



Viewing cancer pathophysiology as a lead in understanding cardiac and vascular disease mechanisms

John A. Loudon

Correspondence: jon.uk1515@gmail.com



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Wetherill Park Medical Centre, Suite 101, Stockland Mall, Polding Street, Wetherill Park, Sydney, NSW, 2164 Australia.

Abstract

This article describes how understanding mechanisms used by cancer cells—both prosurvival (oncogenic) and pro-apoptotic (tumour suppression)—sheds light on important ‘cues’ for prosurvival and apoptotic pathways employed in the cardiac and vascular system. Commencing with the mevalonate pathway, numerous examples are presented whereby cancer oftentimes foretells an understanding of relevant mechanisms for cardiology. Pathologies such as cardiomyopathies including heart failure, hypertension/vascular dysfunction, and reaction to ischaemic-reperfusion injury are discussed. Key features emerge in terms of homeostasis within the cardiac and vascular system and the observation that cardiac pathologies do not present in mere isolation but as co-morbidities. Mechanisms resulting in such pathologies are revealed by considering prosurvival versus pro-apoptotic imbalance (homeostatic disturbance). Overall, one may gain an improved foreknowledge of such mechanisms behind these important regulatory paths in cardiology from studying cancer molecular mechanisms.

Keywords: Apoptosis, atheroma, cancer, cardiomyopathy, cardioprotection, farnesol, heart failure, hypertension, mevalonate pathway, oncogene, prosurvival factor, tumour suppressor, vascular disease

Introduction

Recently [1], it was emphasized that cardioprotective mechanisms/factors targeting ischemia/reperfusion (I/R) injury are of pivotal significance and form a “foremost experimental goal”—a ‘holy grail’ of cardiac and vascular medicine. A model has already been proposed emphasizing that cancer may play a central role for elucidating and indeed forecasting such factors and mechanisms [2]. In that analysis it has been notably demonstrated that cancer and heart tissue react similarly at the molecular level to withstand imposed environmental challenge. In regards this relation, it was stated: “As another feature of the model, ways to better forecast future therapies aimed at augmenting cardioprotective paths is made possible through understanding of pathways used to sustain cancer cells under external challenges.” [2]. In effect, this model represents: “...a novel and important ‘cross road’ between physiology and pathology” [2].

Importantly, not only do prosurvival/cytoprotective pathways match between heart and cancer but also mechanisms relating to tumour suppression/apoptosis and cardiomyocyte damage [2]. Therefore overall, by looking at the cancer prosurvival model

‘in reverse’ one has a means to better understand and ultimately aid in developing targeted therapeutics for heart/vascular diseases. Along this line, it has been further detailed the notion that cancer may forecast factors in respect to cardioprotection [3]. In this regard, cancer prosurvival factors claudin, CASPR3, CDC42-binding protein kinase beta and dihydropyrimidinase-related protein 2 (CRMP2) have not been examined in the heart for their relation to cytoprotection. As such, there remains much scope for productive investigation based on cancer for dissecting target factors involved in heart diseases.

This relation between cancer and the heart has been extended from the prosurvival model [2] to show that cancer biomarkers match with those for cardioprotection—a useful tool for cardiology risk assessment [4]. As a follow on from the cancer prosurvival model, cancer survival factors match with hypertension, cardiohypertrophy and atheroma molecular markers. An upset in homeostasis towards progrowth cellular programming may be adverse for the cardiac/vascular system [5].

The purpose of this article is to emphasize and extend the key and recurring message that cancer prosurvival and apoptotic pathways/mechanisms mimic and oftentimes anticipate such

shared pathways of note within the cardiac and vascular system. Appreciating this shall aid in revealing deficiencies in understanding cardioprotection and heart and vascular diseases in general. Assisting with providing valuable 'cues' for therapies in cardiac and vascular medicine is a central aim of connecting *heart-cancer* molecular and cell biology mechanisms.

Methodology

A literature search was performed using the PubMed database through use of key words joined *via* the Boolean operator 'and' as I have detailed recently [6]. The means of producing novel concepts by bridging seemingly unrelated knowledge fields is known as 'literature-based discovery' (LBD). LBD is based on the hypothesis that two islands/strands of knowledge (concepts) A and C may be related to each other if they share a link to an intermediate concept B (the greater the number of shared links between A and C, the more probable is the relationship between them). This notion is known as Swanson's 'ABC' model [7] and I use this approach to bring to light the productive connection between cancer (concept A) and the cardiac and vascular system (concept C) *via* shared prosurvival/apoptotic molecular mechanisms/factors (concept B).

Literature searches employed the following phrases: cancer/cancer therapy resistance and factor (where the factor is either a prosurvival/oncogene or tumour suppressor); cardioprotection/cardiomyocyte cytoprotection and factor; myocardial ischaemia and factor. Other substituted key terms were hypertension, cardiomyopathy/hypertrophy, heart failure, vascular dysfunction/atheroma. Such searches revealed when the particular factor(s) of interest were *initially* associated with cancer or heart disease. Mechanistic pathways were explored from the cardiac/vascular context in cancer to determine correlations and timing of discovery to highlight the relationship of cancer signaling pathways and relevance to cardioprotection, cardiac hypertrophy, hypertension, atheroma and heart failure.

Results and discussion

For ease of presentation, various aspects of the cardiac and vascular system and pathologies are individually highlighted. The 'logic trail' running throughout is aimed to show that cancer provides an adequate resource to appreciate these aspects from a mechanistic and, following on from this, therapeutics standpoint.

Cardioprotection against ischaemia-reperfusion challenge

In regards the mevalonate pathway [1], it is interesting to note that farnesol is depicted as cardioprotective *via* a novel protein geranylgeranylation (prenylation) mechanism. It was further indicated that G-proteins, including members of Ras superfamily, are involved in signal transduction of I/R injury and cardioprotection, although their prenylation status has

not been examined in this context [1]. My proposition is that prenylation – a post-translational modification – is central in cardioprotection and protein targets are predicted and indeed, defined, through examining cancer. Such cancer prosurvival lipid metabolic pathway mechanisms [8] are closely paralleled in the heart. Notably, consistent with this proposition, by inhibiting lipid metabolic paths, particularly the mevalonate pathway, anti-cancer therapeutics are enhanced [8]. Further, in cancer, prosurvival prenylation reactions have been earlier considered to be suited targets for therapies [9]. Inhibiting protein geranylgeranylation and glycosylation (mediated by Dolichol), prosurvival end-products of the mevalonate pathway [1], by lovastatin inhibits erythropoietin-related cell proliferation in cancer [10]. Predictably, interfering with the Dolichol pathway as seen in dolichol kinase deficiency, leads to heart damage - dilated cardiomyopathy [11].

Farnesol demonstrates a 'U' shaped survival profile in cardio-myocytes, being toxic at higher doses [1]. This factor directs protein prenylation reactions and has a role in Ras activation *via* prenylation, certainly a key process in cancer [12]. At high concentrations, farnesol appears also toxic in cancer and mechanistically, the toxicity connects with NF- κ B and MEK1/2-ERK1/2 pathway and endoplasmic reticulum [13]. Overall, a number of these farnesol-related aspects align between cancer and heart - cancer providing a lead or 'cue' for further investigation in the heart context.

Other intriguing parallels are noted. Earlier, manumycin, a farnesylation inhibitor, was proven effective in targeting cancer [14]. Later, urocortin-II cardioprotection was seen to be abolished by manumycin [15] implicating similar mechanism and forecast by cancer. Further, it has been stated that activation of JNK *via* Rac1 leads to cardiomyocyte cytoprotection [1]. Earlier, the involvement of Rac1 and JNK in oncogenesis was proven [16]. RhoA is cardioprotective [1] and acts *via* an 'unexpected' role for PKD as a downstream mediator [17]. Earlier in cancer [18], both RhoA and PKD were found to have joint key roles in oncogenesis—thus anticipating the role of PKD in RhoA-mediated cardioprotection.

Numerous other instances exemplify the utility of cancer as a lead in cardioprotection pathway discovery. G-protein-coupled receptors, such as Adenosine A₃ receptor, employ adenosine as a key ligand in stimulating cardioprotection [19]. Inhibition of this adenosine receptor is proposed for cancer therapeutics consistent with its prosurvival capacity. Very recently, [20], the Adenosine A₃ receptor agonist 2-Cl-IB-MECA was shown to mediate cardioprotection *via* what the authors of that work considered as a *novel* mechanism involving MEK1/2 (elucidated from targeted U0126 inhibition) and PI3K/Akt. Earlier, [21], adenosine, through A₃ receptor, mediated a proliferative/prosurvival effect on colonic cancer cells. Notably, U0126 blocked the agonist 2-Cl-IB-MECA induced proliferation- this *novel* mechanism for the heart being neatly foretold by cancer. Further, the G-protein- coupled opioid receptor forms a notable example. The κ opioid receptor

is involved in directing cardiomyocyte cytoprotection [22]. Unsurprisingly, *kappa* opioid receptors align with oesophageal carcinoma progression [23].

As further examples, A1/Bfl-1, a Bcl-2 family member, is stimulated by prosurvival NF-*kappa* B to prevent apoptotic release of mitochondrial cytochrome *c* thus providing resistance to chemotherapy induced apoptosis [24]. Prosurvival Bfl-1 is expressed in coronary smooth muscle cells on glucose stimulation in diabetes and may represent an adverse mechanism in the vasculature [25]. Later, in the heart itself, Bfl-1 was noted as a potent cardiocytoprotective factor [26]. In preconditioning cardioprotection, prosurvival Mcl-1 – also a Bcl-2 member - acts in a mechanism with STAT3 and NF-*kappa* B [27]. In the process of oncogenesis this mechanism is mimicked on upregulation of Mcl-1 with NF-*kappa* B and STAT3 [28].

In various energy/metabolic-related aspects, cancer and heart align, as I have previously highlighted [2]. Inhibiting carnitine palmitoyltransferase I (CPT-1), thus targeting fatty acid oxidation, decreases I/R tolerance in the disease-free animal model context [29]. In cancer, [30], CPT-1 forms a convenient, efficient ATP production system *via* beta-oxidation of fatty acids for metabolically active and needy cancer cells. As such, it forms a prosurvival mechanism much like CPT forms a survival path in the context of the disease-free heart [29]. Notably earlier, [31], inhibiting CPT-1 in cancer cells led to apoptosis *via* increasing ceramide and BNIP3 levels. These mechanisms involving CPT have not as yet been explored in the heart and taking the ‘cue’ from cancer, it may be anticipated that a similar pathway may apply for cardiomyocyte metabolic damage.

Like prenylation [1], S-nitrosylation forms a post translational cardioprotective mechanism. Atorvastatin induces cardioprotection and is infarct sparing *via* iNOS/Cox-2 - iNOS producing NO which in turn activates prosurvival Cox-2 *via* S-nitrosylation [32] (see Table 5–below). The importance of the involvement of iNOS/Cox-2/S-nitrosylation mechanism is recapitulated in cancer [33]. In this scenario, iNOS/NO increases activity of Cox-2 and leads to chemoresistance. Further, iNOS/NO activate EGFR/Src *via* S-nitrosylation influencing oncogene prosurvival network: Myc/Akt/STAT3. Such prosurvival machinery and mechanisms in regard S-nitrosylation remain to be explored in detail for the heart – the ‘cue’ here for investigation comes from cancer.

Cardioprotection is afforded by NO both *via* S-nitrosylation as well as *via* the cGMP/PKG pathway [34]. Not unexpectedly, cancer also uses the NO/cGMP/PKG machinery as a prosurvival mechanism [35].

Ion channels represent a further convincing presentation for the relation of cancer factors to heart disease. The cystic fibrosis transmembrane conductance regulator (CFTR) chloride anion channel maintains a central role in cardioprotection [36], yet earlier was considered as a prosurvival target for cancer therapy [37]. Cardioprotection may be also related to cationic channels such as K(ATP) [38]. In parallel, this cation channel

aligns with cancer prosurvival [39] where K(ATP) blockers inhibit cancer cell proliferation.

In short, lipid and general metabolic paths, mitochondrial mechanisms as well as receptor pathways for opioids and cardio-active factors such as adenosine to name a few, all funnel towards demonstrating a close mechanistic *cancer-heart* alignment (Table 1). Therefore this understanding has clear clinical implications in regards appreciating and indeed foretelling cardioprotection against I/R injury.

Table 1. Alignment of mechanisms/factors relating cancer to ischaemic cardioprotection.

Cancer	Cardioprotection
Prenylation (Farnesol) ^a	Prenylation (Farnesol) ^a
Glycosylation (Dolichol) ^b	Glycosylation (Dolichol) ^b
Farnesylation (Manumycin) ^c	Farnesylation (Manumycin) ^c
Rac/JNK ^d	Rac/JNK ^d
RhoA/PKD ^e	RhoA/PKD ^e
Adenosine A ₃ receptor/MEK1/2 ^f	Adenosine A ₃ receptor/MEK1/2 ^f
<i>kappa</i> -opioid receptor ^g	<i>kappa</i> -opioid receptor ^g
A1-Bfl1 ^h	Bfl1 ^h
Mcl1/NF- <i>kappa</i> B/STAT3 ⁱ	Mcl1/NF- <i>kappa</i> B/STAT3 ⁱ
Carnitine palmitoyl-transferase I ^j	Carnitine palmitoyl-transferase I ^j
Nitric oxide/cGMP/PKG ^k	Nitric oxide/cGMP/PKG ^k
S-nitrosylation/Cox-2/iNOS/nitric oxide ^l	S-nitrosylation/Cox-2/iNOS/nitric oxide ^l
Anion channel: CFTR ^m	Anion channel: CFTR ^m
Cation channel: K(ATP) ⁿ	Cation channel: K(ATP) ⁿ

^aPrenylation (the addition of hydrophobic moiety to a protein to assist in cell membrane attachment) is a cancer prosurvival mechanism [8,9] and is a suggested mechanism that may lead also to ischaemic cardioprotection [1] with farnesol being an active component of this process.

^bDolichol, a product of the mevalonate pathway, mediates glycosylation, a cancer prosurvival mechanism [10] and assists in sustaining myocardial integrity [11].

^cFarnesylation (prenylation by means of addition of an isoprenyl group) inhibition by manumycin targets cancer [14] and abolishes urocortin-II mediated cardioprotection [15].

^dRac1-JNK prosurvival cascade is involved in cancer pathophysiology [16] and is also considered to be involved in cardioprotection [1].

^eRhoA-PKD cascade is a prosurvival feature in cancer [18] as well as in cardioprotection [1,17].

^fAdenosine A₃ receptor controls a prosurvival response in cancer [21] involving MEK1/2 and also mediates cardioprotection via the same mechanism [20].

^g*kappa*-opioid receptor aligns with cancer [23] and cardioprotection [22].

^hBfl1 (A1-Bfl1) is a prosurvival factor in cancer [24] and prosurvival in the vascular system in the context of diabetes [25] and directly cardiomyocyte cytoprotective [26].

ⁱCancer employs the prosurvival cascade Mcl1/NF-*kappa* B/STAT3 [28] with the same cascade operating in cardioprotection [27].

^jCarnitine palmitoyltransferase (CPT-1) forms a metabolic prosurvival mechanism in cancer [30,31] and is metabolically a cardioprotective mechanism [29].

^kNitric oxide/cGMP/PKG pathway is employed by cancer as a prosurvival mechanism [35] and forms a cardioprotective cascade [34].

^lS-nitrosylation/Cox-2/iNOS/nitric oxide forms a cancer-related prosurvival mechanism [33] aligning with cardioprotection [32].

^mAnion channel-CFTR forms a cancer prosurvival pathway [37] and represents a cardioprotective mechanism [36].

ⁿCation channel-K(ATP) represents a cancer prosurvival factor [39] and aligns with cardioprotection [38].

Addressing heart failure

Not only do prosurvival but also pro-apoptotic cardiac/vascular mechanisms mechanistically align with cancer [2]. This has significance in heart failure for which biomarkers and mechanisms are highly sought after. For example, dipeptidyl peptidase IV (DPPIV) was found to act *via* SDF-1 modulation as a tumour suppressor [40]. Mechanistically, SDF-1, as down-regulated by DPPIV, was exposed as a regulated prosurvival pathway in cancer [40]. Another prior study, [41] indicated that sanguinarine, a plant derivative, relates to suspected precancerous alterations. This agent is a natural DPPIV inhibitor and assists in explaining a potential oncogenic mechanism [42]. I consider that as a follow-on, sanguinarine is cardioprotective by augmenting SDF levels secondary to DPPIV inhibition.

In heart failure, SDF is beneficial consistent with its prosurvival role [43]. Recently, remote ischaemic preconditioning has been demonstrated to relate to humoral production of SDF-1 with serum levels of DPPIV downregulating this factor [44]. Circulating DPPIV aligns with cardiac dysfunction in heart failure and thus is a suited biomarker and target for same. Such key observations were predicted in cancer from an anti-survival viewpoint (Table 2).

Addressing hypertension and atheroma

As anticipated, tumour suppression as an anti-survival mechanism counters hypertension which represents, to a significant degree, a vascular smooth muscle progrowth imbalance. Induction of senescence *via* Nutlin-3a prevents ubiquitin ligase MDM2, a negative regulator, from interacting with the long established tumour suppressor p53, thus leading to inhibition of proliferation of pulmonary arterial smooth muscle cells [45]. Another well equally established tumour suppressor, PTEN, on upregulation *via* PPAR γ agonist leads to hypoxic apoptosis of pulmonary arterial vascular smooth muscle cells and provides a recent rationale for therapeutics to target pulmonary hypertension [46]. Table 2 summarizes several of these mechanistically shared aspects between cancer and vascular dysregulation seen in hypertension.

Notably, a number of factors, *viz*: angiotensin II, interleukin-6, endothelin, sphingosine-1-phosphate, chromogranin, enolase and VEGF [4,5] relate to cardiocytoprotection and cancer. Any imbalance in expression of these progrowth factors may

Table 2. Alignment of mechanisms/factors relating cancer to cardiac failure, hypertension and atheroma.

Cancer	Cardiac failure, hypertension, atheroma
DPPIV/SDF ^a	DPPIV/SDF-heart failure ^a
p53 ^b	p53-pulmonary hypertension ^b
PTEN ^c	PTEN-pulmonary hypertension ^c
VEGF/NF- κ B ^d	VEGF/NF- κ B-hypertension ^d
Interleukin-6 Chromogranin Enolase Endothelin Sphingosine-1 -phosphate Angiogenic factors: (VEGF/FGF/HGF) ^e	Prosurvival/progrowth factors- atheroma/hypertension ^e

^aProsurvival SDF (stromal cell-derived factor) levels are regulated in cancer by tumour suppressor DPPIV (dipeptidyl peptidase IV) [40], and in heart failure SDF being prosurvival is beneficial [43] with DPPIV opposing this via SDF degradation.

^bTumour suppressor, p53, is involved in inhibition of pulmonary arterial smooth muscle cell growth thus targeting pulmonary hypertension [45].

^cTumour suppressor, PTEN, is also involved in inhibiting pulmonary arterial smooth muscle cell growth and targets pulmonary hypertension [46].

^dProsurvival cancer VEGF/NF- κ B axis [48] has been considered a target for hypertension [47].

^eIn addition to their cardiocytoprotective role [4,5], progrowth factors align with hypertension and atheroma formation-reflecting vascular dysfunction.

promote hypertension and vascular dysfunction/atheroma [4,5]. Interestingly, in regards the latter factor, VEGF, prosurvival factor NF- κ B was found to be involved in a novel mechanism regulating VEGF-related stretch-induced cardiac hypertrophy [47]. Here it was stated that: '*Elucidation of this novel mechanism may provide a target for developing future pharmacotherapy to treat hypertension and heart disease*'. Notably, the VEGF and linked NF- κ B prosurvival mechanism was foreshadowed in therapy resistant, relapsing cancer [48] (Table 2). Unsurprisingly, statin treatment, *via* RhoA prenylation inhibition, induces vascular smooth muscle cell apoptosis thus opening a further therapeutic window for hypertension and atheroma management [49] (see Table 5-below). This also aligns with the cancer mechanism [50]. In apoE(-/-) mice which were provided with a Western-type diet, atherosclerotic lesions readily formed [51]. Simvastatin led to an up-regulation of Bcl-2 and Bcl-xL expression which are classical cancer oncogenes and decreased tumour suppressor p53 expression. This statin may therefore be said to prevent apoptosis in the labile atherosclerotic plaque thus potentially leading to plaque stabilization (see Table 5-below). Importantly, this recently uncovered statin-related interplay of established cancer prosurvival/pro-apoptotic factors in the context of atheroma is reflective of the value of comparison of cancer

mechanisms to the cardiac/vascular context.

Overall, in terms of clinical relevance, therapeutics that shall either promote tumour suppression (anti-growth) or agents that target excessively produced progrowth, proinflammatory factors, may well be able to address hypertension and atheroma (Table 2). The treatment puzzle is made complex by the fact that progrowth factors are in themselves cardioprotective and anti-growth mechanisms may promote cardiac damage and lead to exacerbating heart failure. To aid addressing this, I have already stated the importance for maintaining a balance or homeostasis in regards pro-survival vs pro-apoptotic factors as the key message for clinicians [5].

Addressing cardiac hypertrophy

In cardiac hypertrophy one would anticipate that pro-survival pathways are unbalanced in favour of excessive progrowth stimuli. Notably, statins target cardiac hypertrophy via inhibition of RhoA geranylgeranylation/prenylation and membrane localization [52] (see Table 5-below). This neatly aligns with the mechanism for statin targeting RhoA in cancer [50].

Hypertrophic-related Ras is pro-growth in the heart and its balancing tumour suppressor, RASSF1A, downregulates the Ras-Raf1-Erk1/2 cardiac circuit – truly a case of ‘where the heart and cancer meet’ [2,53]. It was observed that the relationship between signal paths controlling tumour growth and cardiac hypertrophy (viz: proto-oncogenes positively impacting on the development of hypertrophy) is of very significant interest and importance [53]. Thus appreciating the precise mechanisms involved is key and notably pro-apoptotic factors such as tumour suppressors maintain a balance in regulating hypertrophic signaling and form tangible therapeutic targets for cardiac hypertrophy.

KCNQ1 is a potassium channel protein and aids in cardiomyocyte repolarisation. Already in cancer, it is seen that low expression of KCNQ1 is associated with poor survival and this channel factor is thus classified as a tumour suppressor [54]. Recently [55], in a model for cardiac hypertrophy, a major reduction in expression of KCNQ1 is evident. This is consistent with KCNQ1 as a growth inhibitor antagonizing excessive pro-survival stimulus in the heart. This factor thus forms part of growth control-homeostatic balance-as forecast from cancer. A summary of these relationships is presented in Table 3.

Addressing co-morbidities

Cardiac and vascular diseases oftentimes present as co-morbid conditions. For example, hypertension with cardiac hypertrophy share an imbalance of progrowth mechanisms that cancer also displays (above). Shared pro-apoptotic, anti-survival mechanisms, may explain, for example, such co-morbid features as heart failure with aneurysm formation. In this scenario, the transcriptional regulator Kruppel-like factor 15 (Klf15) levels are markedly reduced in heart failure and aortic aneurysm [56]. In Klf15 deficient animal models these

Table 3. Alignment of mechanisms/factors relating cancer and cardiac hypertrophy.

Cancer	Cardiac hypertrophy
RhoA prenylation ^a	RhoA prenylation ^a
Ras/RASSF1A ^b	RASSF1A/Ras ^b
KCNQ1 ^c	KCNQ1 ^c

^aRhoA prenylation is a post-translational pro-survival pathway in cancer [50]—the same mechanism is present in cardiac hypertrophy [52].

^bRas is a noted pro-survival path in cancer and is balanced by its tumour suppressor, RASSF1A [53] with the same mechanism applying in the heart regulating cardiac hypertrophy [53].

^cKCNQ1 (a potassium channel factor) is a tumour suppressor [54] and is lowered in cardiac hypertrophy [55].

co-morbid pathologies develop in a p53-dependent and p300 acetyltransferase-dependent manner. Activation of Klf15 inhibits p300-mediated acetylation of p53 and deficiency of pro-survival Klf15 produces hyperacetylation of p53 in heart and aorta. Importantly, p300-mediated p53 acetylation is proving to be a key post-translational modification for p53 function and is reduced by MDM2 inhibitor [57]. Thus there is a molecular commonality between these co-morbidities that rests on a balance between pro-survival/apoptotic regulation via Klf15. Recently, vascular smooth muscle cell apoptosis in aneurysms was related to MDM2 inhibitor reduction with resultant increase in p53 activity [58]. This is reminiscent of MDM2 involvement in regulating p53 in the context of proliferation of pulmonary arterial smooth muscle [45].

Unsurprisingly, this balance in pro-survival/apoptosis has been mechanistically reflected within the context of cancer, where Kruppel-like factor (Klf6) silencing resulted in p53 upregulation and apoptosis in hepatic carcinoma cells [59]. Clearly, the Kruppel-like factor balance of pro-survival/apoptosis in the cardiac/vascular system is closely mimicked and forecast via cancer.

Not only are co-morbid features recognized within the cardiac and vascular system but also it must be recalled that cardiac-vascular diseases are not isolated in their context—they oftentimes present concurrently alongside metabolic disturbances such as insulin resistance and obesity. Proinflammatory factors such as adipocytokines and oncoproteins/pro-survival factors in concert support cardiac hypertrophy and upset homeostatic balance to favour hypertension/atheroma (above). Examples are interleukin-6 and TNF α [5]. Further, as TNF and interleukin-6 relate to atheroma, hypertension and cardiomyopathy, this may be considered an overall excessive ‘pro-survival’ reaction. These are feature hallmarks of obesity-associated diabetes with the metabolic syndrome. In addition, DPPIV, a cancer tumour suppressor and agent countering cardioprotection (above) and playing a role in heart failure is itself an adipocytokine [60]. This shines a clearer light on the link between obesity/metabolic disease and potentially

damaging consequences this has on the cardiac-vascular system. Thus both pro-survival and pro-apoptotic pathways are involved that mimic the cancer context. An overall summary is given in **Table 4**.

Table 4. Mechanisms/factors including inflammation relating cancer to cardiac-vascular diseases and co-morbidities.

Cancer	Cardiac-vascular diseases/ Co-morbidities
Kruppel-like factor/p53 ^a	Kruppel-like factor/p53–heart failure/aneurysm ^a
Adipocytokine-il-6/TNF ^b	il-6/TNF–cardiomyopathy/hypertension/atheroma/insulin resistance/obesity ^b
Adipocytokine-DPPIV ^c	DPPIV–heart failure ^c
Inflammation: NF- <i>kappa</i> B/ ox-LDL–LOX1 ^d	Inflammation: NF- <i>kappa</i> B/ ox-LDL–LOX1–atheroma ^d

^aKruppel-like factor, family member Klf6, downregulates p53 tumour suppressor in the cancer context, thereby providing a pro-survival signal [59]–Kruppel-like factor, family member Klf15, inhibits p53 activation and deficiency of this factor relates to co-morbid development of heart failure with aneurysm [56].

^bProinflammatory cytokines, such as adipokines interleukin-6 and TNF from adipose tissue, may favour a progrowth response (the latter via NF-*kappa* B activation) relevant in the cancer context and evident in cardiomyopathy/hypertension/atheroma [5] alongside being related to co-morbid features such as obesity/insulin resistance.

^cAdipokine DPPIV is a tumour suppressor and counters cardioprotection [60].

^dInflammation forms a notable mechanistic commonality between cancer and cardiac/vascular disease, as exemplified by ox-LDL and its receptor LOX-1 activating the NF-*kappa* B inflammatory cascade which in turn promotes cancer and atheroma/vascular dysfunction [62].

Addressing inflammation—a common link between cancer and heart diseases

As I have detailed [5,6], inflammation is a major mechanistic common linkage between many conditions such as atheroma/vascular disease, cardiac disease, cancer and neurological disease. Obesity and diabetes, important co-morbidities of cardiac and vascular diseases, are related to ‘metinflammation’, or metabolic inflammation, resulting in insulin resistance [61].

Targeting inflammatory response *via* modulating the NF-*kappa* B signaling axis—a central player—by such newly ‘repurposed’ immune modulatory agents as Amlexanox may hold significant promise for a multitude of inflammatory-related conditions such as atheroma [6]. Interestingly, the link between cancer and inflammation, and NF-*kappa* B and atheroma has been strongly underlined with ox-LDL and its receptor LOX-1 [62]. This ligand-receptor complex activates the inflammatory pathway through NF-*kappa* B leading to cell transformation. LOX-1 maintains the transformed state in a diverse range of

Table 5. The aligning of therapeutics for cancer and cardiac-vascular diseases.

Cancer	Cardiac/vascular
iNOS/Cox-2/S-nitrosylation ^a RhoA prenylation ^b Bcl-2–Bcl-xL/p53 ^c	Statin: iNOS/Cox-2/ S-nitrosylation–infarct sparing ^a Statin: hypertension/cardiac hypertrophy ^b Statin: Bcl-2–Bcl-xL/p53 atheroma ^c
NSAID: Cox-2/ PKC delta; EGFR/MAPK /Cox-2 ^d	NSAID: Cox-2/PKC delta–infarct sparing; Cox-2/EGFR/MAPK–cardiac hypertrophy; Cox-2–pulmonary hypertension/atheroma ^d
DHA: Lox/Cox-2/ NF- <i>kappa</i> B ^e	DHA: Lox/Cox-2/ NF- <i>kappa</i> B–atheroma; hypertension ^e
Allicin: Nrf2 ^f	Allicin: Nrf2–cardiac hypertrophy ^f

^aiNOS/Cox-2/S-nitrosylation is pro-survival in cancer [33] and this pathway may be modulated by statin therapy to lead to cardioprotection [32].

^bRhoA prenylation, a cancer pro-survival mechanism, may be targeted by statin therapies to moderate hypertension [49] and cardiac hypertrophy [52].

^cCancer pro-survival/oncogenic factors Bcl-2 and Bcl-xL and tumour suppressor p53 may be regulated via statin therapeutics to beneficially increase atherosclerotic plaque stability [51].

^dNon-steroidal anti-inflammatory agents (NSAIDs) target Cox-2 and PKC delta, a pro-survival pathway both in cancer [66] and the heart [65] and interfere with this infarct-sparing mechanism. Cox-2/EGFR/MAPK signal cascade acts in cancer [67] as well as being a pro-hypertrophic mechanism in the heart [68]. Following on, targeting Cox-2 may be beneficial in hypertension [69] and atheroma/vascular dysfunction [70].

^eThe omega-3 polyunsaturate Docosahexaenoate, DHA, downregulates Cox-2 and NF-*kappa* B pro-survival signaling axis in cancer [72] via the arachidonic lipoxygenase Lox [73]. In the vascular system, DHA counters pro-survival mechanisms in hypertension [74] and by downregulating Cox-2/NF-*kappa* B pro-survival axis also counters atheroma formation [71] notably via the metabolic products of Lox.

^fAllicin (diallyl thiosulfinate), increases Nrf2 to induce cancer cell apoptosis [79] and counters pro-growth stimulus that results in cardiac hypertrophy [78].

cancers and supports tumor growth. Upregulation of LOX-1 by ox-LDL is connected to endothelial cell dysfunction, smooth muscle cell growth and migration seen in atheroma and these are all matching features of the tumorigenic phenotype. It was stated: ‘As in atherosclerosis, ox-LDL and its receptor LOX-1 activate the inflammatory pathway through nuclear factor-kappa B, leading to cell transformation.’ [62] (Table 4). This leaves no doubt in respecting the tight relation between cancer and vascular disease—a theme that I have portrayed in extending to cardiac and vascular diseases generally (Figure 1).

Addressing therapeutics

One of the central aspects arising from the close relation between

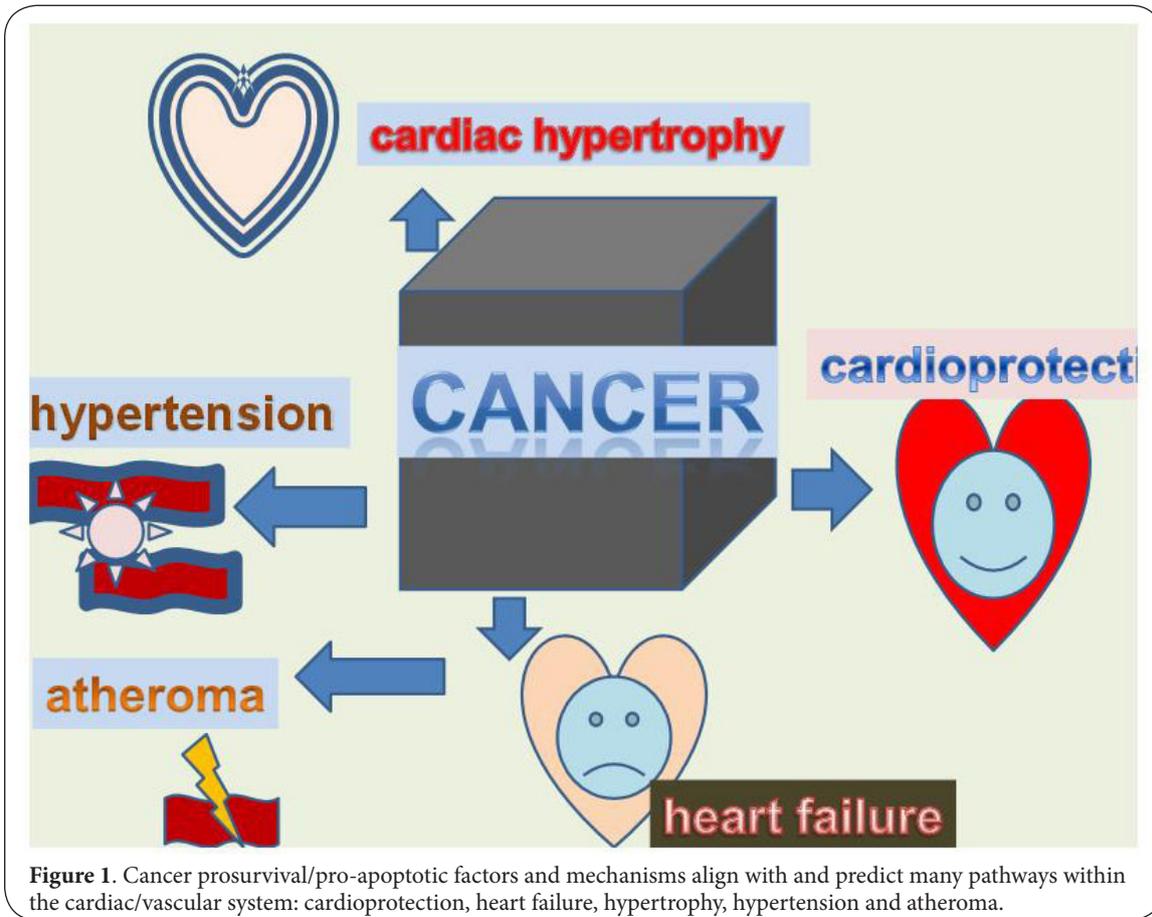


Figure 1. Cancer pro-survival/pro-apoptotic factors and mechanisms align with and predict many pathways within the cardiac/vascular system: cardioprotection, heart failure, hypertrophy, hypertension and atheroma.

heart and cancer pro-survival and apoptotic mechanisms is the fact that agents targeting cancer shall have a detrimental effect on cardiomyocyte physiology [2]. This defines the relatively new field of *cardio-oncology* [63]. Recently, it was indicated that human epidermal growth factor receptor-2 (HER2) signaling is pro-survival not only in mammary gland carcinoma but also is a matching pro-survival mechanism in cardiomyocytes [64]. Thus, toxicity towards the heart is certainly a negative issue in terms of employing HER2 targeted therapeutics for cancer. Means to optimize such anti-cancer therapeutics were considered through screening against induced pluripotent stem cells in an attempt to idealize cancer therapy selection on an individual patient (personalised medicine) basis [64].

The relation of statins to mechanisms involved in cancer may be usefully adapted for cardiac and vascular disease therapeutics—a theme pursued throughout this article. For example, Atorvastatin induces cardioprotection and is infarct-sparing *via* cancer mechanisms [32]. Further, statin therapy may, *via* RhoA prenylation inhibition, a cancer therapeutic target, result in vascular smooth muscle cell programmed cell death, thence delivering prospective therapeutics for vascular diseases such as hypertension [49]. Simvastatin, by increasing expression of Bcl-2 and Bcl-xL pro-survival oncogenic factors,

and diminishing levels of tumour suppressor p53 expression, targets labile atherosclerotic plaques leading to plaque stabilization [51]. In respect to cardiac hypertrophy, statin therapy *via* targeted inhibition of RhoA geranylgeranylation/prenylation and membrane localization—a cancer pro-survival mechanism—addresses a means to combat cardiac hypertrophy [52].

The established non-steroidal anti-inflammatory (NSAID) drug target, Cox-2, is highly relevant to my discussion of cardiac and vascular diseases and cancer overall. It is understood that Cox-2 is cardioprotective and pro-survival factor in cancer [2]. Anti-inflammatory agents such as NSAIDs logically increase cardiac risk status as these drugs target Cox-2. Mechanistically, Cox-2 is cardiocytoprotective *via* PKC delta [65]—a mechanism involving Cox-2/PKC delta as foretold by cancer [66]. Further, the pro-survival cascade involving EGFR, Cox-2 and MAPK acts in cancer [67] and again foretells the mechanism for prohypertrophic cardiac signaling involving Cox-2/EGFR/MAPK [68]. In the vascular system, Cox-2 is also pro-survival, thus targeting Cox-2 may alleviate pulmonary hypertension [69]. In atherogenesis, pro-survival Cox-2 is involved as a mediator. Somewhat predictably, it is involved in endothelial dysfunction/resistance to apoptosis seen in diabetic vasculature for example [70]. Along with TNFalpha

and interleukin-6, prosurvival Cox-2 forms a therapeutic target for anti-atherogenic therapies.

Further, in terms of relevance to Cox-2 mechanisms, are dietary polyunsaturated fatty acids, which may be considered broadly speaking as potential therapeutic agents in their own right. The omega-3 polyunsaturate docosahexaenoate (DHA) targets and inhibits Cox-2 along with NF- κ B and thus reduces pro-inflammatory stimuli for atheroma development [71]. Specifically, the arachidonic lipoxygenase 15-LOX-1 metabolizes DHA, with the products of which act to downregulate Cox-2. In parallel with this observation, DHA downregulates Cox-2 and NF- κ B in cancer [72] and the 15-LOX-1 metabolites are noted in particular in this respect [73]. Unsurprisingly, of late, DHA as an anti-growth factor is found to counter hypertension [74]. Having said this, and understanding the prosurvival mechanisms targeted by DHA from cancer, it is to be anticipated that DHA may well fail in terms of prevention of heart disease overall – a conclusion that is becoming apparent [75]—hence limiting DHA as a therapy in itself. This may be understood in light of the notion that DHA potentially targets prosurvival mechanisms in cardiomyocytes, thus countering any potential benefit to be gained from its vascular effects. This scenario underscores the importance of viewing the cardiac and vascular systems as two parts of one whole [5] when cross-comparing to cancer prosurvival mechanisms.

Other more novel therapeutics stem from considering the concept linking heart and cancer mechanistically. It is noted that increasing cellular signaling factor cAMP *via* phosphodiesterase III (PDEIII) targeting with cilostazol acts in concert with a DPPIV inhibitor, MK0626, in cardioprotection [76]. These effects in the diabetic disease model are associated with increase in cardiomyocyte cAMP levels and PKA activity and downregulation of tumour suppressor PTEN level alongside downstream oncogenic prosurvival cascade activation. Amlexanox, an agent employed for decades as an immunomodulator [6], *via* targeting NF- κ B noncanonical kinases TBK1 and *ikkepsilon*, reduces activation of the adipocyte phosphodiesterase, PDE3B. Thus Amlexanox therapy is capable in the animal model to restore PKA signaling and augment cAMP in adipocytes [77] similar to the infarct sparing cardiomyocyte mechanism in diabetes [76]. In this regard, its ability to target adipose tissue thus countering obesity and thereby have an impact on insulin-resistance lends a major future potential for this novel ‘repurposed’ agent for management of obesity/diabetes-related cardiac/vascular disease.

An interesting further potential addition to the therapeutic armamentarium is the agent Allicin, (diallyl thiosulfinate), an active component in freshly crushed garlic [78]. This counteracts cardiac hypertrophic changes by decreasing levels of reactive oxygen species. Allicin significantly increased mRNA expression and protein levels of Nrf2- antioxidant signaling pathway. Notably, Allicin has been shown to act through

enhancing Nrf2 levels in cancer to induce apoptosis and forms an anti-survival strategy in that context [79]. Hence cancer studies foretold Allicin’s mechanism to reduce an imbalance in pro-growth stimulus leading to cardiac hypertrophy. **Table 5** outlines shared therapeutics between cancer and cardiac/vascular diseases.

Conclusion

As was stated earlier [80], atheroma and cardiac disease such as hypertrophy and ultimate heart failure is notably in part due to a series of unbalanced growth promoting activities in the system as a whole - the ‘*coronary hypothesis in hypertension*’. Blood pressure lowering alone does not reverse cardiac pathology in itself and this prompts a totalistic approach— directing attention to the overall imbalance in cardiac and vascular homeostasis [5]. Disease-related imbalances and mechanisms involved in growth promotion versus inhibition in the cardiac-vascular system may be forecast from studying cancer. The aim of this article is to bring to the foreground this much overlooked strategic approach. As a reflection of this association, it has been recently stated in regards pulmonary arterial hypertension (PAH): “...PAH shares common aberrantly activated pathways with cancers that lead to proliferation and survival of pulmonary arterial smooth muscle cells, among others, within the artery wall and narrowing the lumen” [81]. Therefore, cancer pro-growth factors not only align with cardio-protection but also are pro-hypertensive/atherogenic/cardio-hypertrophic. In the field of *cardio-oncology*, it is emphasized that by targeting cancer one may also be targeting the heart/vascular system [2,64]. Clinicians need to be clearly aware of this firm relation between the two since prosurvival/anti-survival mechanisms between heart/vascular system and cancer align. By taking the mechanistic ‘cue’ from cancer, one may bring forward novel therapeutics into cardiac and vascular medicine. My contention is that the highly sought after ‘*holy grail*’ of understanding cardioprotective mechanisms along with improved appreciation of vascular/heart disease overall may well be greatly facilitated *via* a detailed cross-examination of cancer itself.

Competing interests

The author declares that he has no competing interests.

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