Inflammation in cardio-oncology: beyond immunotherapies

Anne Lise Ferrara1, Stefania Loffredo1,2,3,4, and Carlo Gabriele Tocchetti 1,4,5,6*

1Department of Translational Medical Sciences, Federico II University, Naples, Italy; 2Institute of Experimental Endocrinology and Oncology (IEOS), National Research Council, Naples, Italy; 3World Allergy Organization (WAO) Center of Excellence, Naples, Italy; 4Center for Basic and Clinical Immunology Research (CISI), Federico II University, Naples, Italy; 5Interdepartmental Center of Clinical and Translational Sciences (CIRCET), Federico II University, Naples, Italy; and 6Interdepartmental Hypertension Research Center (CIRIAPA), Federico II University, Naples, Italy

This editorial refers to ‘Rescue of cardiac dysfunction during chemotherapy in acute myeloid leukaemia by blocking IL-1α’, by X. Zhou et al., https://doi.org/10.1093/eurheartj/ehae188.

Role of IL-1α in cardiac dysfunction during chemotherapy for acute myeloid leukemia

An antibody, anti-IL1, secreted by necrotic cancer cells treated with daunorubicin is able to block cardiac dysfunction caused by metabolic disturbance

DNR, daunorubicin; IL1R, interleukin 1 receptor; PGC1α, peroxisome proliferator-activated receptor-gamma co-activator 1α; TCA, tricarboxylic acid

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* Corresponding author. Tel: +39 081 746 2242, Emails: carlogabriele.tocchetti@unina.it, cgtocchetti@gmail.com

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The link between metabolic alterations and cardiac dysfunction has been extensively studied for decades,1–3 arguably reaching its peak with sodium–glucose co-transporter 2 (SGLT2) inhibitors being used as heart failure (HF) drugs (and not simply as antidiabetic drugs).2,4 Metabolic alterations are also central in anthracycline cardiotoxicity, with production of reactive oxygen species (ROS) always being considered to play a central role in these processes.6,7 Doxorubicin (DOXO) deranges Fe2+ metabolism, leading to activation of ferroptosis through ROS production, disruption of IRP-1 activity, and iron accumulation into mitochondria. These events are hallmarks of mitochondrial dysfunction that leads to a block of fatty acid oxidation (FAO) and an enhancement in glycolysis, as a consequence of AMP-activated protein kinase (AMPK) inhibition. Acetyl-CoA carboxylase (ACC), a direct downstream target inhibited by AMPK, is overactivated and catalyses the formation of malonyl-CoA, blocking FAO irreversibly. At the plasma membrane, DOXO stimulates glucose uptake via GLUT4 through insulin-mediated activation of AMPK and AKT2. In addition, DOXO increases the expression of GLUT1, an insulin-independent glucose transporter, normally absent in the adult heart. Following the insulin desensitization induced by tumour-secreted factors, AKT1 signalling is disrupted and promotes FOXO1 nuclear translocation, initiating the activation of the apoptotic pathway through the expression of proapoptotic members of the Bcl-2 family. Finally, DOXO cardiomyopathy has been associated with dysregulation of autophagy. DOXO inhibits autophagy by activating mitochondrial target of rapamycin (mTOR) or by blocking AMPK, resulting in accumulation of undegraded autophagosomes and mitochondrial dysfunction with augmented generation of ROS.8 More recently, Gamble and colleagues have shown impairment of high-energy phosphate metabolism in the myocardium and skeletal muscle of patients with breast cancer following anthracycline chemotherapy.2

In this issue of the European Heart Journal, by performing a very large number of experiments, Zhou and colleagues10 investigated the role of the cross-talk between the tumour and the heart in the induction of acute cardiac dysfunction during chemotherapy. The authors show that cardiotoxicity of the anthracycline daunorubicin (DNR) in a mouse model of acute myeloid leukaemia (AML) is associated with disrupted cardiac metabolism and mediated by interleukin 1α (IL-1α) released by tumour cells in response to DNR (and possibly other cytotoxic chemotherapy).8 This suppresses peroxisome proliferator-activated receptor-gamma co-activator (PGC)-1α transcription via IL-1 receptor type 1 (IL1R1)/NF-xB. Moreover, they show that blockade of IL-1α prevents DNR cardiotoxicity. Hence, the authors bring up the concept that cancer may play a major role in the development of anticancer-related cardiotoxicity and that the latter may be prevented by tackling the mechanisms of the interaction between cancer and anticancer drugs (Graphical Abstract).

The mechanism hypothesized here is of particular interest. The involvement of IL-1α further supports the evidence that abnormal inflammation is a common driver of cardiovascular disease (CVD) and cancer.11 HF is characterized by a state of low chronic systemic inflammation, with enhanced circulating concentrations of inflammatory cytokines, among which are tumour necrosis factor-α (TNF-α), IL-1, and IL-6. As stated, there is a huge literature (reviewed by Russo and colleagues9) supporting the role of metabolic derangements in anthracycline cardiotoxicity, but the involvement of inflammatory cytokines in these metabolic alterations induced by anthracyclines is a novel concept. Interestingly, a recent paper from the Rassaf lab12 in a previous issue of the European Heart Journal, for the first time in a mouse model of anti-PD1-therapy also showed dysregulated metabolism, with changes in cardiac protein expression most commonly related to oxidative phosphorylation, inner mitochondrial membrane complexes, and the regulation of ATPase activity. Michel and colleagues12 also recapitulated their animal findings in a series of patients. Blockade of TNF-α was assessed as a novel preventive treatment for early stages of cardiotoxicity, similar to what has been observed by Zhou and co-workers10 with IL-1α. Michel and collaborators12 also found that left ventricular (LV) dysfunction was detected in tumour-bearing mice upon anticancer therapy but not in tumour-free (TF) mice treated with immune checkpoint inhibitor therapy, analogously to what has been highlighted by Zhou and colleagues in their study,10 who, indeed, identified tumour cell-derived IL-1α as a primary factor leading to DNR-induced cardiotoxicity. This latter finding is very relevant, since the authors used a low dose of anthracycline more similar to that administered in clinical practice. At a higher dose, DNR cardiotoxicity was also observable in TF mice, but this is due to the fact that high-dose DNR could induce necrosis in normal marrow cells and IL-1α would then be released from them, which suggested that the cardiotoxicity caused by high-dose DNR might be partially explained by increased plasma IL-1α. This is in line with older studies that demonstrated that only a small amount of i.v. DNR accumulates in the heart,13 supporting the hypothesis that, in addition to its direct effects on cardiomyocytes, other mechanisms underlie its cardiotoxicity. Hence, in this new hypothesized mechanism, it is the cross-talk between tumour cells and cardiomyocytes during chemotherapy that could disturb cardiac energy metabolism and impair heart function. Of note, the IL-1α-neutralizing antibody that was shown to limit cardiac dysfunction by improving cardiac metabolism in AML + DNR mice did not affect the antitumour activity of the drug.

More specifically, cardiac dysfunction induced in this DNR model was associated with expansion of cardiac fibroblasts. The increased percentage of fibroblasts might be related to the reduction in the number of cardiomyocytes caused by DNR cardiotoxicity. This is a part of the body’s response to cardiac injury and is associated with the process of reparative fibrosis. The expansion of cardiac fibroblasts, which are key effector cells in cardiac fibrosis, is primarily driven through the activation of resident cell populations in the heart. These activated fibroblasts are critical for maintaining structural integrity in the damaged ventricular area.14 In addition, a previous study showed that fibroblast-specific IL-1R1 knockout could reduce adverse cardiac remodelling,15 indicating that tumour-derived IL-1α might mediate the expansion of fibroblasts via IL-1 signalling in AML patients.

The previous experience of IL-1β blockade with canakinumab in the CANTOS trial16 points out that identifying crucial players of the inflammatory response is essential to tackle both cancer and CVD. In conclusion, targeting IL-1α might be a promising strategy for alleviating chemotherapy-induced cardiotoxicity in AML patients. More in general, this intriguing finding adds to the evidence that inflammation is indeed at the crossroads between cancer, cardiotoxicity of anticancer therapies, and HF.11

Disclosure of Interest
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