Cardiac dysfunction in cancer patients: beyond direct cardiomyocyte damage of anticancer drugs. Novel cardio-oncology insights from the joint 2019 meeting of the ESC Working Groups of Myocardial Function and Cellular Biology of the Heart

Short title: Novel cardio-oncology insights

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ABSTRACT

In the Western countries cardiovascular disease and cancer are the leading causes of death in the ageing population. Recent epidemiological data suggest that cancer is more frequent in patients with prevalent or incident cardiovascular disease, in particular heart failure. Indeed, there is a tight link in terms of shared risk factors and mechanisms between heart failure and cancer. Heart failure induced by anticancer therapies has been extensively studied, primarily focusing on the toxic effects that antitumor treatments exert on cardiomyocytes. In this Cardio-Oncology update, members of the ESC WGs of Myocardial Function and of Cellular Biology of the Heart discuss novel evidence interconnecting cardiac dysfunction and cancer via pathways in which cardiomyocytes may be involved, but are not central. In particular, the multiple roles of cardiac stromal cells (endothelial cells, fibroblasts) and inflammatory cells are highlighted. Also, the gut microbiota is depicted as a new player at the crossroads between heart failure and cancer. Finally, the role of non-coding RNAs in Cardio-Oncology is also addressed. All these insights are expected to fuel additional research efforts in the field of Cardio-Oncology.

1. Introduction

In the industrialized world, cardiovascular (CV) disease and cancer are the leading causes of death in the ageing population [1]. Left ventricular dysfunction (LVD) and heart failure (HF) are not rare across the broad population of cancer patients. In cancer patients, CV disease is the most frequent non-cancer cause of death [2]. HF and cancer share the same risk factors (e.g. ageing, smoking, obesity, diabetes, dyslipidemia, alcohol intake, inflammation) [3, 4]. Furthermore cancer and HF may have ancillary factors linking the two together [5]. Registries have observed that HF patients have a higher cumulative incidence of cancer, with a worse prognosis when both co-exist [6], suggesting that cancer surveillance may be useful in the management of HF patients [7]. Finally, an increased cumulative incidence of cancer among HF patients 30 days after MI has been reported, compared to HF-free patients 30 days after MI [8].

When considering these observations, it should be taken into account that there may be a surveillance bias, due to the fact that these study patients usually undergo an intense follow-up program that may lead to anticipate cancer diagnosis, sometimes discovering malignancies that would have gone undiscovered. Moreover, some of the most common therapies used to treat HF patients may play a role in revealing tumors otherwise asymptomatic (e.g. a latent intestinal neoplasm can bleeding due to anti-thrombotic therapy)[3]. Clinical presentations can also be difficult to distinguish between HF and cancer, since the 2 conditions can share some common symptoms (fatigue, dyspnea, weight loss, muscle wasting, oedema) [1, 3]. This may delay the diagnosis of new-onset cancer in HF patients due to the overlap in clinical manifestation. Furthermore, CV function and predictors of exercise capacity have been shown to be impaired in patients with cancer *per se*[9]. Hence, symptoms due to a tumor may overlap with those of HF and be attributed to heart disease. This may even delay cancer diagnosis, as symptoms might be thought of as due to advancing disease rather than new cancer [3]. Although the relationship

between cancer and HF is not well-defined in clinical studies, there are increasing data to suggest mechanistic links between the two conditions that we discuss in our manuscript.

Beside these reciprocal relations, cancer and HF carry an independent risk of mortality and also limit optimal treatment of the other condition when they co-exist, contributing to higher mortality. In addition, the cardiotoxicity risk related to treatment with anticancer drugs may unmask or deteriorate pre-existing HF [3]. The mechanisms driving HF triggered by anticancer therapies have been extensively investigated over the last 20 years and important insights have been uncovered [10-12]. Nonetheless, major questions are still open, and the answers to these questions may lay the foundations for new strategies to detect, monitor and treat cancer-therapy induced cardiotoxicity. On the other hand, research into the common pathways linking cancer and HF regardless of anticancer drugs has just begun [13].

The latest insights in translational Cardio-Oncology were discussed during the joint meeting of the Working Groups of Myocardial Function and the WG of Cellular Biology of the Heart of the European Society of Cardiology, held in Naples, Italy, in May 2019. In particular, given the systemic involvement of both HF and cancer, the Cardio-Oncology session focused on the contribution of organs, systems and cells other than cardiomyocytes to the pathogenesis of cardiac dysfunction in cancer patients, and to the interconnection between cancer and HF, primarily via inflammation. Opportunities and the current limitations in the use of microRNAs (miRNA) in cardio-oncology were also discussed. These topics are reviewed here, to provide the reader with updated information and further stimulate research in the field.

2. Role of non-cardiomyocytes in cancer treatment-related cardiotoxicity

The heart is a multicellular organ composed by cardiomyocytes, fibroblasts, neurons, endothelial and hematopoietic-derived cells. In fact, cardiomyocytes are not the most abundant cell type [14]. The different cardiac cell populations have diverse functions, but also interact

through complex intercellular communications [15]. Most studies performed so far have focused on the effects of anticancer drugs on cardiomyocytes, in both *in vitro* systems and *in vivo* models [16] (see table 1). Briefly, among the many forms of cardiotoxicity caused by several anticancer drugs (table 2), cardiac dysfunction due anthracyclines such as doxorubicin (DOXO) has historically been the most relevant [17]. From a pathophysiological point of view, anthracyclines induce cardiomyocyte death, mainly apoptosis and necrosis, via different molecular mechanisms, including but not limited to induction of oxidative stress, activation of DNA damage responses and impairment of mitochondrial biogenesis and metabolism [18-20]. Among other mechanisms involved in anthracycline-induced cardiotoxicity, abnormalities in myocardial energetics have slso been studied [21, 22]. Also biological drugs, designed to target specific oncologic pathways may be cardiotoxic, since these pathways play a major role in the maintenance of cardiac homeostasis, especially during stressful conditions, such as hypertension or hypertrophy [23]. For instance, *human epidermal growth factor receptor 2 (HER/ErbB2)* and *angiogenesis inhibitors* profoundly affect cardiomyocytes metabolism and contractile proteins, as discussed in comprehensive reviews [16, 24-26].

In addition, antitumor therapies likely also affect non-cardiomyocytes in the heart. For instance, DOXO has been shown to exert toxic effects on cultured cardiac endothelial cells [27] and fibroblasts [28-30]. This direct activity on non-cardiomyocytes may partly account for the cardiotoxicity of the drug, e.g. endothelial cells lose their barrier function with increased permeability and myocardial injury.

The impact of the toxicity of DOXO and any other antitumor treatment on non-cardiomyocytes can be better understood when it is placed into the context of the intercellular cross-talks in the heart. This concept is exemplified by the current knowledge about the cardiotoxicity of anti-HER2 drugs [31]. Besides being expressed in breast cancer cells, HER2/ErbB2 is also physiologically present in cardiomyocytes together with another receptor

tyrosine kinases (RTK) of the same family, HER4/ErbB4 [32]. Upon binding of HER4/ErbB4 by neuregulin-1 (NRG) and other ligands secreted by cardiac microvascular endothelial cells, HER2/ErbB2 and HER4/ErbB4 form heterodimers and initiate protective signaling cascades. Therefore, drugs targeting HER/ErbB2 are postulated to disrupt the NRG1-HER2/ErbB2-mediated endothelial cell-cardiomyocyte crosstalk and make cardiomyocytes more vulnerable to other stressors (Figure 1). It is notable that trastuzumab, used in the treatment of human epidermal growth factor receptor (HER)-2+ breast cancer, also directly damages cardiomyocytes and endothelial cells [33]; [34].

The inhibitors of the RTK for vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) cause cardiac microvascular dysfunction secondary to depletion of coronary microvascular pericytes [35]. The resulting myocardial hypoxia leads to sustained expression of hypoxia-inducible factor alpha (HIF-α), which was demonstrated to be sufficient to cause cardiomyopathy [36],[37]. Indeed, enhanced vascular permeability and reversible microvascular vasoconstriction have been reported in patients receiving therapies targeting VEGF and PDGF receptor (VEGFR and PDGFR, respectively) [38]. Moreover, this mechanism of toxicity well explains the clinical observation that cardiomyopathy associated with anti-VEGFR/PDGFR agents is reversible [39].

However, evidence obtained over the last years suggests that blockade of VEGF signaing also interrupt endothelial cell-cardiomyocyte communication (Figure 1). VEGF binds VEGFR on endothelial cells to stimulate angiogenesis, but also to induce the release of angiocrines (including ErbB4 and ErbB1 ligands) that modulate the function and homeostasis of adjacent cardiomyocytes [40]. Thus, drugs that inhibit VEGFR may alter cardiac function by interfering with the VEGF-VEGFR signaling axis, as well as by promoting endothelial cell dysfunction and death [41, 42]. High-throughput screening of RTK inhibitors pinpointed those

targeting VEGFR2 and PDGFR as the most toxic in human induced pluripotent stem cell (hiPSC)–derived endothelial cells [43].

Experimental models and analyses of human biopsies indicate that some features of HF with preserved ejection fraction (HFpEF) are at least in part driven by cardiac endothelial cell dysfunction. This latter elicits inflammatory infiltration of the myocardium, fibroblasts activation to deposit collagen excessively and increased stiffness triggered by a reduction of nitric oxide-dependent signaling [44-46]. Consistently with the epidemiological finding that the risk of HFpEF is correlated with prior radiotherapy for breast cancer [47], similar features were demonstrated in rats receiving cardiac radiation [48]. Since non-proliferating cardiomyocytes are considered resistant to ionizing radiation, other cell types, and in particular endothelial cells, are predicted to be the main target of radiation therapy leading leads to HF [49].

Fibroblasts also regulate cardiomyocytes and inflammatory cells through their secretome [50, 51]. In a recent study, DOXO caused both apoptosis of cardiac fibroblasts and secretion of Fas ligand, which in turn promoted cardiomyocyte death in a paracrine manner [52]. Conditional deletion of ataxia telangiectasia mutated kinase (ATM) in cardiac fibroblasts attenuated cardiac cell apoptosis, LVD and mortality in response to DOXO, suggesting that fibroblast are central in the pathogenesis of DOXO cardiotoxicity through ATM. The interactions between fibroblasts and other cardiac cell types, and the mechanisms in the cardiotoxicity of anticancer therapies, are an important area for future research [52]. Senescence of fibroblasts and possibly other cardiac stromal cells is especially worth being investigated, since it has been proposed that it plays a major role in the pathogenesis of heart disease [53].

In conclusion, oncological drugs and radiotherapy induce abnormalities in non-cardiomyocytes, which secondarily derange the networks with cardiomyocytes and may lead to LVD and HF. Additional studies are needed, [54, 55] also considering that cardiotoxicity may be evident in an already damaged myocardium, but may remain latent or hidden in the healthy

heart [56]. Since cardiac diseases and their comorbidities significantly change the global cardiac transcriptome, proteome and metabolome, it is not surprising that several drugs may act differently on the diseased versus healthy hearts [57, 58]. Novel cardiac safety testing platforms involving combined experimental models of cardiac diseases in the presence and absence of major cardiovascular co-morbidities and/or co-treatments are needed [59]. In this regard, cardiac organoids may allow modelling the complexity of the interactions between the different cardiac cell populations and, thereby, comprehensively evaluate the effects of anticancer therapies [55].

3. Interconnections between cancer and heart failure

Recently, attention has been drawn to the fact that cancer and heart disease have a reciprocal relationship: while the presence of cancer may cause LVD, the presence of HF associates with excess incident cancer [3-5, 60]. The communication between these two threatening diseases is complex, intriguing and involves many components.

First, during life and aging, several risk factors accumulate, which lead to chronic inflammation, oxidative stress, and protein and DNA instability. Classical CV risk factors, including obesity, diabetes, dyslipidemia and inflammation, are also associated with the development of cancer. Many of these risk factors lead to accumulation of fat mass, which is an active endocrine organ, secreting inflammatory factors and adipokines, which in turn have been associated with new onset CV disease (CVD) and new onset cancer [3-5, 60].

Second, genetic mutations that accumulate throughout life, such as clonal hematopoiesis of indeterminate potential (CHIP), defined as the presence of clonal leukocytes with impaired immune proprieties derived by acquired mutation in hematopoietic stem cells, have been associated with both cancer and CVD, including HF [61-65]. These mutations usually occur in a few genes, including DNMT3A, TET2, ASXL1, PPM1D, JAK2, TP53, SF3B1, and SRSF2[66]. The risk of developing CHIP increases with aging and, although it rarely results in development

of hematologic malignancies, it seems to be tightly linked to increased CV events and worse HF prognosis[61-65, 67].

Also, genetic mutations in sarcomeric proteins predispose to HF in patients undergoing chemotherapy. Unrecognized rare variants in cardiomyopathy-associated genes, particularly *Titin* truncating variants, have been shown to increase the risk for systolic dysfunction and cardiac events in a relatively small population of both children and adults undergoing chemotherapy. In specific populations, genotype variant testing, along with cumulative chemotherapy dosage and traditional cardiovascular risk factors, may be useful to improve the identification of cancer patients with a higher risk for developing HF upon chemotherapy [68].

Other CV risk factors, such as hypertension and trace albuminuria, have been related to cancer development. Therefore, systemic risk factors likely exert effects on several damage pathways, and it is hypothesized that individual additional risk factors, such as genetic predisposition or pre-existing conditions, will also contribute to the risk of one or both conditions.

Third, cancer and CVD are both associated with profound changes in tissue structure, either growth of entirely new tissue or tissue deformation, remodeling, and scarring of pre-existing tissues, such as heart, endothelial cells and matrix. Neoplasms are characterized by stroma, which is matrix tissue supporting the tumor, providing a scaffold, structure, and connections to adjacent organs. Further, most cancers, and especially metastases, rely on strong neovascularization requiring mitogenic endothelial cells and pericytes, where multiple growth factors play a role. In comparison, damaged cardiac tissue leads to dysfunctional cardiomyocytes, and also may develop extracellular matrix remodeling, fibrosis and scar. Matrix is produced by activated fibroblasts and multiple cell types homing in, including monocytes, macrophages and neutrophils. The cardiac scar is not a static structure, but rather is a dynamic and secreting structure [69].

4. Psychological convergence of HF and cancer

There is a well established psychological impact on patients suffering from chronic conditions, notably heart failure. This is one of the main aims of cardiac rehabilitation programmes in these patients. Unfortunately, rehabilitation programmes have only recently been implemented in cancer patients, in a generic "one fits all" umbrella rather than bespoke guidelines for specific cancers. It is notable however, the recognition that both cardiac dysfunction syndromes and cancers have a significant impact in regards to neuronal changes. Whilst these have only just been thought of, the molecular and cellular mechanisms of neuro-biology change remain relatively unknown. It is likely that both neuronal changes per se as well as modifications in signaling and transmission underlie the clinical states of depression or cognitive changes in these patients. The most likely culprit remains the chronic systemic inflammatory state present in both, probably responsible for an enhanced level of oxidative stress, DNA damage, mitochondrial dysfunction as well as synaptic modifications [70]; [71].

Whilst there is available evidence to support a link between certain chemotherapies and peripheral neuropathy (for example cisplatin), the issue of clinical states of depression/cognitive changes and them per se being a basis for autonomic dysfunction seen in these patients is far more complex and yet undemonstrated. At this current time it does not have the level of evidence and merrits further exploration.

5. Inflammation at the crossroad between cancer, cardiotoxicity of anticancer therapies and heart failure

Abnormal inflammation is increasingly recognized as a common driver of CVD and cancer [72, 73]. HF is characterized by a state of mild chronic systemic inflammation, with increased circulating concentrations of pro-inflammatory cytokines, such as tumor necrosis

factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). Myocardial injury itself triggers the recruitment and the activation of immune cells, which in turn produce pro-inflammatory cytokines and contribute to a self-perpetuating inflammatory state that underlies adverse tissue remodeling, primarily associated with capillary dysfunction and fibrosis [74]. Doxorubicin-induced damage also involves inflammation (Figure 2), with upregulation of pro-inflammatory toll-like receptor 4 (TLR4) in macrophages [75], higher levels as TNF-α and IL-6 and reduced levels of the anti-inflammatory cytokine IL-10 [76]. Cardiac function was preserved and survival improved in TLR2 knock-out mice after DOXO exposure compared to wild-types [77]. DOXO also induces local modulators of inflammation and fibrosis, produced by both macrophages and fibroblasts. Increased production of the matricellular protein thrombospondin-2 (TSP2) is protective in mice treated with DOXO. Enhanced myocyte damage in the absence of TSP-2 was associated with impaired activation of the Akt signaling pathway. Inhibition of Akt phosphorylation in cardiomyocytes significantly reduced TSP-2 expression, unveiling a unique feedback loop between Akt and TSP-2 [78]. Importantly, CCL2/CCR2-dependent recruitment of functional antigen-presenting cells into tumors is a desired therapeutic effect of anthracyclines [79].

Indeed, for decades oncologists have been developing strategies to modulate inflammation in order to achieve therapeutic anticancer immune responses [80]. The first attempts were not really successful, since cancer escapes T-cell-mediated cancer-specific immunity via inhibitory pathways mediated by cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1) (all depressing the antineoplastic activity of T lymphocytes) [81]. On the opposite, in the last years, Immune Checkpoint Inhibitors (ICIs), such as monoclonal antibodies (mAbs) targeting CTLA-4, PD-1 and PD-L1, have dramatically improved the outcome of many malignancies, but serious immune related cardiovascular adverse events have been observed [82-84] (Figure 2). Interfering

with the CTLA-4 and PD-1 axes can bring to autoimmune myocarditis and dilated cardiomyopathy[85], suggesting that these molecules play an important role in preventing autoimmunity[86]. Hence, immunosuppressive therapies may be necessary to halt immune related adverse events (IRAEs) and major adverse cardiovascular events (MACE) [87-89].

More recently, engineered T cells with chimeric antigen receptors (CAR-T cells) have been approved by the U.S. Food and Drug Administration (FDA) as the first genetically modified autologous T-cell immunotherapeutic agents that target CD-19. CD-19 is broadly expressed on most B-cell malignancies and has limited expression beyond B-cell lineage [90, 91]. Unfortunately, CAR-T cells are burdened by cytokine release syndrome (CRS) that is due to elevated levels of inflammatory cytokines released by activated CAR-T cells and other immune cells such as macrophages, with fever and tachycardia that may be associated with hypotension and hypoxia. Also, cardiac dysfunction and extremely serious complications such as vascular leak syndrome with circulatory collapse and multiorgan failure can be dreadful side effects of these therapies [92, 93] (Figure 2). Beside CAR-T cells, bispecific antibodies such as blinatumumab (that targets CD19 and CD3 and is increasingly used in the treatment of Philadelphia chromosome negative B cell acute lymphoblastic leukemia (ALL)) can also lead to CRS and cardiomyopathy[94].

Interestingly, inflammation in cancer plays a dual role. On the one hand it is essential to recognize and destroy cancer cells; on the other hand it provides a fertile milieu for tumorigenesis and plays key roles in different steps of tumor development, from initiation and promotion to invasion and metastasis. Tumor-associated inflammation favors proliferation and survival of malignant cells, promotes angiogenesis and metastasis, undermines adaptive immune responses, and potentially interferes with responses to hormones and chemotherapeutic agents [95, 96]. The finding that anti-inflammatory agents are effective in the prevention of cancer and CVD further advocates inflammation as a common contributor to both diseases. A 2019

study concluded that chronic systemic low-grade inflammation, measured by CRP levels <10 mg/L, is a risk factor for incident cancer, in particular lung cancer, in patients with stable CVD. The relation between inflammation and incident cancer is seen in former and current smokers and is uncertain in never smokers [97]. Blockade of the pro-inflammatory cytokine IL-1β with canakinumab was shown to significantly reduce the rate of recurrent CV events in patients with previous myocardial infarction (CANTOS trial). At the same time, blocking IL-1β appeared to protect from lung cancer mortality [98, 99]. Mice exposed to DOXO showed an increase in serum IL-1β along with other inflammatory factors [100]. Moreover, the IL-1β receptor antagonism protects against DOXO cardiotoxicity [101]. Similarly, the IL-6 inhibitor tocilizumab can protect against MACE in CAR-T patients[93].

The experience of IL-1β blockade highlights that the identification of key players of the inflammatory response is important to tackle both cancer and heart disease. Among intriguing candidates are PI3Ks, and more specifically the PI3Kγ isoform that is enriched in both cardiomyocytes and leukocytes (Figure 2). This implies a key role for this isoform not only in the control of cardiomyocyte pathobiology, but also in the orchestration of the inflammatory response associated to different types of cardiovascular injury [102]. PI3Kγ is upregulated in patients as well as in mouse models of atherosclerosis, and directs leukocyte infiltration of the arterial wall, which is a key pathogenic event in atherosclerosis[103]. PI3Kγ-mediated inflammation is also pivotal to the cardiac response to pressure overload [104].

Besides directing the cardiac response to stress, macrophage PI3Kγ expression critically contributes to tumor growth and progression. Intriguingly, macrophages play opposite roles in non-oncological inflammatory conditions and cancer. In response to pathogens or injury, macrophages express cytokines that stimulate cytotoxic T cells to clear infected or damaged cells. Conversely, in cancer macrophages express anti-inflammatory cytokines that induce immune suppression, inhibit T cell-mediated tumor killing and promote resistance to

immunotherapies (i.e. T cell checkpoint inhibitors). PI3Kγ has been recently proposed as the molecular switch controlling immune stimulation and suppression in cancer [105]. The unique feature of macrophage PI3Kγ, playing a maladaptive role both in heart disease and in cancer, makes this enzyme the ideal pharmacological target to "kill two birds with one stone", i.e. to halt the tumor and at the same time treat the heart [106]. This is particularly relevant for cancer patients treated with chemotherapy and suffering from iatrogenic cardiotoxicity [15, 105 107]. Results from clinical trials assessing the combined anticancer effect of such compounds in a context of cardiac protection are awaited.

6. The gut microbiome in Cardio-Oncology

HF has long been recognized to be associated with altered gut function [108, 109]. Low cardiac output in HF results in intestinal ischaemia, with congestion of the splanchnic circulation, bowel wall oedema and impaired intestinal barrier function (Figure 3). This condition increases the overall inflammatory state as well as oxidative stress as a consequence of HF-induced ischaemia and congestion within the gut via enhanced bacterial translocation and the presence of bacterial products in the blood circulation. Increased leakiness modifies the gut environment and affects its resident microbial population [110].

Among the conditions that can influence the gut composition, including individual genetic variability, lifestyle, colonization and delivery at birth [111-113], also changes in diet, presence of diseases and relative treatments have to be considered [114]. Interestingly, genetic composition of gut microbiota, defined as microbiome, also influences cancer development and progression in different ways [115]. Several types of cancers (head and neck, lung, colorectal and cervical carcinomas) promote a shift in microbiome composition [116-118]. In addition, chemotherapy directly impacts the gut microbiota and its efficacy is strongly influenced by microbiome composition (Figure 3) [119, 120].

Metabolites generated by the gut microbiota derive from the fermentation of indigestible fibres to short-chain fatty acids, that have protective properties (reducing inflammation, oxidative stress [121, 122] and improving vascular tone). Dietary sources of choline, phosphatidylcholine, l-carnitine, and other methylamine-containing nutrients provide substrates for microbiota-mediated generation of trimethylamine (TMA) that accesses the portal circulation and is converted by the hepatic flavin-containing monooxygenase (FMO) family of enzymes into trimethylamine *N*-oxide (TMAO, Table 3). TMAO can favor the development of atherosclerosis, thrombosis, kidney disease, and HF (Figure 3). High plasma levels of TMAO have been suggested to be predictive of cardiovascular events of mortality, independently from renal function and cardiovascular comorbitities[110].

Additionally, the bacterial transformation of bile acids can result in altered bile acid profiles, that in turn can impact systemic inflammatory and fibrotic processes [110]. Importantly, microbiota-derived peptide mimics may also drive HF, by inducing a lethal inflammatory cardiomyopathy. Cardiac myosin-specific TH17 cells are being imprinted in the intestine by a commensal Bacteroides species peptide mimic. These cells promote cardiac inflammation and dysfunction in genetically susceptible individuals [123].

Several studies reported SCFAs-producing bacteria perturbation in patients with CVDs [124]. Among these SCFA generated by the gut microbiota, butyrate (BUT) has multiple beneficial effects for our cardiovascular system through different mechanisms [125-131, 120] (Table 3). BUT exerts major epigenetic effects, acting as a potent inhibitor of histone deacetylase (HDACs) activity. Inhibition of HDACs is well-known to protect the heart from pathologic hypertrophy and ischaemia [132-135]. Among HDAC inhibitors, BUT has been shown to exert anti-neoplastic properties *in vitro* [136, 120]; while its derivatives can enhance the anticancer cytotoxic effects of DOXO while protecting against cardiotoxicity [137] and can decrease cardiac apoptosis and myocardial dysfunction induced by DOXO, by lowering endoplasmic reticulum stress-initiated

apoptotic signalling and HDAC-inhibition mechanisms [138], [139]. The cardioprotective effect of BUT and analogues is associated with the production of anti-inflammatory molecules, cytoprotection, modulation of angiogenesis, limiting the occurrence of cardiotoxic manifestations caused by DOXO treatments, with reduction of nitrosative and oxidative stress, counteracting mitochondrial dysfunction [121]. In turn, DOXO is reported to induce GUT-microbiota dysbiosis in mice, while the administration of BUT attenuates the inflammation state induced by DOXO [140], fuelling nutraceutical as a new promising area of research to cardio-oncology

7. Opportunities and limitations in the use of noncoding RNAs in Cardio-Oncology

Multiple evidence seems to suggest an involvement of circulating microRNAs (miRNAs) in anthracyclines-induced cardiotoxicity both *in vivo* and in the clinical setting, evidencing a very heterogeneous situation. In particular, when focusing on DOXO, miR-1 [141, 142] and miR-34a [143-146], showed a drug-induced regulation in tissues and plasma samples, both in patients and animal models. miR-1 is one of the most investigated and most highly expressed miRNAs in cardiac and skeletal muscle, both in physiological [146, 147] and pathologic [148, 149] condition. While many groups have indicated miR-1 as a specific circulating marker of heart disease, there is no clear indication about its unambiguous cardiac origin, particularly in anthracyclines-induced toxicity, which is a systemic phenomenon. Similarly, miR-34a was demonstrated to be modulated by anthracyclines both in experimental models [144, 145, 150] and in breast cancer patients [151]. Piegari and co-authors, showed that tissue regulation of miR-34a by DOXO was not restricted only to the heart [144], hinting at a multi-tissue contribution to the circulating levels of this miRNA. Indeed, besides cardiomyocytes, smooth muscle cells, fibroblasts, cardiac progenitor cells and endothelial cells may also play a role in DOXO-induced cardiomyopathy [152]. Acute DOXO treatment in mice was shown to reduce microvessel density

and VEGF-A expression with a parallel increase in miR-320a [153]. Inhibition of miR320a improved cardiac function, decreased apoptosis, and increased microvessel density in DOXO-treated mice, while overexpression of miR-320a worsened DOXO-induced LV dysfunction [154]. Conversely, overexpression of the miR-320a target VEGF-A prevented detrimental effects of miR-320a in DOXO-cardiotoxicity experimental model confirming VEGF as a direct downstream target molecule [153]. Mechanistically, the overexpression of the pro-hypertrophic miR-212/132 cluster in primary rodent and human iPSC-derived cardiomyocytes as well as in in vivo models has been shown to inhibit doxorubicin-induced toxicity [155] Also, another class of noncoding RNAs, circular RNAs, may play a crucial role in mediating cardiotoxicity of doxorubicin; indeed, overexpression of the RNA binding protein Quaking 5 (*Qki5)* strongly attenuated the toxic effect of doxorubicin in a mouse model by regulating a set of circular RNAs including those derived from titin (*Ttn*; [156]).

The role of miRNAs as markers of cardiotoxicity has also been investigated. Ruggeri and coworkers [150] showed that after one month from DOXO administration, only a part of the drug-treated mice presented cardiac dysfunction, similarly to the clinical context. miR-1 was again among the circulating miRNAs regulated after cardiotoxicity onset, together with miR-499-5p. In an acute DOXO cardiotoxicity model, the same authors showed that miR-34a-5p and miR-451a were dysregulated in all cardiac chambers, with miR34a-5p showing opposite trends of regulation between the atria and the ventricles of treated mice. In another study using DOXO both in vivo and in vitro acutely and chronically treated cardiomyocytes, DOXO-dependent downregulation of miR-30 led to increased cardiomyocyte apoptosis and abnormalities of cardiomyocyte β-adrenergic receptor signaling [157].

Importantly, only part of circulating miRNAs overlapped with their cardiac counterparts, suggesting only a partial contribution of the heart to the variations in circulating levels of miRNAs upon drug administration. Limitations of the studies are the number of

animals, the number of screened miRNAs (often only selected cardiovascular miRNAs), the acute phase observed, the absence of tumor in the experimental models, and the lack of additional cancer treatments.

Besides the few miRNAs showing a "reproducible sensitivity" to anthracycline treatment, there is a highly heterogeneous picture composed by past and present investigations. While the discrepancies in terms of results could be in part explained by the different experimental models and by the different malignancies and therapies adopted in patients-based investigations, there are at least two fundamental issues that should be addressed in future works. A striking feature of many, if not all, published papers is that no study described a decline of LVEF below the "normal" threshold of 50%, possibly because of lack of a long-term follow-up. Moreover, the vast majority of human-based research studies concentrated on the acute phase of cardiotoxicity [158], and the same limitations often apply also to *experimental* researches, which rarely go beyond a few days' time span from treatment to sacrifice.

Additional data on the main non-coding RNAs are summarized in Table 4.

8. Concluding remarks

We discussed several of the novel exciting insights that are emerging in the ever-expanding field of cardio-oncology. More research is required to identify and investigate the pathways and mechanisms underpinning the intimate relationship between CVD and cancer. Current studies focus on shared risk factors, both acquired/modifiable and genetic. The substantial structural changes in diseased organs prompt further studies in an effort to learn how disease in one organ may communicate with another organ. Learning from each disease mechanisms may help to combat both CVD disease and cancer.

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Conflict of interest

PF is the founder and CEO of Pharmahungary Group, a group of R&D companies. TT has filed and licensed patents in the field of noncoding RNAs. TT is founder and shareholder of Cardior Pharmaceuticals GmbH. The UMCG, which employs RAdB has received research grants and/or fees from AstraZeneca, Abbott, Bristol-Myers Squibb, Novartis, Novo Nordisk, and Roche. RAdB received speaker fees from Abbott, AstraZeneca, Novartis, and Roche.

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Figure legend.

Figure 1

Besides directly affecting cardiomyocytes and the other cardiac cell populations, cancer treatments may disrupt the intercellular communications between cardiomyocytes and non-cardiomyocytes. The inset in the lower part of the Figure shows key endothelial cell (green)-cardiomyocyte (red) paracrine signaling axes that may be impaired by antitumor therapies.

NRG-1: neuregulin-1; VEGF: vascular endothelial growth factor; VEGFR2: vascular endothelial growth factor receptor type 2; NO: nitric oxide; cGMP: cyclic guanosine monophosphate; PKG: protein kinase G

Figure 2

Inflammation at the intersection of the anti-cancer action and cardiac side effects of major oncological treatments.

Besides directly killing tumor cells, doxorubicin triggers cardiac inflammation via activation of macrophages and fibroblasts and the ensuing release of local modulators of inflammation and fibrosis, such as TNF-α, IL-1β and IL-6. Major players of the inflammatory response induced by doxorubicin include macrophage TLR-4, the matricellular protein thrombospondin-2 (TSP-2) and leukocyte PI3Kγ. On the other hand, immune check point inhibitors (ICIs) inhibit molecules such as cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1) and its ligand PD-L1. As a consequence, anti-tumor immune cell responses are reactivated and lead to tumor cell death, but concomitantly drives myocarditis. Although these new immunotherapies have notable anti-cancer effects, multiple mechanisms of immune

resistance exist, and these might be overcome by using PI3Kγ inhibitors that re-shape the tumor immune microenvironment. Finally, engineered T cells with chimeric antigen receptors (CAR-T cells) boosts T cell-mediated tumor killing, but are burdened by cytokine release syndrome (CRS) leading to extremely serious complications, including cardiac and vascular dysfunction, and ultimately to multiorgan failure.

Figure 3

GUT Microbiome Dysbiosis can be influenced by both HF and cancer. HF has long been associated with congestion of splanchnic circulation, leading to bowel wall edema, impaired intestinal barrier function and increased systemic inflammation, that drastically affect GUT microbiome composition and response to HF treatments. At the same time, cancer-mediated disruption of metabolism and the production of cancer-derived metabolites modifies the microbiome. Such altered gut microbiome generates cardiotoxic metabolites such as TMAO and Bile Acids, eventually leading to HF worsening.

Table 1. Main direct toxic effects of cancer therapies on cardiomyocytes

Cellular toxicity	**Treatment(s) most commonly involved**
Type II topoisomerase poisoning *	Anthracyclines
Mitochondrial dysfunction	Anthracyclines, VEGFR / multitargeted RTK inhibitors
Oxidative stress	Anthracyclines
Impaired authophagy	Anthracyclines, proteasome inhibitors
Altered protein handling	Proteasome inhbitors
Induction of HIF pathways	VEGFR / multitargeted RTK inhibitors

* This toxicity is peculiar of anthracyclines.

VEGFR: vascular endothelial growth factor receptor; RTK: receptor tyrosine kinase; HIF: hypoxia-inducible factor.

Table 2. Cardiovascular toxicities of cancer therapies

Type of toxicity	Treatment(s) most commonly involved
LVD, HF	Anthracyclines, HER2-targeting drugs, VEGFR / multitargeted RTK inihibitors, proteasome inhibitors, radiation therapy (HFpEF)
Myocardial ischemia	Fluoropyrimidines, VEGFR inhibitors, radiation therapy
Myocarditis	ICIs, cyclophosphamide (rarely)
Atrial fibrillation	Ibrutinib
QT prolongation	Arsenic trioxide, vandetanib,androgen deprivation therapy (enzalutamide)
Valvular heart disease	radiation therapy
Pericarditis	ICIs,cyclophosphamide
Hypertension	VEGFR inhibitors
Peripheral artery disease	Nilotinib, ponatinib
Vascular thrombosis *	Cisplatin, nilotinib, ponatinib, thalidomide and lenalidomide, VEGFR inhibitors, proteasome inhibitors, aromatase inhibitors
Pulmonary arterial hypertension	Dasatinib, cyclophosphamide

* Acute myocardial ischemia will ensue if thrombosis occurs at coronary artery atherosclerotic plaques.

LVD: left ventricular dysfunction; HF: heart failure; VEGFR: vascular endothelial growth factor receptor; RTK: receptor tyrosine kinase; HFpEF: heart failure with preserved ejection fraction; ICIs: immune checkpoint inhibitors

Table 3

Role of TMAO and Butyrate in Cardio-Oncology

Cardiovascular field		Cancer field	
TMAO	Butyrate	TMAO	Butyrate
Prognostic 5 years follow-up marker in patients with heart failure. Prognostic biomarker in in chronic systolic HF. Predictive biomarker in patients with Acute Heart Failure Prognostic biomarker in patients associated with NYHA III and IV ischaemic aetiology and adverse outcomes Predictive biomarker for mortality and CV mortality in HFrEF but not HFpEF patients [110]*	Inhibition of maladaptive hypertrophy and heart failure[132]; [133]; [135] Reduction of myocardial ischemia-reperfusion injury[134]) Cardioprotective action against DOXO toxicity [137] Alleviation of DOXO-induced ER stress[138];[139]) Prevention of DOXO-induced mitochondrial dysfunction and ROS/RNS production[121]	Predictive biomarker of colorectal cancer[159]) Predictive biomarker of aggressive prostate cancer[160]	Induction of cytodifferentiation and inhibition leukemic cells proliferation; inhibition of Lewis lung carcinoma cells growth[136] Increase of the antineoplastic effect of DOXO[137]

*High levels of TMAO in patients have been suggested to be predictive of cardiovascular events of mortality, independently from renal function and cardiovascular comorbitities[110].

1309 **Table 4**

1310 **Non-coding RNAs in Cardio-Oncology**

	Cardiovascular field		Cancer field	
	Circulating forms (biomarkers)	**Intracellular forms (epigenetic activity)**	**Circulating forms (biomarkers)**	**Intracellular forms (epigenetic activity)**
miR-1	Marker Of Myocardial Infarction.[161]; Biomarker Of Atherosclerosis, Coronary Artery Disease, Acute Coronary Syndrome.[148]	Involved In Cardiogenesis, Heart Function, Cardiac Pathology [162] Involved In Heart Disease And Cardioprotection. [163]	Non-Invasive Biomarkers In Breast Cancer: Early Diagnosis And Metastasis Prediction[164] Correlation With Clinico-Pathologic Characteristics And Lung Cancer Detection.[165]	Inhibition Of Proliferation And Metastasis Of Breast Cancer. [166]; Differential Expression In Different Human Cancers.[167]
miR-34a	Biomarker Of Aging [168] Marker Of Anthracycline Treatment[169]	Regulation Of Cardiac Ageing And Function. [170] Contribution To Doxorubicin-	Non-Invasive Biomarkers In Breast Cancer: Early Diagnosis And Metastasis Prediction[164]	Potential Tumor Suppressor And Therapeutic Candidate In Cancer[173]

		Induced Cardiotoxicity.[171]	Potential Biomarker For Early Diagnosis Of Esophageal Cancer[172]	Associated With Aggressive Breast Cancer[174]
miR-320a	Biomarker Of Arrhythmogenic Cardiomyopathy [175] Predictive Biomarker For Left Ventricular Remodelling[176]	Mediator Of Doxorubicin-Induced Cardiotoxicity [153] Involved In Human Myocardial Infarction[177]	Early Detection Of Pancreatic Neoplasia[178] Circulating Biomarker Of Melanoma[179]	Regulation Of Cell Metastasis And Invasion In Non-Small Cell Lung Cancer[180] Modulation Of Cell Growth And Chemosensitivity In Gastric Cancer[181]
miR-212/132 cluster	Estimation Of Atherosclerosis Presence[182]	Prevention Of Doxorubicin-Mediated Atrophy And Cardiotoxicity[155]	Biomarker Of Pancreatic Cancer Risk [185]	Suppression Of Proliferation Of Human Lung Cancer Cells[187]

	Risk Prediction For Heart Failure [183]	Regulation Of Cardiac Hypertrophy And Cardiomyocyte Autophagy[184]	Diagnostic Biomarker Of Malignant Mesothelioma[186]	Regulated In Ovarian Cancer Cells[188]
miR-451a	Modulated In Acute Model Of Doxorubicin-Induced Cardiotoxicity[143] Marker Of Type 2 Diabetes[189]	Regulation Of Doxorubicin-Induced Cardiotoxicity[190] Decreased In Hypertrophic Cardiomyopathy And Regulates Autophagy[191]	Biomarker And Potential Therapeutic Target For Cancer[192] Biomarker For The Diagnosis Of Esophageal Squamous Cell Carcinoma And Squamous Dysplasia[193]	Regulation Of Papillary Thyroid Carcinoma Cells[194] Involved In Breast Cancer[195]
miR-30	Biomarkers Of Acute Coronary Syndrome And Stable Coronary Artery Disease[196]	Cardioprotection In Doxorubicin-Induced Heart Failure And Inhibition Of Cardiomyocytes Autophagy[198]	Prognosis Of Ovarian Cancer[200] Prognosis Of Bladder Cancer[201]	Involved In Cancer Progression[202] Involved In Breast Cancer

	Marker Of Stable Atherosclerotic Disease[197]	Involvement In Ventricular Remodeling: The Mir-30 Family[199]		Invasion, Osteomimicry, And Bone Destruction[203]

1311

Figure 1

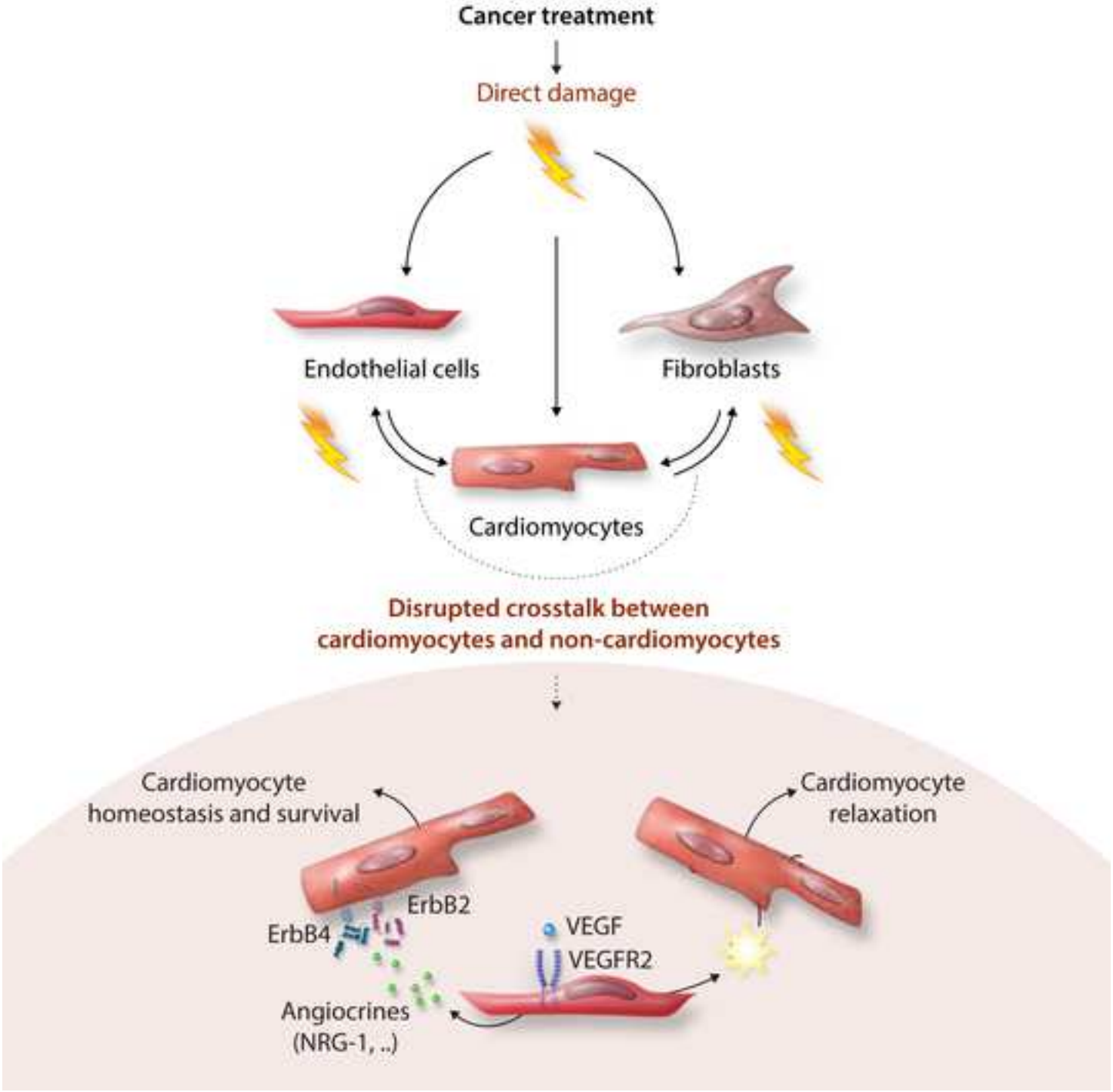

Figure 2

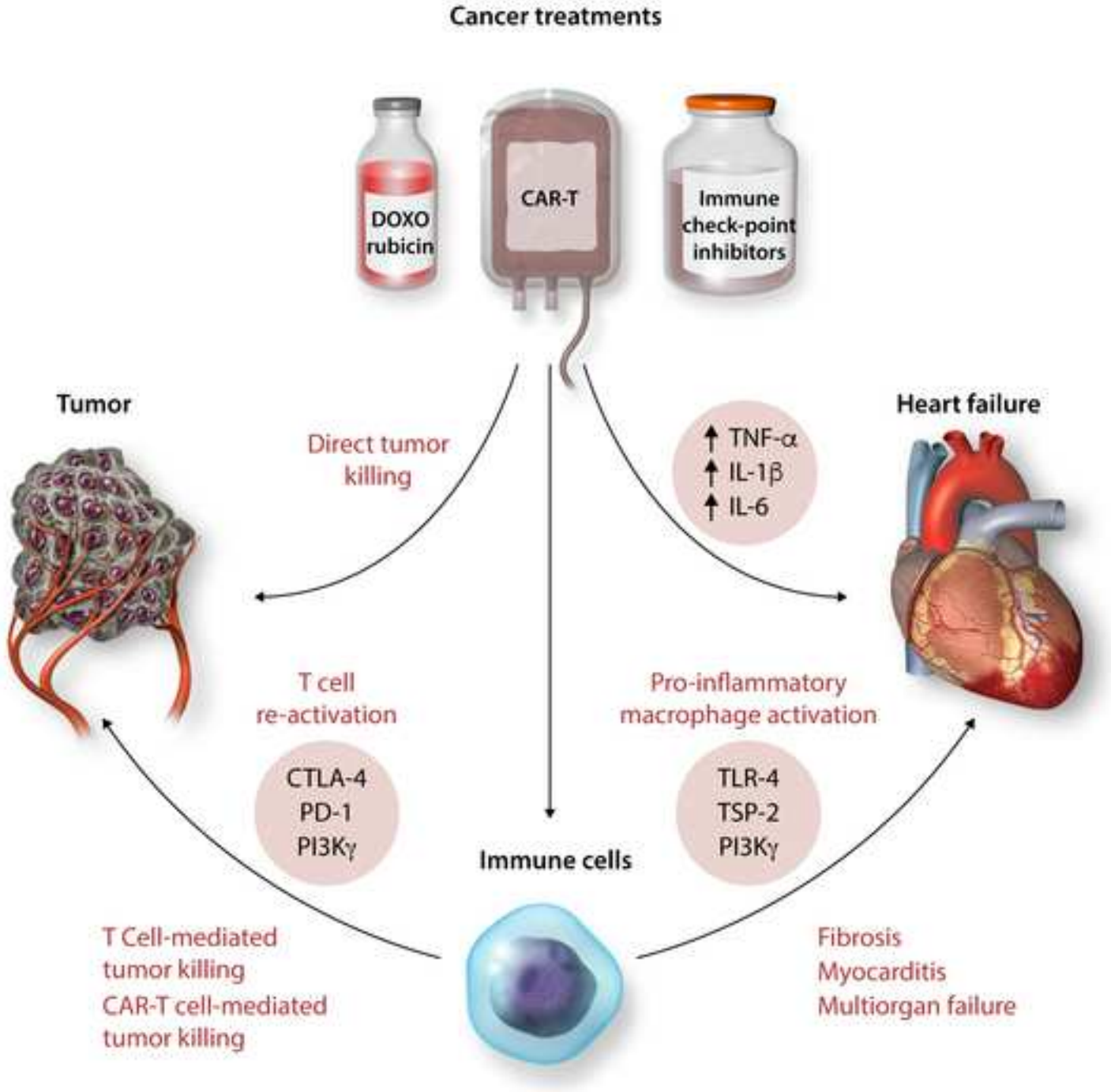

Figure 3