseases, such as fibrosis, metabolism, and angiogenesis, which are likely to play a role in HF-induced oncogenesis as well and should be considered in future research.

The mounting evidence that HF and cancer are connected serves as an incentive to develop strategies that simultaneously study the 2 diseases and their connections in experimental studies and clinical cohorts and trials (Figure). Mechanistic studies coming in at steady

pace not only form the foundation for future clinical surveillance, diagnosis, and treatment, but shift the paradigm for the clinical community to reconsider the HF-cancer connection and recognize the bidirectional cross talk between them.

ARTICLE INFORMATION

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