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Common cardiovascular medications in cancer therapeutics

Christos Vaklavas [a,b], Yiannis S. Chatzizisis [c], Apostolia Maria Tsimberidou [a,*]

[a] Phase 1 Program, Department of Investigational Cancer Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA
[b] Department of Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL, USA
[c] 1st Cardiology Department, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece

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ABSTRACT

Cardiac glycosides, statins, β-blockers, angiotensin-I converting enzyme inhibitors (ACEIs), and angiotensin II type 1 receptor blockers (ARBs) are widely used cardiovascular medications with pleiotropic properties. Many of these medications have been investigated in other diseases, including cancer. Cardiac glycosides and statins have advanced to clinical trial testing in cancer therapeutics, with variable success.

Early observations in breast cancer were consistent with a more benign histologic phenotype among women taking digitalis compared to their counterparts who did not receive cardiac glycosides. Cardiac glycosides can induce apoptosis in cancer cells through various mechanisms and sensitize them to the effects of antitumor therapy. By blocking the generation of prenyl units, statins impair prenylation, an important posttranslational modification of proteins whose function depends on membrane anchoring. Statins also impair protein folding and N-glycosylation and inhibit the upregulation of cholesterol synthesis associated with chemotherapy resistance. Stress and catecholamine release promote tumor growth and angiogenesis, effects that can be mitigated by β-blockers. Components of the renin–angiotensin–aldosterone system are expressed in various cancers and are involved in carcinogenesis and tumor progression. Angiotensin II has potent mitogenic and angiogenic properties that can be blocked with ACEIs and ARBs.

Although it is unclear whether the promising preclinical activity of many cardiovascular medications has clinically meaningful implications beyond the benefit in cardiovascular morbidity and mortality, the prevention or improvement of prognosis of common malignancies with medications known to reduce cardiovascular morbidity and mortality is encouraging and deserves further clinical investigation.

Contents

1. Introduction

Many widely used cardiovascular medications have at times attracted the attention of clinicians and researchers in cancer medicine because their versatile properties may be useful in cancer therapeutics and prevention. Insightful research has shed light on the pleiotropic properties of the cardiac glycosides, statins, β-blockers and inhibitors of the renin–angiotensin–aldosterone system in many disease states including cancer. Cardiac glycosides and statins have

Abbreviations: ACEI, angiotensin-I converting enzyme inhibitors; ARB, angiotensin II type 1 receptor blockers; ATP, adenosine triphosphate; DNA, deoxyribonucleic acid; HIF-1, hypoxia inducible factor 1; NF-κB, nuclear factor kappa B; GDP, guanosine diphosphate; GTP, guanosine triphosphate; PI3K, phosphatidylinositol 3-kinase; RAAS, renin–angiotensin–aldosterone system; Rab, ras-associated binding; Rheb, ras homolog enriched in brain; Rho, Ras homologous; RNA, ribonucleic acid; VEGF, vascular endothelial growth factor.

* Corresponding author at: The University of Texas M. D. Anderson Cancer Center, Department of Investigational Cancer Therapeutics, Unit 455, 1515 Holcombe Boulevard, Houston, TX 77030, USA. Tel.: 713 792 4259; fax: 713 794 3249.
E-mail address: atsimber@mdanderson.org (A.M. Tsimberidou).

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A

Cardenolides

Digitalis purpurea and Digitalis lanata
Digoxin, digitoxin, gitoxin, digitonin, lanatoside A-C

Nerium oleander
Oleandrin, cardenolide N-1, cardenolide N-4

Strophanthus gratus
ouabain

Beaumontia brevituba
Digitoxigenin, oleandrigenin, α-L-cymaroside

Asclepias curassavica
Calotropin, 16α-acetoxycalotropin, 15β-hydroxycalotropin, calactin, asclepin, uscharidin, uscharin, uzarigenin

Calotropis procera
Calotropin, calactin, uscharin, voruscharin, 2''-oxovoruscharin

Bufadienolides

Bufo bufo gargarizans
Bufalin, cinobufalin

Bufo marinus
marinobufagin

Urginea maritima
Proscillaridin A, scillaren A

Urginea lydenburgensis
Scillicyanosidin, lydenburgenin

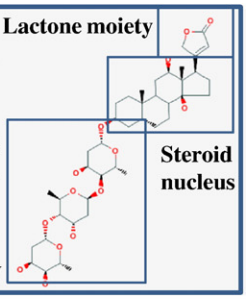
Urginea altissima
urginin

Drimia robusta
12β-hydroxyscillirosidin; 6β-acetoxy-3β,8β,14β-trihydroxy-12-oxobufa-4,20,22-trienolide

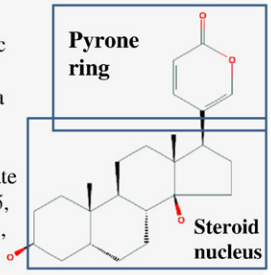
Helleborus niger
Helleborein, helleborin, hellebrin, hellebrigenin

B

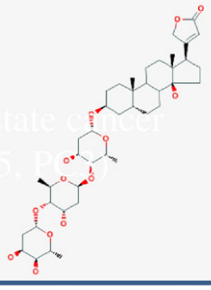
Digoxin
Concentration for cardiac indication: 0.64 – 2.6 nM
0.1 – 10 μM: prostate cancer (PC3 M-Pro4, PC3 M-LN4, LNCaP, DU145, PC3), epithelial cancers (HeLa)



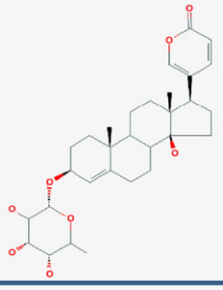
Bufalin
0.1 – 10 μM: monocytic leukemia (THP1), lymphoblastic leukemia (MOLT-3), colon adenocarcinoma (COLO320DM), prostate cancer (LNCaP, DU145, PC3), leukemia (THP-1, U937)



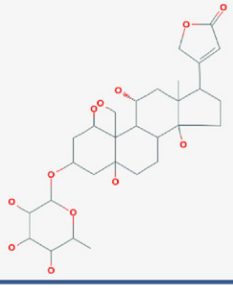
Digitoxin
Concentration for cardiac indication: 20 – 33 nM
1 – 10 μM: prostate cancer (LNCaP, DU145, PC3)
3 – 33 nM: renal adenocarcinoma (TK10), breast cancer (MCF-7), melanoma (UACC-62), leukemia (K562)



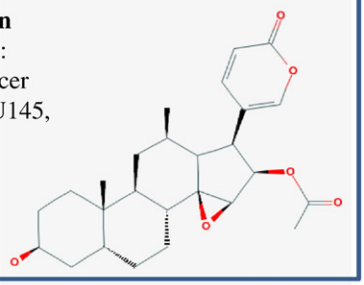
Proscillaridin A
30 – 100 nM: breast cancer (MCF-7)



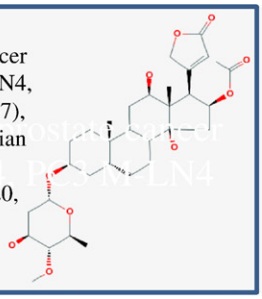
Ouabain
0.1 – 10 μM: prostate cancer (PC3 M-Pro4, PC3 M-LN4, LNCaP, DU145, PC3), epithelial cancers (HeLa), breast cancer (MDA-MB-435 s)



Cinobufagin
0.1 – 10 μM: prostate cancer (LNCaP, DU145, PC3)



Oleandrin
0.1 – 1 μM: prostate cancer (PC3 M-Pro4, PC3 M-LN4, DU145), leukemia (U937), melanoma (BRO) , ovarian cancer (CaOV-3), lung cancer (Calu1, NCI-H520, Sklu1, A549)



advanced to clinical trial testing in cancer therapeutics, with variable success.

Although at the preclinical level there may be enough evidence to suggest a beneficial antitumor effect, at the clinical level such an effect may not be easily discerned secondary to the coexisting confounding cardiovascular morbidity. It is largely still unclear whether the promising preclinical activity seen with many cardiovascular medications translates into clinically meaningful outcomes beyond the indisputable benefit in cardiovascular morbidity and mortality. However, the prospect of preventing or improving the prognosis of common malignancies with safe and affordable medications that already reduce the morbidity and mortality of the leading cause of death in the developed world is very appealing and deserves further clinical investigation.

The purpose of this review was to summarize the preclinical evidence of antitumor activity of cardiac glycosides, statins, β-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers — medications that are widely prescribed for cardiovascular indications. The rationale for their use in cancer therapeutics and prevention, as well as results of early phase clinical trials, are also discussed.

2. Cardiac glycosides

Cardiac glycosides comprise a large family of naturally derived compounds (Fig. 1, panel A) (Prassas & Diamandis, 2008). Although they show considerable diversity, they share a common structural motif (Prassas & Diamandis, 2008). The core structure consists of a common steroid nucleus, which constitutes the minimum structure for receptor recognition and induction of protein conformational changes (Fig. 1, panel B) (Schonfeld et al., 1985). The nature of the lactone moiety attached at position 17 of the steroid nucleus defines the class of the glycoside. Compounds extracted from foxglove and oleander, such as digitalis, digoxin, and oleandrin, belong to the cardenolide class and share a five-membered unsaturated butyrolactone ring at position 17. Compounds extracted from plants as well as animals (mainly toads), such as proscillaridin A and bufalin, belong to the bufadienolide class and share a six-membered unsaturated pyrone ring at position 17 (Mijatovic et al., 2007; Newman et al., 2008; Prassas & Diamandis, 2008). A sugar moiety attached at position 3 of the steroid nucleus affects the pharmacokinetic and pharmacodynamic properties of each cardiac glycoside (Fig. 1, panel B) (Prassas & Diamandis, 2008).

Members of the cardiac glycoside family have been in clinical use for many years for the treatment of heart failure and atrial arrhythmias. The mechanism of their positive inotropic effect has been well characterized. By inhibiting the Na^+K^+-ATPase, they increase the intracellular concentration of Na^+, thereby decreasing the driving force for the Na^+/Ca^{++} exchanger. The intracellularly retained Ca^{++} is accumulated in the sarcoplasmic reticulum and is released on subsequent depolarizations, leading to enhanced contractility.

2.1. Clinical observations of cardiac glycosides

The antiproliferative effect of cardiac glycosides has been known for years (Shiratori, 1967). Early observations in breast cancer included more benign histologic characteristics and lower proliferative capacity in tumors from women on digitalis treatment compared with their counterparts not taking cardiac glycosides (Stenkvist et al., 1979). Women on cardiac glycosides also had a lower recurrence rate (Stenkvist et al., 1982), and in a 20-year follow up study, their death rate from breast carcinoma was significantly lower compared with that of their counterparts (Stenkvist, 1999). Case-control studies, however, have shown high morbidity and mortality in patients on digitoxin, primarily due to cardiac disease and old age, which highlights the inherent difficulty in isolating, in epidemiologic studies, an anticancer effect attributable to cardiac glycosides (Haux et al., 2001).

2.2. Experimental data for cardiac glycosides

On the basis of animal models, it was once thought that the doses of cardiac glycosides required to achieve an antitumor effect in humans would be toxic (Haux et al., 2001; Perne et al., 2009). This concept was challenged, however, by subsequent studies that showed that cardiac glycosides can inhibit growth and induce apoptosis in various human cell lines at non-toxic concentrations (Kawazoe et al., 1999a; McConkey et al., 2000). Indeed, there are species-related differences in sensitivity to cardiac glycosides making extrapolations from animal models to humans difficult (Gupta et al., 1986).

2.3. Antitumor effects of cardiac glycosides

The antitumor effects of cardiac glycosides are summarized in Fig. 2. The unifying characteristic of cardiac glycosides is inhibition of the Na^+K^+-ATPase. However, not all antitumor effects seem to be associated with this inhibition (Newman et al., 2008), and in addition, the downstream effects may not be uniform among the various cancer types.

2.3.1. Cardiac glycosides induce apoptosis in cancer cells

Apoptosis, a form of programmed cell death, is dysregulated in more than 50% of neoplasms (Hotchkiss et al., 2009). Cardiac glycosides were shown to induce apoptosis in cancer cells by various mechanisms. They reduce the membrane potential and increase the intracellular concentration of Na^+ and Ca^{++} in tumor cells, consistent with their activity in cardiac myocytes. Unlike in cardiac myocytes, however, reduction in membrane potential and increases in the intracellular concentration of Na^+ were shown to induce apoptosis in human colon adenocarcinoma, monocytic and lymphoblastic leukemia cell lines (Kawazoe et al., 1999a). Sustained intracellular Ca^{++} increases in prostate adenocarcinoma cell lines treated with cardiac glycosides preceded the induction of apoptosis (McConkey et al., 2000). Oleandrin, via increases in intracellular Ca^{++}, led to increased mitochondrial permeability, release of proapoptotic proteins, and activation of caspases, a family of aspartate-specific cysteine proteases that cleave cytoskeletal proteins and lead to DNA degradation, chromatin condensation, and lamin cleavage (McConkey et al., 2000). Overexpression of the antiapoptotic protein bcl-2, which, at least in part, prevents alterations in intracellular Ca^{++} (McConkey & Orrenius, 1997), rendered the tumor cells resistant to cardiac glycoside-induced apoptosis (Kawazoe et al., 1999a). Increases in the intracellular Ca^{++} induced by cardiac glycosides can also lead to activation of calcineurin (a serine/threonine phosphatase) and transcriptional upregulation of the fibroblast-associated cell surface ligand (FasL/CD95/APO-1) (Raghavendra et al., 2007). FasL can induce apoptosis via association with its cognate receptor Fas (CD95, tumor necrosis factor receptor superfamily, member 6), a prototypical death receptor that regulates tissue homeostasis through the induction of apoptosis (Nagata, 1999).

Fig. 1. Panel **A** provides a list of the cardiac glycosides according to class. The major source of the glycoside is shown in italics. Panel **B** shows the chemical structure of the major cardiac glycosides [data retrieved from ChemBank Database (http://chembank.broadinstitute.org/)] and the range of concentrations in which a growth inhibitory or apoptosis inducing effect was reported. Literature, (Watabe et al., 1998; Kawazoe et al., 1999a; Manna et al., 2000; McConkey et al., 2000; Kurosawa et al., 2001; Smith et al., 2001; Yeh et al., 2001, 2003; Kometiani et al, 2005; Lopez-Lazaro et al., 2005; Bielawski et al., 2006; Frese et al., 2006; Newman et al., 2006; Ramirez-Ortega et al., 2006; Mijatovic et al., 2007; Newman et al., 2008).

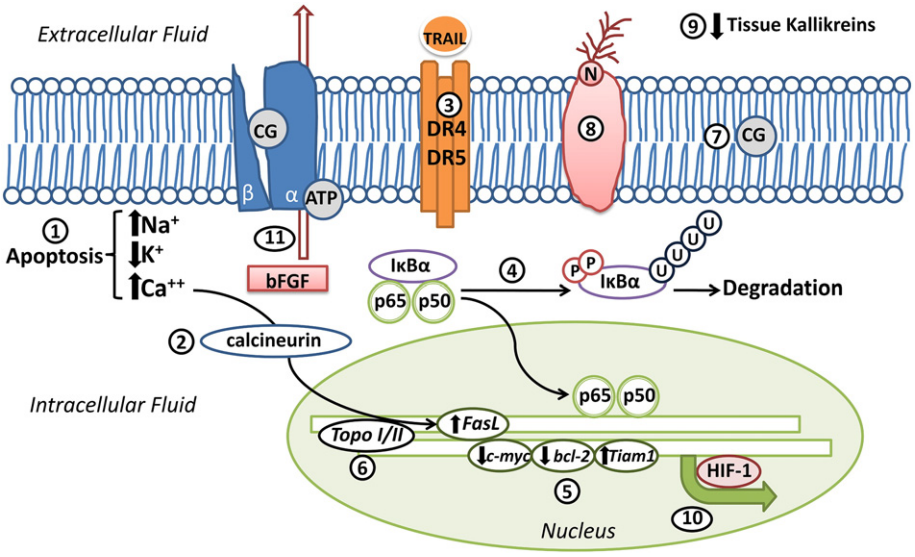


Fig. 2. Schematic representation of the actions of cardiac glycosides in cancer cells. 1. Cardiac glycosides reduce membrane potential and the intracellular concentration of K^+, and increase the intracellular concentration of Na^+ and Ca^{++}, thereby inducing apoptosis in cancer cells (Hughes et al., 1997; Kawazoe et al., 1999a; McConkey et al., 2000). 2. Increases in the intracellular Ca^{++} lead to activation of calcineurin and upregulation of FasL (Raghavendra et al., 2007). 3. Cardiac glycosides upregulate DR4 and DR5 and render cancer cells susceptible to apoptosis (Frese et al., 2006). 4. Cardiac glycosides suppress NF-κB by inhibiting the phosphorylation and degradation of its inhibitory subunit, IκBα (Manna et al., 2000). 5. Cardiac glycosides downregulate the expression of the *c-myc* and *bcl-2* oncogenes (Masuda et al., 1995) associated with resistance to apoptosis and upregulate the expression of *Tiam1* (Kawazoe et al., 1999b). 6. The bufadienolide proscillaridin A can inhibit DNA topoisomerase I and II (Bielawski et al., 2006). 7. Cardiac glycosides interact with membrane phospholipids leading to decreased binding of growth factors and cytokines such as interleukin 8 (Manna et al., 2006). 8. Cardiac glycosides modify protein N-glycosylation in malignant cells and inhibit their migration, invasion, and metastatic potential (Beheshti Zavareh et al., 2008). 9. Cardiac glycosides inhibit the transcription of tissue kallikreins (Prassas et al., 2008). 10. Cardiac glycosides inhibit HIF-1, which mediates adaptation to hypoxic conditions (H. Zhang et al., 2008). 11. Cardenolides inhibit the leaderless export of bFGF from cells (Florkiewicz et al., 1998). Abbreviations: α: alpha subunit of Na^+K^+-ATPase; ATP: adenosine triphosphate; β: beta subunit of Na^+K^+-ATPase; bcl-2: B-cell leukemia 2; bFGF: basic fibroblast growth factor; CG: cardiac glycosides; c-myc: myc oncogene; DR4: death receptor 4; DR5: death receptor 5; FasL: fibroblast associated cell surface ligand; HIF-1: hypoxia inducible factor 1; IκBα: inhibitory subunit of nuclear factor kappa B (NF-κB); P: phosphate; p50: NF-κB p50 subunit; p65: NF-κB p65 subunit; Tiam1: T cell lymphoma invasion and metastasis 1; Topo I/II: topoisomerase I and II; TRAIL: tumor necrosis factor–related apoptosis inducing ligand; U: ubiquitin.

Cardiac glycosides also decrease the intracellular concentration of K^+ and such an event is a prerequisite for apoptosis (Hughes et al., 1997). Intracellular K^+ loss has been associated with the activation of two key apoptotic enzymes, the caspase-3-like protease and the internucleosomal DNA cleavage nuclease (Hughes et al., 1997). It is clear that cardiac glycosides cause perturbations in the intracellular concentrations of electrolytes, which have different effects on cardiac myocytes and tumor cells.

Besides upregulation of FasL, cardiac glycosides were shown to induce apoptosis along the death receptor pathway via upregulation of death receptor 4 (DR4) and death receptor 5 (DR5) (Frese et al., 2006). In non-small cell lung cancer cells, cardiac glycosides upregulated the expression of DR4 and DR5, thereby rendering the cells susceptible to apoptosis induced by the cognate receptor ligand, tumor necrosis factor-related apoptosis-inducing ligand (Apo2L/TRAIL) (Frese et al., 2006).

Another mechanism by which cardiac glycosides can promote apoptosis is via suppression of nuclear factor kappa B (NF-κB) (Manna et al., 2000). NF-κB is a nuclear transcription factor that regulates the expression of various genes that play principal roles in apoptosis, tumorigenesis, and inflammation. Activation of NF-κB (as can occur with cytotoxic chemotherapy and radiation) has been shown to block apoptosis and promote proliferation (Wang et al., 1998). Inhibition of this transcription factor increases the sensitivity of cancer cells to the apoptotic effects of antitumor therapy (Wang et al., 1999). Oleandrin was shown to suppress NF-κB by inhibiting the phosphorylation and subsequent degradation of the inhibitory subunit of NF-κB, IκBα (Manna et al., 2000). This effect was shown to be cell-type non-specific, as NF-κB activation was inhibited by oleandrin in diverse human tumor cell lines including histiocytic lymphoma, T cells, ovarian and epithelial cancer cells (Manna et al., 2000).

At the transcriptional level, cardiac glycosides were shown to influence the expression of apoptosis related genes in favor of apoptosis. In human leukemia cells, bufalin downregulated the expression of the *c-myc* and *bcl-2* oncogenes (Masuda et al., 1995) and upregulated the expression of *Tiam1* (*T cell lymphoma invasion and metastasis 1*) (Kawazoe et al., 1999b). Tiam1 is a guanine nucleotide exchange factor that activates its substrate small GTPase proteins RhoA, Rac1, and Cdc42 (Minard et al., 2004). It facilitates the exchange of GDP for GTP as these proteins cycle between an inactive GDP-bound and an active GTP-bound state. Apoptosis was strongly induced by bufalin in leukemia cell lines expressing sense RNA for Tiam1, whereas cells expressing antisense Tiam1 RNA were significantly resistant to bufalin-induced apoptosis (Kawazoe et al., 1999b). Tiam1 has multiple roles in regulating cellular functions which likely depend on the cell type, microenvironment, transformation status, and the activation state of the small GTPase proteins in a given cell (Minard et al., 2004).

2.3.2. Cardiac glycosides have other diverse antitumor effects

Digoxin and ouabain were found to inhibit DNA topoisomerase II in breast cancer cell lines but the cytotoxic concentrations were higher than the concentrations required to inhibit Na^+K^+-ATPase in cardiac myocytes (Bielawski et al., 2006). Proscillaridin A, however, was found to inhibit DNA topoisomerase I and II in clinically relevant concentrations (Bielawski et al., 2006). Oleandrin was found to interfere with the fluidity of the cytoplasmic membrane possibly by interacting with its phospholipids (Manna et al., 2006). This interference was shown to lead to the decreased binding of certain growth factors and cytokines, such as interleukin 8, to their cognate receptors in neutrophils and macrophages; the binding of other factors, however, was unaffected. Inhibition or downregulation of IL-8 — mediated immune responses in the tumor microenvironment may play an important role in downregulation of inflammation, angiogenesis, and metastasis (Manna et al., 2006).

Another mechanism by which cardiac glycosides were shown to exert their antitumor effects is modulation of N-glycosylation (Beheshti Zavareh et al., 2008). Malignant cells display distinct N-glycan profiles

on surface glycoproteins, including receptors and transporters that contribute to their malignant characteristics (Dennis et al., 1999). In fact, some of the enzymes that mediate these changes in protein N-glycosylation were shown to be regulated by signaling pathways commonly activated in tumor cells such as the RAS-RAF-MAPK (mitogen-activated protein kinase) pathway (Dennis et al., 1999). Digoxin and other cardiac glycosides were shown to modify protein N-glycosylation by blocking N-glycan branching in malignant cells, which blunted the migration, invasion, and metastatic potential of these cells (Beheshti Zavareh et al., 2008). Indeed, in mouse models of metastatic prostate cancer, treatment with digoxin was shown to inhibit distant metastasis formation. The mechanism by which cardiac glycosides exert their N-glycosylation modifying effect is unknown in its details, but it was shown to be related with the inhibition of the Na^+K^+-ATPase (Beheshti Zavareh et al., 2008).

Unbiased drug library screening has shown that cardiac glycosides inhibit the transcription of tissue kallikreins (Prassas et al., 2008) and hypoxia inducible factor (HIF) 1α and 2α (Zhang et al., 2008). Tissue kallikreins such as prostate specific antigen (PSA) comprise a group of extracellular serine proteases aberrantly expressed in cancer and involved in various cancer related processes. Their overactivation leads to the degradation of multiple components of the extracellular matrix and the promotion of tumor growth, invasion and metastasis (Prassas et al., 2008). HIF-1 is a transcription factor that is upregulated in the hypoxic tumor microenvironment and it, in turn, regulates the expression of genes that help the cancer cell adapt in hypoxic conditions (Zhang et al., 2008). In mouse xenograft models, digoxin blocked the expression of *HIF-1α* as well as downstream HIF-1α target genes in engrafted transformed human B lymphocytes and prostate cancer cells and inhibited their growth in a dose-dependent manner (Zhang et al., 2008).

There is accumulating evidence that the functions of the Na^+K^+-ATPase extend well beyond the cellular exchange of Na^+ and K^+. The α subunit of the Na^+K^+-ATPase, the target of cardiac glycosides, was identified to be a modulator of "leaderless" protein excretion, i.e. an alternative protein exocytic pathway that does not involve the endoplasmic reticulum and the Golgi apparatus (Florkiewicz et al., 1998). The cardenolide class of cardiac glycosides was found to inhibit the leaderless export of basic fibroblast growth factor (a potent angiogenic agent) from fibroblast cell lines without affecting conventional protein excretion. This action was shown to be associated with the binding of the cardiac glycosides to the α subunit of the Na^+K^+-ATPase and was independent of the activity of the Na^+K^+-ATPase as an ion transporter (Florkiewicz et al., 1998).

2.4. Clinical trials of cardiac glycosides in cancer

Despite the promising preclinical data, no randomized clinical trials have yet validated the initial promising observations. A phase I clinical trial of an aqueous extract of the plant *Nerium oleander*, which contains various cardiac glycosides, showed no objective antitumor responses (Mekhail et al., 2006). However, a phase I clinical trial of the investigational drug PBI-05204, which contains oleandrin, showed activity in diverse tumor types, with 20% of evaluable patients (n = 15) achieving stable disease for more than 4 months (Bidyasar et al., 2009). This trial is ongoing(http://clinicaltrials.gov/ct2/show/NCT00554268, 2010). In a Phase II clinical trial in non-small cell lung cancer, digoxin failed to increase the response rate of erlotinib (an orally bioavailable inhibitor of the epidermal growth factor receptor) as a second-line therapy (Kayali et al., 2009). However, the addition of digoxin to bioimmunotherapy in the treatment of stage IV melanoma has yielded promising results (Khan et al., 2007). Although the number of patients in the latter clinical trial was small (n = 27), the overall response rate of 44.4% (Khan et al., 2007) compares favorably with the 19.5% response rate reported with bioimmunotherapy alone (Atkins et al., 2008). A study to examine the effects of lapatinib on the pharmacokinetic properties of digoxin in metastatic Her2/neu positive breast cancer was recently completed (http://clinicaltrials.gov/ct2/show/NCT00650910, 2010). A randomized, placebo controlled phase II clinical trial of the traditional Chinese medicine huachansu (which contains cardiac glycosides of the bufadienolide class) with gemcitabine in pancreatic cancer is currently ongoing (http://clinicaltrials.gov/ct2/show/NCT00837239, 2010). Although there are inherent difficulties in studying the pharmacologic properties of agents that contain many potentially active compounds, the results of this study are anticipated with great interest.

3. Statins

Statins are competitive inhibitors of the 3-hydroxy 3-methyl glutaryl coenzyme A (HMG CoA) reductase (Istvan & Deisenhofer, 2001), an enzyme of the endoplasmic reticulum that catalyzes the rate-limiting step in endogenous cholesterol synthesis (Goldstein & Brown, 1990). Statins, which share an HMG-like moiety, bind to HMG CoA reductase with three orders of magnitude greater affinity than HMG CoA, effectively displacing the natural substrate (Istvan & Deisenhofer, 2001).

Many large-scale clinical trials have established the beneficial effect of statins in primary and secondary prevention of acute coronary syndromes, cerebrovascular events (Amarenco et al., 2006), and venous thromboembolism (Glynn et al., 2009). Conceptually, cancer and atherosclerotic disease share similar molecular underpinnings such as abnormal metabolic pathways and a proinflammatory phenotype; statins target lipid metabolism, have significant anti-inflammatory properties, and also reduce cardiovascular morbidity and mortality in cancer patients (Katz, 2005).

3.1. Epidemiologic studies of statins in cancer

Many clinical studies attempted to dissect the preventive role of statins in cancer. Large randomized clinical trials that investigated the role of statins in cardiovascular prevention did not show a significant decrease in cancer incidence associated with statin use, although a trend toward fewer cancer deaths on longer follow-up was seen (Pedersen et al., 2000). In fact, systematic reviews and meta-analyses of these randomized clinical trials concluded that statins did not prevent cancer (Bonovas et al., 2006; Dale et al., 2006; Browning & Martin, 2007). However, in these trials, cancer incidence was not an end point and the follow-up periods were relatively short (Farwell et al., 2008). In contrast, two large-scale retrospective observational studies showed that statin use was associated with a decrease in all-site cancer incidence (Farwell et al., 2008; Karp et al., 2008), even after multivariable adjustment (Farwell et al., 2008). Multiple other studies have shown decreased incidences of common site-specific cancers among statin users, including prostate (Shannon et al., 2005), colorectal (Poynter et al., 2005), breast (Cauley et al., 2003), uterine (Blais et al., 2000), and lung (Khurana et al., 2007) cancers; lymphoma (Fortuny et al., 2006), and melanoma (Downs et al., 1998). Among cancer patients, statin use has been associated with better outcomes in prostate cancer treated with radiation therapy (Gutt et al., 2010), rectal cancer treated with chemoradiation (Katz et al., 2005), colorectal cancer (Siddiqui et al., 2009), hepatocellular cancer (Kawata et al., 2001), and follicular lymphoma (Nowakowski et al., 2010). Lastly, statin use in cancer patients has been associated with decreased incidence of venous thromboembolism (Khemasuwan et al., 2010).

3.2. Mechanisms of statin antitumor activity

At a preclinical level, statins were shown to induce apoptosis and inhibit tumor growth, angiogenesis, and metastases in multiple cell lines. The molecular underpinnings of their antitumor effects are

multiple. By blocking the generation of prenyl units, statins impair prenylation, an important posttranslational modification of multiple proteins whose function depends on membrane anchoring. Protein folding and N-glycosylation of surface proteins may be impaired as well. Statins also inhibit histone deacetylation and the upregulation of cholesterol synthesis associated with chemotherapy resistance. In addition to tumor cells, these effects may involve cells of the tumor microenvironment, which facilitate processes such as angiogenesis and metastasis.

3.2.1. Statins inhibit the prenylation of multiple proteins involved in cancer

Very important intermediates of the endogenous biosynthetic pathway of cholesterol are geranyl pyrophosphate (G-PP) and farnesyl pyrophosphate (F-PP). Apart from the biosynthesis of cholesterol, F-PP and G-PP are involved in the prenylation of various cellular proteins, many of which play key roles in cancer (Table 1). Prenylation involves the irreversible covalent attachment of farnesyl (15-carbon) or geranylgeranyl (20-carbon) isoprenoids to conserved cysteine residues at or near the C-terminus (Ali et al., 2010).

Of the many proteins that undergo prenylation, the Ras family of small GTPases has attracted much attention because of its established role in carcinogenesis (Malumbres & Barbacid, 2003). Activating mutations in Ras are commonly encountered in many tumor types and non-mutated Ras can be activated by various mechanisms such as overexpression or activating mutations of upstream receptor tyrosine kinases (Cox & Der, 2002). Statins were shown to disrupt Ras prenylation, and thus, its membrane anchoring and signal transduction in numerous human cell lines (Bouterfa et al., 2000; van de Donk et al., 2002; Stirewalt et al., 2003; Khanzada et al., 2006; Laezza et al., 2008; Ogunwobi & Beales, 2008; Kang et al., 2009). These observations, however, were not uniform. Mutated, constitutively activated Ras was shown to be resistant to the effects of statins (Shachaf et al., 2007), possibly because mutated Ras does not require localization to plasma membrane to mediate its oncogenic effect (Chiu et al., 2002). The discovery that farnesylation of Ras proteins is required and sufficient for Ras membrane interactions and activity led to the development of farnesyltransferase inhibitors with the objective of blocking this transforming effect (Bustinza-Linares et al., 2010). However, Ras proteins that are most frequently mutated in human cancers may escape the prenylation block incurred by statins (Sebti & Der, 2003).

In vitro, however, multiple cell lines were shown to be sensitive to statins. This sensitivity is not consistently associated with inhibition of Ras signaling (DeClue et al., 1991; Stirewalt et al., 2003), because other prenylated proteins mediate cancer related processes as well. Indeed, statins induced apoptosis in anaplastic thyroid carcinoma cell lines (Zhong et al., 2003) and inhibited the proliferation and invasion of aggressive breast carcinoma cell lines (Denoyelle et al., 2001) by blocking the geranylgeranylation of the Rho GTPases; these effects were not mediated by blocking the farnesylation of Ras. Rho GTPases regulate a variety of cellular functions including cell cycle, adhesion, polarity, migration, and cytoskeletal organization (Karlsson et al., 2009). Overexpression of Rho GTPases is seen in many human tumors and often correlates with tumor progression (Karlsson et al., 2009). Indeed, overexpression of RhoA and RhoC has been associated with poor prognosis in breast cancer and targeted silencing of the latter inhibited proliferation and invasion in aggressive breast cancer cell lines (Pille et al., 2005).

Ras associated binding (Rab) small GTPases are members of the Ras superfamily principally involved in vesicular transport. Increased expression of Rab25 has been associated with tumor progression and an aggressive phenotype in ovarian and breast cancers (Cheng et al., 2004). Rab25 overexpression clinically translated into shorter disease-free and overall survival in ovarian and breast cancer patients, respectively (Cheng et al., 2004). By blocking the generation of prenyl units and, thereby, the geranylgeranylation of Rabs, statins blocked the membrane targeting of Rabs (Ali et al., 2010).

Ras homologue enriched in brain (RHEB) is a small GTPase of the Ras superfamily that in its activated GTP-bound state directly activates the mammalian target of rapamycine complex 1 (mTORC1)(Lu et al., 2010). When induced, mTORC1 stimulates growth by promoting ribosomal biogenesis and protein synthesis. RHEB is an integral component of the phosphatidylinositol 3-kinase (PI3K) — mTORC1 pathway which is frequently activated in human malignancies secondary to amplifications or mutations of upstream receptors, activating mutations in PI3K, or loss-of-function mutations of negative pathway regulators. Overexpression and upregulation of RHEB was identified in diverse human malignancies and was associated with poor prognosis in breast and head and neck cancers (Lu et al., 2010). Its oncogenic transformation potential depends on its farnesylation (Jiang & Vogt, 2008), a modification that can be effectively blocked by statins. Indeed, inhibition of RHEB farnesylation effectively blocked downstream signaling cascades, induced apoptosis, and enhanced the sensitivity of breast cancer, ovarian cancer, and non-small cell lung cancer cell lines to tamoxifen, docetaxel, and cisplatin, respectively (Basso et al., 2005; Zheng et al., 2010).

Blocking the generation of prenyl units may have implications in the posttranslational modification and function of multiple other proteins (Table 1). Inhibition of the farnesylation of centromere protein E (CENP-E) and F (CENP-F/mitosin) was shown to lead to

Table 1
A selected list of prenylated proteins implicated in tumorigenesis and cancer progression whose prenylation, and hence their function, may be adversely affected by statins.

Protein	Role in cancer
Ras family (H-Ras, N-Ras, K-Ras4A and K-Ras4B)	Signal transduction
Rho (Ras homologous) family (22 members)	Gene transcription, survival, adhesion, cytoskeleton reorganization (Mulloy et al., 2009)
Rab (Ras associated binding) family (>70 member proteins)	Vesicle generation, uncoating, trafficking, and fusion (Stenmark, 2009)
Rheb (Ras homolog enriched in brain) family	Component of the phosphatidylinositol 3-kinase (PI3K) – target of rapamycin (TOR) pathway (Jiang & Vogt, 2008)
Centromere protein E (CENP-E) and F (CENP-F/mitosin)	Capture and attachment of spindle microtubules by the kinetochore (Schafer-Hales et al., 2007) (CENP-E) and chromosome segregation (CENP-F) during mitosis (Ashar et al., 2000)
Protein tyrosine phosphatase (PTP) $_{CAAX1}$ and PTP_{CAAX2}	Oncogenic protein tyrosine phosphatases (Cates et al., 1996)
DnaJ-like heat shock chaperones (HSP40)	Co-chaperones for Heat Shock Protein (HSP) 70. They stabilize the interaction of HSP70 with its substrate proteins (Qiu et al., 2006). HSP70 has been associated with resistance to apoptosis, poor prognosis, and resistance to chemotherapy (Patury et al., 2009).
Nucleosome assembly protein NAP-1-like (NAP1L1 and NAP1L4)	Histone chaperones: participation in nucleosome assembly and disassembly, histone exchange, and creation of specialized chromatin structures (Okuwaki et al., 2010).
Lamins (prelamin A, lamin B_1, and lamin B_2)	Nuclear intermediate filament proteins with structural and chromatin organizational roles (Gonzalez-Suarez et al., 2009). Lamin A was shown to promote tumor invasiveness in colorectal cancer (Willis et al., 2008), whereas its epigenetic silencing has been associated with poor outcomes in diffuse large B cell lymphoma (Agrelo et al., 2005)
Interferon-inducible guanylate-binding protein (GBP) 2	A GTPase induced by interferons whose expression has been associated with a proliferative phenotype in esophageal squamous cell carcinoma (Guimaraes et al., 2009)

mitotic delay owing to mitotic chromosomal alignment defects and impaired kinetochore–microtubule associations (Schafer-Hales et al., 2007). Protein tyrosine phosphatase (PTP) $_{CAAX1}$ and PTP_{CAAX2} overexpression was shown to lead to oncogenic transformation of epithelial cells (Cates et al., 1996); the effects of blocking PTP prenylation are unknown. Heat shock protein 40 (HSP40) is a co-chaperone for HSP70 (Qiu et al., 2006), and blocking its prenylation may accentuate the cellular stress induced by the aggregation of unfolded or misfolded proteins in cancer cells. Lastly, the effects of dysprenylation of the nucleosome assembly protein 1 and 4 (NAP1L1 and NAP1L4) and the nuclear filament proteins prelamin A and lamins B_1 and B_2 have not been investigated. NAP1L1 and NAP1L4 are histone chaperones involved in nucleosome formation (Okuwaki et al., 2010). Besides being key structural components of the nucleus, lamins are also involved in nuclear architecture and chromatin structure (Gonzalez-Suarez et al., 2009). Dysprenylation of lamins may have implications in chromatin remodeling, DNA replication and repair, and gene transcription and silencing. So far, lamin A has been shown to promote tumor invasiveness in colorectal cancer (Willis et al., 2008), whereas its epigenetic silencing has been associated with poor outcomes in diffuse large B cell lymphoma (Agrelo et al., 2005).

3.2.2. Statins inhibit the N-glycosylation of surface proteins

Dolichols are mevalonate derivatives that mediate the N-glycosylation of nascent polypeptides in the endoplasmic reticulum. Dolichols serve as carriers as well as sites whereupon the core oligosaccharide unit for protein glycosylation is assembled. By depleting the cells of mevalonate, the building blocks of dolichol, lovastatin impaired the dolichol-mediated N-glycosylation of insulin-like growth factor — 1 receptor (IGF-1R) (Dricu et al., 1997). IGF-1R became significantly hypoglycosylated and the number of functional membrane-bound receptors was significantly reduced resulting in growth arrest of melanoma cell lines (Carlberg et al., 1996). The role of insulin-like growth factor pathway in multiple cancer processes is increasingly being recognized (Samani et al., 2007; Pollak, 2008).

3.2.3. Statins inhibit histone deacetylase activity

Computational modeling and enzymatic assays have revealed an interaction between the carboxylic moiety of statins and the catalytic site of histone deacetylase 2 (HDAC2)(Lin et al., 2008). The inhibition of HDAC2 led to reversal of the transcriptional repression of p21, a regulator of cell cycle progression, resulting in inhibition of cell proliferation in vitro and tumor growth in vivo (Lin et al., 2008). Loss of histone acetylation and transcriptional repression is a common finding in human cancer (Fraga et al., 2005). So far, targeting histone deacetylases has had clinical success in some leukemias and lymphomas, and statin use has been associated with improved event-free survival in follicular lymphoma (Nowakowski et al., 2010).

3.2.4. Statins inhibit adaptive upregulation of cholesterol synthesis

Upregulation of de novo cholesterol synthesis and, to a lesser extent, cholesterol import has been shown to be an adaptive protective response of acute myelogenous leukemia cells exposed to chemotherapy and radiation (Li et al., 2003). Targeting this response has been shown to restore sensitivity and augment the cytotoxic effect of chemotherapy (Li et al., 2003). These observations were successfully translated into a phase I clinical trial, where the addition of pravastatin to induction chemotherapy in acute myelogenous leukemia yielded promising results, especially in newly diagnosed patients with unfavorable cytogenetics (Kornblau et al., 2007).

The exact mechanism by which increased cholesterol mediates resistance to chemotherapy and radiation is not entirely clear. Besides being a required building block for rapidly proliferating cells, cholesterol is a critical component of the lipid rafts (Li et al., 2006). Lipid rafts are microdomains of plasma membrane, abundant in surface receptors and membrane bound signaling molecules, such as Ras. Increased cholesterol in cancer cells has been proposed to lead to raft coalescence and the sequestration of activated oncogenic signaling pathways (Freeman & Solomon, 2004). Simvastatin was shown to deplete cholesterol from plasma membrane, disrupt lipid raft formation, and impair signaling through the rafts' constituents (Li et al., 2006). Cancer cells, which were shown to contain more lipid rafts than their normal counterparts, were also more sensitive to cholesterol depletion, which led to anoikis-like apoptosis (Li et al., 2006).

3.3. Clinical trials of statins in cancer

The promising preclinical evidence of statin antitumor activity has spawned a wide range of clinical trials, many of which are currently ongoing. A list of selected published clinical trials is provided in Table 2. Initial clinical trials with statins in multiple myeloma showed encouraging results (Schmidmaier et al., 2007), but subsequent trials failed to demonstrate a benefit (van der Spek et al., 2007; Sondergaard et al., 2009). Two clinical trials so far have shown the benefit of pravastatin in hepatocellular carcinoma following transarterial embolization (Kawata et al., 2001; Graf et al., 2008). Lovastatin has shown some activity in anaplastic gliomas and glioblastomas in two clinical trials (Thibault et al., 1996; Larner et al., 1998). Overall, statins may not be effective when given alone, as evidenced by the paucity of response in many phase I clinical trials (Thibault et al., 1996; Knox et al., 2005; Holstein et al., 2006). The reasons why statins are ineffective alone may be multiple. It should be noted that the doses in which statins were shown to be effective in vitro may not be easily achieved in clinical practice. Moreover dose escalation in patients with cancer may be hindered by drug interactions, limited hepatic or renal reserves, and susceptibility to myotoxicity related to the frequently present cachexia. When combined with cytotoxic chemotherapy, however, statins may significantly enhance the antitumor effect, as seen with the addition of pravastatin to induction chemotherapy in acute myelogenous leukemia (Kornblau et al., 2007).

Besides being useful in the therapeutic setting, statins may also be clinically effective in preventing tumor recurrence. A prospective, randomized, placebo-controlled, phase III clinical trial of rosuvastatin in patients with resected stage I or II colon cancer is ongoing (http://clinicaltrials.gov/ct2/show/NCT01011478, 2010). A similar phase II clinical trial with atorvastatin in colorectal neoplasia was recently completed (http://clinicaltrials.gov/ct2/show/NCT00335504, 2010), and the results are anticipated soon.

4. Beta blockers

4.1. Clinical and experimental observations

Stress, depression, and lack of social support have been invariably linked with cancer onset and progression (Antoni et al., 2006). Catecholamines are the major neuroendocrine transmitters of the sympathetic nervous system stress response. Beta adrenergic receptors, which mediate most of the effects of catecholamines, have been identified on nasopharyngeal (Yang et al., 2006), pancreatic (Weddle et al., 2001), breast (Vandewalle et al., 1990), and ovarian (Thaker et al., 2006) cancer cells. In vitro experiments and experiments in mouse models have elucidated the mechanisms by which catecholamines mediate cancer onset and progression and ways to block these effects with β-blockers.

4.2. Beta 2 adrenergic stimulation promotes tumor growth and angiogenesis

An overview of the effects of catecholamine stimulation and blockade on cancer growth and development is provided in Table 3. Beta 2 adrenergic stimulation in the context of stress-induced catecholamine release led via the cyclic adenosine monophosphate

Table 2
Selected published clinical trials using statins as anticancer therapy.

Study (phase)	Tumor type	Patients	Regimen	Notes
Lee et al. (II) (J. Lee et al., 2009)	Metastatic colorectal cancer	49	FOLFIRI[a] + simvastatin 40 mg PO daily	The addition of simvastatin to standard chemotherapy for colorectal cancer was not associated with additional adverse events and modestly prolonged time to tumor progression
Graf et al. (non randomized controlled) (Graf et al., 2008)	Hepatocellular carcinoma	52	TACE[b] + pravastatin 20–40 mg PO daily	The addition of pravastatin to TACE[b] improved the median overall survival
Sondergaard et al. (II) (Sondergaard et al., 2009)	Multiple myeloma	6	Simvastatin 15 mg/kg PO daily for 1 week q4 weeks	Dose reductions required due to nausea and diarrhea. No favorable effect of high dose simvastatin in heavily pretreated multiple myeloma
van der Spek et al. (II) (van der Spek et al., 2007)	Multiple myeloma	12	VAD[c] + simvastatin 15 mg/kg PO daily for 1 week q4 weeks	High dose simvastatin did not reverse clinical resistance to VAD[c] chemotherapy
Schmidmaier et al. (II) (Schmidmaier et al., 2007)	Multiple myeloma	6	Simvastatin 80 mg PO daily (2 days prior to 2 days after chemotherapy) + bortezomib + bendamustine	The addition of simvastatin may help overcome drug resistance to bortezomib or bendamustine
Kornblau et al. (I) (Kornblau et al., 2007)	Acute myeloid leukemia	37	Pravastatin 40–1680 mg PO daily (days 1–8) + idarubicin + high dose cytarabine	The addition of pravastatin did not result in excess toxicity. A dose limiting toxicity was not reached. Clinical response rate was encouraging, most notably among newly diagnosed patients with unfavorable cytogenetics
van der Spek et al. (I) (van der Spek et al., 2006)	Multiple myeloma and non-Hodgkin lymphoma	28	Simvastatin 5–15 mg/kg PO daily for 1 week prior to chemotherapy	The maximum tolerated dose was 15 mg/kg daily. Dose limiting toxicity was neutropenic sepsis and grade 3 gastrointestinal adverse events
Holstein et al. (I) (Holstein et al., 2006)	Any type	32	Lovastatin 10–415 mg/m^2 PO q6 hours for 4 days q 4 weeks	Dose limiting toxicity not reached. No antitumor responses were observed
Knox et al. (I) (Knox et al., 2005)	Squamous cell carcinoma of the head, neck, and cervix	26	Lovastatin 5 – 10 mg/kg PO daily for 2 weeks q3weeks & lovastatin 7.5 mg/kg PO for 3 weeks q4 weeks	Reversible muscle toxicity was the dose limiting toxicity. The maximum tolerated dose was 7.5 mg/kg PO for 3 weeks q4 weeks. No objective antitumor responses were seen
Kim et al. (II) (Kim et al., 2001)	Gastric adenocarcinoma	16	Lovastatin 35 mg/kg PO daily for 1 week q4 weeks	Ubiquinone coadministered to prevent myotoxicity. One patient achieved stable disease for 4 months. Two patients experienced mild myalgia.
Kawata et al. (randomized controlled) (Kawata et al., 2001)	Hepatocellular carcinoma	41	Pravastatin 40 mg PO daily (following TAE[d] and PO 5-fluorouracil)	Pravastatin slowed tumor progression and significantly prolonged overall survival. No difference in muscle related adverse events between groups.
Larner et al. (I/II) (Larner et al., 1998)	Anaplastic glioma and glioblastoma multiforme	18	Lovastatin 20 – 30 mg/kg PO daily for 1 week q4 weeks ± concurrent radiation	No myotoxicity or neurotoxicity reported; 3 patients achieved partial response.
Thibault et al. (I) (Thibault et al., 1996)	Any type	88	Lovastatin 2 – 45 mg/kg daily for 1 week q4 weeks	Myopathy was the dose limiting toxicity, reversed with ubiquinone. Myopathy can be prevented with ubiquinone. One minor response maintained for 8 months achieved in a patient with anaplastic astrocytoma

[a] FOLFIRI, Irinotecan + 5-fluorouracil + leucovorin.
[b] TACE, Transarterial chemoembolisation.
[c] VAD, vincristine + doxorubicin + dexamethasone.
[d] TAE, transarterial embolization.

(AMP)–protein kinase A pathway to increased angiogenesis and tumor invasion in an orthotopic mouse model of ovarian cancer (Thaker et al., 2006). In vitro, this highly invasive phenotype associated with stress levels of catecholamines was abrogated by the β adrenergic antagonist, propranolol (Sood et al., 2006). By activating the focal adhesion kinase, β_2 adrenergic stimulation also led to resistance to anoikis, the process by which cells enter apoptosis when separated from their microenvironment (Sood et al., 2010). Resistance to anoikis is a hallmark of malignant transformation that allows detached cells to survive and migrate to other sites of attachment. Focal adhesion kinase activation was also blocked by propranolol (Sood et al., 2010). Coupled with the resistance to anoikis, β_2 adrenergic stimulation was also shown to promote integrin-mediated cell adhesion, a process that facilitates cell migration, cell division, and reactions to mechanical stress (Rangarajan et al., 2003). Similar observations were made in pancreatic cancer, where studies on cell lines (Zhang et al., 2010) and hamsters (Al-Wadei et al., 2009) showed that β adrenergic blockade can effectively inhibit its development and progression. Lastly, in mice with ovarian cancer, β adrenergic receptor signaling was shown to mediate the pro-growth and proangiogenic effects of surgical stress on micrometastases and residual tumors (J.W. Lee et al., 2009). Although in addition to catecholamines, other chemokines and cytokines were also elevated during surgery, propranolol mitigated the effects of surgical stress on tumor growth and angiogenesis (J.W. Lee et al., 2009).

4.3. Clinical studies of β-blockers in cancer

Despite the involvement of β adrenergic stimulation in cancer progression, no clinical trials have investigated the role of β-blockers in cancer therapeutics. Two clinical trials are currently investigating the preventive role of perioperative propranolol and etodolac (a cyclooxygenase 2 inhibitor) in cancer recurrence and progression in patients with breast (http://clinicaltrials.gov/ct2/show/NCT00502684,

Table 3
Overview of the effects of catecholamine stimulation and blockade on cancer growth and development.

Model	Cancer type	Effect
Mice (Thaker et al., 2006)	Ovarian	Catecholamines enhanced VEGF, MMP2, and MMP9 expression. Propranolol blocked the effects of stress.
Cell lines and mice (Landen et al., 2007)	Ovarian	Catecholamines led to STAT3 activation resulting in increased MMP production, tumor growth and invasion. Propranolol inhibited STAT3 activation.
Mice (Sood et al., 2010)	Ovarian	Norepinephrine and epinephrine rendered cancer cells resistant to anoikis by activating FAK.
Mice (J.W. Lee et al., 2009)	Ovarian	Catecholamines mediated the tumor pro-growth and pro-angiogenic effects of surgical stress. Propranolol blocked the effects of surgical stress.
Cell lines (Yang et al., 2006)	Nasopharyngeal	Catecholamines enhanced (whereas propranolol inhibited) VEGF, MMP2, and MMP9 expression.
Cell lines and mice (Palm et al., 2006)	Prostate	Norepinephrine promoted (whereas propranolol inhibited) metastasis formation.
Cell lines (Zhang et al., 2010)	Pancreatic	β_2 receptor blockade suppressed invasion and proliferation by inhibiting the activation of the transcription factors NF-κB, AP-1, and CREB.
Hamsters (Al-Wadei et al., 2009)	Pancreatic	Propranolol reversed the activation of CREB and ERK 1/2 and upregulation of EGF and VEGF associated with pancreatic carcinogenesis.

AP-1: activator protein 1; CREB: cyclic adenosine monophosphate response element binding protein; EGF: epidermal growth factor; ERK 1/2: extracellular signal regulated protein kinase 1/2; FAK: focal adhesion kinase; MMP2: matrix metalloproteinase 2; MMP9: matrix metalloproteinase 9; NF-κB: nuclear factor kappa B; STAT3: signal transducer and activator of transcription 3; VEGF: vascular endothelial growth factor

2010) and colorectal (http://clinicaltrials.gov/ct2/show/NCT00888797, 2010) cancer undergoing surgery with curative intent.

The role of β-blockers in mitigating the cardiotoxic effects of chemotherapy has, however, been well characterized. In a small, randomized, placebo-controlled clinical trial, the prophylactic administration of carvedilol in patients receiving treatment with anthracyclines was associated with lower rates of systolic and diastolic cardiac dysfunction and reduction of left ventricular ejection fraction (Kalay et al., 2006). The importance of early detection of cardiac dysfunction and therapeutic intervention with angiotensin-converting enzyme inhibitors and β-blockers in patients previously treated with anthracyclines was shown in a prospective clinical study (Cardinale et al., 2010). In this study, a decrease of approximately 4-fold in the chance of complete recovery from cardiac dysfunction for each doubling in time-to-heart failure treatment was identified (Cardinale et al., 2010). A clinical study to investigate the cardioprotective effect of carvedilol or lisinopril in breast cancer patients receiving treatment with trastuzumab is ongoing (http://clinicaltrials.gov/ct2/show/NCT01009918, 2010).

5. Inhibitors of the renin–angiotensin–aldosterone system (RAAS): angiotensin I converting enzyme inhibitors (ACEIs) and angiotensin type I receptor blockers (ARBs)

The renin–angiotensin–aldosterone system plays a major role in the renal and cardiovascular homeostasis. The renally secreted renin cleaves angiotensinogen to produce angiotensin I, which is further cleaved into angiotensin II by the action of the angiotensin I-converting enzyme (ACE). Angiotensin II is the primary effector of the RAAS and it promotes vasoconstriction and adrenal aldosterone secretion through its interaction with the angiotensin II type 1 receptors. ACEIs and ARBs are widely prescribed medications to treat hypertension; to reduce cardiovascular morbidity and mortality associated with left ventricular systolic dysfunction, heart failure, and postmyocardial infarction; and to slow the progression to dialysis or transplantation in diabetic nephropathy.

5.1. Polymorphisms of the RAAS genes are associated with cancer

Polymorphisms of the *ACE* gene associated with higher plasma ACE levels have been linked with greater risk for breast cancer in Asian women (Koh et al., 2003). A specific polymorphism of the *ACE* gene has also been linked with the development of early-stage gastric cancer (Ebert et al., 2005), and when combined with simultaneous expression of angiotensin II type 1 receptors, it was found to correlate with nodal spread (Rocken et al., 2007). Certain polymorphisms in the angiotensinogen gene (Gonzalez-Zuloeta Ladd et al., 2007) and in the promoter region of angiotensin II type 1 receptor gene (Koh et al., 2005) have also been linked with higher breast cancer risk. Common genetic variants of the angiotensinogen gene have also been associated with increased risk of renal cell carcinoma in hypertensive and overweight subjects (Andreotti et al., 2010). Although these observations were made in miscellaneous ethnic groups, the conclusions may not apply to the general population.

5.2. Epidemiologic studies of inhibitors of the renin–angiotensin–aldosterone system in cancer

In a retrospective cohort study, a lower relative risk of cancer incidence and mortality was identified among ACEI users compared to users of other antihypertensive medications (Lever et al., 1998). This cancer preventive effect was more pronounced among female ACEI users and more evident with longer follow up (more than 3 years) (Lever et al., 1998). A subsequent large-scale, population-based cohort study failed to confirm these results; in fact, an excess risk of renal cancer was identified among the ACEI users, which was attributed to the underlying hypertension (Friis et al., 2001). Despite this discrepancy, both studies identified a decreased incidence of nonmelanomatous skin cancers among the ACEI users. This observation was subsequently confirmed in two studies where ACEI and/or ARB use was associated with a decreased incidence of keratinocyte skin cancers among patients who underwent renal transplantation (Moscarelli et al., 2010) and with a decreased recurrence of basal and squamous cell carcinomas in patients with a recent history of such cancers (Christian et al., 2008).

Although the preclinical carcinogenicity studies of ARBs in rats and mice were negative, in a meta-analysis of randomized clinical trials, a modestly increased risk of new cancer occurrence was seen among ARB users (Sipahi et al., 2010). As ARBs block only angiotensin II type 1 receptors, unopposed angiotensin II type 2 receptor stimulation (which has different distribution and signaling pathways than type 1 receptors) (Sipahi et al., 2010) and feedback upregulation of the renin–angiotensin axis may underlie this clinical observation.

5.3. Components of the renin–angiotensin–aldosterone system are expressed in cancer and participate in tumor-related processes

Expression of angiotensin II type 1 receptors has been identified in human pancreatic cancer (Fujimoto et al., 2001); their stimulation promoted angiogenesis (Anandanadesan et al., 2008), whereas their selective inhibition had a significant antiangiogenic and growth inhibitory effect (Fujimoto et al., 2001). Angiotensin II type 1 receptors are minimally expressed in normal pancreatic tissues; their expression, however, seems to be upregulated even in premalignant lesions implying a role in tumorigenesis and progression (Anandanadesan et al., 2008). Components of the RAAS were found to be expressed in breast cancer cells and, at least in hormone receptor-negative breast cancer, stimulation of angiotensin II type 1 receptors was associated with the upregulation of angiogenesis-

related genes(Herr et al., 2008). In ovarian cancer, upregulation of the expression of angiotensin II type 1 receptors has been observed with progression from benign to malignant phenotype; their stimulation was associated with increased angiogenesis and acquisition of an invasive phenotype (Suganuma et al., 2005). In mouse models of ovarian cancer, selective inhibition of the angiotensin II type 1 receptors blocked peritoneal dissemination and tumor angiogenesis (Suganuma et al., 2005). Other tumors in which expression of RAAS components has been identified and shown to participate in tumor progression include gastric cancer (Carl-McGrath et al., 2007), glioblastoma (Juillerat-Jeanneret et al., 2004), hepatic metastases of colorectal cancer (Neo et al., 2010), melanoma (Otake et al., 2010), and cholangiocarcinoma (Okamoto et al., 2010). Furthermore, experiments in angiotensin II type 1 receptor deficient mice have illustrated the role of expression of RAAS components by cells of the tumor microenvironment (Fujita et al., 2005; Imai et al., 2007). Angiotensin II, through angiotensin II type 1 receptor signaling in both tumor cells and cells of the microenvironment, promoted tumor growth through promotion of angiogenesis. Selective inhibition of the angiotensin II type 1 receptors blunted the progrowth and proangiogenic effect of angiotensin II (Imai et al., 2007).

5.4. Effects of angiotensin II and its inhibition in cancer

A schematic representation of the effects of angiotensin II on cancer cells and the tumor microenvironment is provided in Fig. 3.

5.4.1. Mitogenic effect

Angiotensin II can activate multiple mitogenic signaling pathways, leading to cancer cell proliferation. In breast cancer cells, angiotensin II type 1 receptor stimulation led to cell proliferation via protein kinase C activation and epidermal growth factor receptor transactivation (Greco et al., 2003). Activation of the PI3K–protein kinase B (AKT) pathway by angiotensin was also reported (Zhao et al., 2010). In prostate cancer cells, angiotensin II type 1 receptor stimulation led to activation of MAPK and signal transducer and activator of transcription 3 (STAT3) (Uemura et al., 2003). In all experiments, angiotensin II type 1 receptor blockade effectively inhibited mitogenic signaling.

5.4.2. Proangiogenic effect

The proangiogenic effect of angiotensin II is primarily mediated by the potent induction of vascular endothelial growth factor (VEGF) (Deshayes & Nahmias, 2005). Similar to the effects of angiotensin II on the vascular smooth muscle cells (Richard et al., 2000), upregulation of HIF1α may underlie the upregulation of VEGF expression in tumor cells and/or tumor microenvironment. Moreover, angiotensin II may synergistically promote the proliferation of endothelial progenitor cells with VEGF (Imanishi et al., 2004). Furthermore, the downstream cleavage products of angiotensin II, angiotensin III and angiotensin IV, also possess proangiogenic properties (Khakoo et al., 2008). Inhibition of the respective cleavage enzymes, aminopeptidase A and aminopeptidase N, was associated with inhibition of tumor angiogenesis (Khakoo et al., 2008). Multiple experiments in vivo and in vitro have demonstrated inhibition of angiogenesis by targeting angiotensin signaling (Fujimoto et al., 2001; Suganuma et al., 2005; Herr et al., 2008).

5.4.3. Proinflammatory effect

Angiotensin II promotes vascular smooth muscle and endothelial inflammation primarily through activation of NF-κB (Han et al., 1999; Takahashi et al., 2008). The consequences of this effect in cancer are unknown but it may contribute to aberrant angiogenesis and thrombogenic propensity.

5.5. Clinical studies of inhibitors of the renin–angiotensin–aldosterone system in cancer

Angiotensin converting enzyme inhibitors can mitigate the cardiovascular toxicity associated with chemotherapy (Jensen et al., 1996; Cardinale et al., 2006, 2010). The clinical implications of RAAS inhibition in cancer therapeutics have not, however, been investigated. In a pilot study in hormone-refractory prostate cancer, the combination of candesartan with androgen ablation was associated with a 34.8% response measured by PSA stability or reduction (Uemura et al., 2005). Patients with PSA reductions also experienced improvements in performance status. The mean time to PSA progression was 8.3 months (Uemura et al., 2005). A clinical trial combining enalapril with doxorubicin in breast cancer is ongoing (http://clinicaltrials.gov/ct2/show/NCT00895414, 2010).

6. Conclusions

Cardiac glycosides, statins, β-blockers, ACEIs, and ARBs are widely used cardiovascular medications with pleiotropic properties. Their beneficial effects in patients with cancer extend beyond reduction of cardiovascular morbidity and mortality, as these medications have shown promising preclinical antitumor activity with meaningful clinical implications.

Cardiac glycosides can induce apoptosis in diverse cancer cells by multiple mechamisms. Although they have been tested in vivo in a large variety of cell lines (Fig. 1, panel B), it is unclear which tumor types will benefit the most. Moreover, clinical investigations are preliminary to answer this question.

Statins were shown to exert their antitumor effect by blocking the prenylation of proteins which play key roles along upregulated pathways in cancer. Experiments with diverse cell lines have elucidated the effects of dysprenylation of individual proteins. By blocking IGF-1R processing and prenylation of downstream signaling molecules such

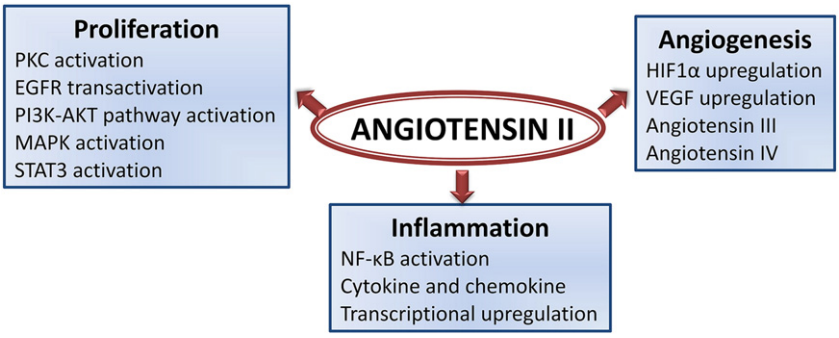


Fig. 3. Schematic representation of the effects of angiotensin II in cancer. Angiotensin II may have mitogenic, proangiogenic, and proinflammatory effects on cancer cells and their microenvironment. Abbreviations: EGFR: epidermal growth factor receptor; HIF-1α: hypoxia inducible factor 1 alpha; MAPK: mitogen activated protein kinase; NF-κB: nuclear factor kappa B; PI3K-AKT: phosphatidylinositol 3-kinase–protein kinase B; PKC: protein kinase C; STAT3: signal transducer and activator of transcription 3; VEGF: vascular endothelial growth factor.

as Ras, statins may synergistically deprive cancer cells of growth signals. In this regard, the addition of statins may be particularly relevant in the treatment of sarcomas where IGF1R inhibitors are being investigated (Olmos et al., 2010). So far, promising results have been observed by combining statins with induction chemotherapy in acute leukemia. Large-scale clinical trials investigating the preventive role of statins in tumor recurrence are ongoing.

Widely used β-blockers can mitigate the progrowth and proangiogenic effects of stress and catecholamine release. Most preclinical experiments have been conducted with ovarian cancer cell lines so it is reasonable to pursue further clinical testing in this type of cancer.

Lastly, angiotensin II has potent mitogenic and angiogenic properties that can be blocked with ACEIs or ARBs. Many tumors including pancreatic, breast, and ovarian cancer express components of the RAAS which may participate in tumorigenesis and tumor progression. ACEIs or ARBs may have a preventive effect and, when combined with conventional therapeutic strategies, a synergistic antitumor effect in these cancer types may be seen.

Overall, despite the promising preclinical and even early clinical observations, further clinical research is needed to better assess the role of commonly used cardiovascular medications in cancer therapeutics.

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