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Writing Assignment Master Drug Innovation

Anti-cancer mechanisms of the most used drugs worldwide: old drugs, new insights

By

Gijs van Slobbe

6907903

Daily supervisor and 1st accessor
Dr. E.E (Ed) Moret
Department of Pharmaceutical Sciences
Chemical Biology and Drug Discovery group
e.e.moret@uu.nl

2st accessor
Prof. Dr. A.F.M. (Maarten) Altelaar
Department of Pharmaceutical Sciences
Biomolecular Mass Spectrometry and Proteomics Group
m.altelaar@uu.nl

1 Abstract

Despite recent therapeutical improvements, cancer remains the second leading cause of death. Therefore there is an emerging need for novel cancer treatments. Development of novel anti-cancer drugs to fulfill the need for novel treatments is expensive, takes a long time and goes along with a low change of gaining marketing authorization. An alternative cheaper and faster approach to fulfil the need of new anti-cancer drugs is drug repurposing. The worldwide most used drugs could be potential candidates for drug repurposing since their intensive use provides extensive safety data. Therefore, mechanisms that clarify anti-cancer activity of eight of the most used drugs worldwide and the drug classes where they belong to were investigated in this study. Literature review showed that the drug gabapentin and the drug classes statins, renin angiotensin system (RAS) inhibitors, selective betablockers (BBs), dihydropyridine calcium channel blockers (CCBs), biguanides and protein pump inhibitors (PPIs) showed potential anti-tumorigenic effects *in vitro* and *in vivo*. The anti-cancer effects were established by targeting of several cancer hallmarks including: sustaining proliferation, induction of invasion and metastasis, avoiding immune destruction, induction of angiogenesis, deregulation of cellular energetics, genome instability and resisting cell death. Beside the drug effects on cancer hallmarks, it was shown that some drugs induced the delivery of chemotherapeutic drugs. In addition, the drug classes statins, RAS inhibitors, selective BBs, biguanides and PPIs showed combinational effects with conventional anti-cancer drugs, which increases the changes of successful drug repurposing since drugs have higher changes to get authorized as repurposed drugs if they will be combined. Overall, anti-cancer mechanisms were identified for all the investigated drugs. These mechanisms support suggested anti-cancer activity of the investigated drugs and therefore it was concluded that the drug gabapentin and the drug classes statins, RAS inhibitors, selective betablockers, dihydropyridine CCBs, biguanides and PPIs have the potential to be used for cancer drug repurposing. Since the drug classes statins, RAS inhibitors, selective BBs, biguanides and PPIs showed combinational effects with conventional treatments, these drug classes were especially considered as potential agents for cancer drug repurposing.

2 Layman's summary

Ondanks jaren onderzoek is kanker nog steeds een moeilijk te behandelen en dodelijke ziekte. Om deze reden zijn er nieuwe kankertherapieën nodig die de behandeling van kanker kunnen verbeteren. Voor deze nieuwe kankertherapieën zouden nieuwe kankermedicijnen ontwikkeld kunnen worden, maar de ontwikkeling van nieuwe kankermedicijnen is duur, kost veel tijd en deze nieuwe medicijnen hebben vaak maar een kleine kans om uiteindelijk op de markt te komen. Een alternatieve methode om nieuwe kankermedicijnen te ontdekken, is het toepassen van medicijnen die al gebruikt worden voor de behandeling van andere ziektes, ook wel bekend als drug repurposing. Drug repurposing is een goedkopere en snellere manier om nieuwe medicijnen te ontdekken doordat er onder anderen geen tijd en geld nodig is om het medicijn te ontwikkelen. De beste kandidaten voor drug repurposing zijn medicijnen die veel gebruikt worden, doordat het vele gebruik goed inzicht geeft over de veiligheid en de bijwerkingen van deze medicijnen. Omdat veel gebruikte medicijnen veelbelovende zijn voor drug repurposing, is er in dit onderzoek literatuur onderzoek gedaan of de wereldwijd meest gebruikte medicijnen anti-kanker effecten hebben en of er mechanismes zijn beschreven die deze anti-kanker effecten kunnen verklaren.

In literatuur was gevonden dat het medicijn gabapentine en de drugklassen statines, renine angiotensine systeem (RAS) remmers, selectieve bètablokkers, dihydropyridine calcium kanaal blokkers (CKBs), biguaniden en proton pomp remmers (PPR) anti-kanker effecten lieten zien in zowel laboratorium experimenten als in dierstudies. De drugs lieten anti-kanker effecten zien door verschillende kenmerken van kanker te beïnvloeden. De kankerkenmerken die werden beïnvloed door de medicijnen waren: het ontregelde energiemetabolisme van de kankercellen, ongeremde deling, het voorkomen van celdood, het induceren van invasie en metastase, het induceren van bloedvaatontwikkeling, het ontwijking van de immuunrespons tegen de kanker en het aangepaste herstel van DNA schade in kankercellen. Naast deze directe effecten op kankercellen, lieten sommige medicijnen zien dat ze er voor zorgden dat conventionele kankermedicijnen beter in de tumor terechtkwamen en daardoor de effectiviteit van deze medicijnen verbeterden. Ook lieten de drugklassen statines, RAS remmers, selectieve bètablokkers, biguaniden en PPRs combinatie effecten zien met conventionele medicijnen, wat de kans op succesvolle drug repurposing vergroot omdat medicijnen een grotere kans hebben om ge-repurposed te worden indien ze als combinatie gebruikt gaan worden.

Samengevat werden er voor het medicijn gabapentine en de drugklassen statines, RAS remmers, selectieve bètablokkers, dihydropyridine CKBs, biguaniden en PPRs anti-kanker mechanismes geïdentificeerd. Daarom werd er geconcludeerd dat deze drugklassen de potentie hebben om gebruikt te worden voor kanker drug repurposing. Omdat statines, RAS remmers, selectieve bètablokkers, biguaniden en PPRs combinatie effecten lieten zien met conventionele therapieën werd er geconcludeerd dat deze drug klassen de grootste potentie hebben om gebruikt te worden voor kanker drug repurposing.

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4 Introduction

Cancer is the second leading cause of death worldwide[1]. In most cases, cancer is still incurable and therefore, there is an emerging need for novel treatments. Development of novel drugs to fulfill the need for novel treatments is expensive, takes a long time and has only a limited change to gain marketing authorization[2]. For example, 95% of the anti-cancer drugs that are tested in phase I trials will not gain marketing authorization[3]. This low change of successful drug development can partly be declared by the flexibility of cancer cells to adapt themselves upon treatment. As shown in Figure 1, tumor growth is dependent on ten different biological processes which are known as the hallmarks of cancer[4]. These hallmarks can be targeted therapeutically, but a notable number of these targeted therapies only showed transiently effects since cancer cells showed to have the flexibility to upregulate other hallmarks when a certain hallmark was targeted with targeted therapies[4]. For example, inhibition of the hallmark angiogenesis initially showed promising effects in some preclinical cancer models[5,6], but these studies showed over time upregulation of the cancer hallmark "activation of invasion and metastasis" which resulted in severe metastasis and treatment relapse. Since it is challenging to develop effective new anti-cancer drugs, it is understandable that novel drugs are not always as effective as hoped. Indeed there is skepticism whether recently approved anti-cancer drugs really have beneficial effects compared to conventional drugs [7–10]. In summary, it is challenging, expensive and it takes a long time to develop effective new anti-cancer drugs. However, the earlier new treatments will be available, the earlier cancer patients would benefit from it. Therefore it could be helpful to find alternative faster and cheaper approaches to develop novel cancer treatments.

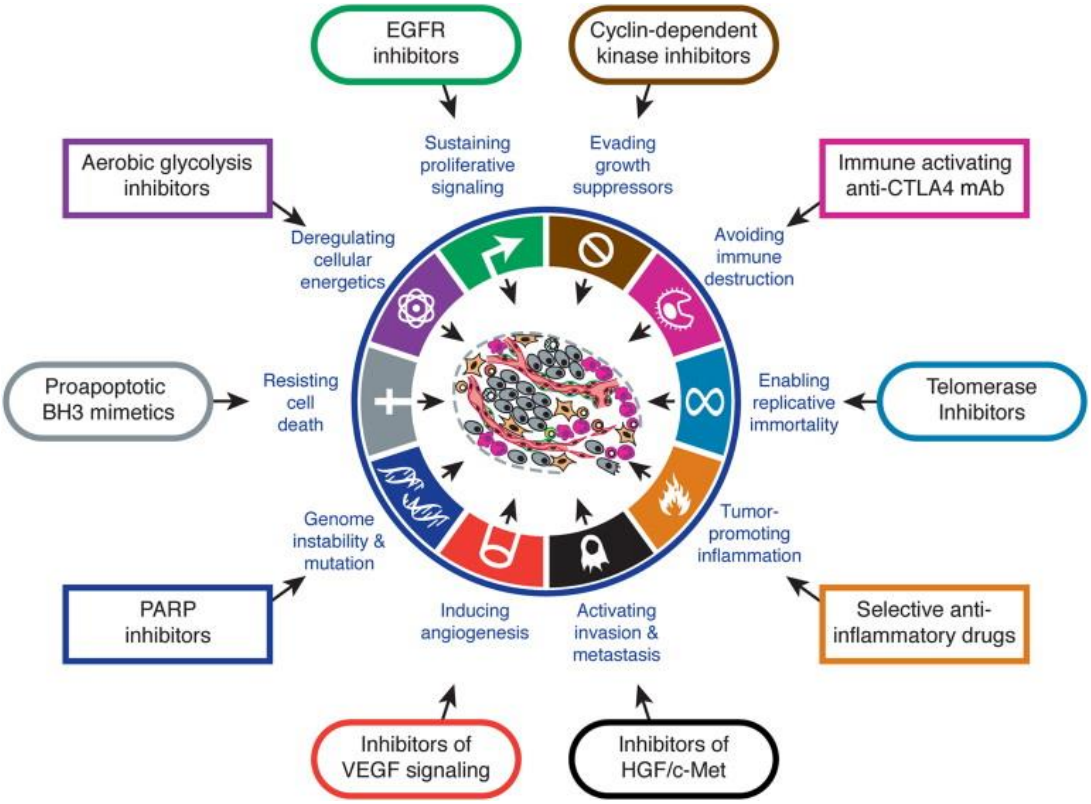

Figure 1. The ten hallmarks of cancer and examples of therapeutical agents to target them[4].

An alternative approach to develop novel cancer treatments is drug repositioning/repurposing of approved drugs[11,12]. Repositioning of approved drugs enables quick entry to clinical trials since these drugs already went through extensive toxicity and safety profiling[13]. In addition, the authorization

process of approved drugs is estimated to be 50-60 percent cheaper compared with novel compounds[14]. Therefore, repositioning of approved drugs is a promising and cost-effective approach to develop novel cancer therapies. Often prescribed drugs are good candidates for drug repositioning since high drug utilization provides extensive safety data. The most used drugs worldwide, see table 1, could therefore be promising agents for drug repurposing. Interestingly, anti-cancer activity had been suggested for eight of the ten drug classes that are involved in this list[12,15–23]. It is therefore interesting to further investigate the potential of these drugs for cancer drug repurposing. It is especially interesting to identify mechanisms that clarify anti-cancer activity. These mechanisms will provide evidence of anti-cancer activity and will help to estimate whether the drugs are candidates for cancer drug repurposing. Therefore, mechanisms that support anti-cancer effects of the drug classes: statins, renin angiotensin system (RAS) inhibitors, dihydropyridine calcium channel blockers (CCBs), selective betablockers (BBs), biguanides PPIs and the drug gabapentin were further investigated in this literature review.

In order to clarify suggested anti-cancer mechanisms of each drug, it was questioned (1) which hallmark of cancer is affected by exposure to the drug and (2) what is the proposed mechanism that clarifies this effect?

Relevant literature was searched using the literature databases pubmed and scopus. In the first place, review articles were searched in pubmed using key words like “cancer”, “statins” (and all other drug classes) “metoprolol” (and all other drugs) etc. Papers were partly selected for further investigation based on the number of citations according to scopus. For some papers, it was decided to look for follow-up studies or more recent findings by checking which papers cited the respectable paper using scopus.

Table 1. Characteristics of the top 10 most prescribed drugs in 2019[24].

Drug name	**Prescriptions in 2019**	**Indication**	**Drug class**	**Mode of action**	**Effect**
Atorvastatin	112,104,359	Hyperlipidemia	Statins, Lipid lowering drugs	Inhibition of HMG-CoA reductase	Lowering of cholesterol synthesis
Levothyroxine	102,595,103	Hypothyroidism	Synthetic hormone	Molecule with the same effect as natural occurring T4	Increases the amount of bioavailable T4
Lisinopril	91,862,708	acute myocardial infarction, hypertension and as an adjunct therapy for heart failure.	ACE inhibitor, RAS inhibitors	Inhibition of angiotensin converting enzyme	Decreased conversion of angiotensin I to angiotensin II resulting in downstream lowering effect on blood pressure
Metformin	85,739,443	Diabetes type II	Biguanides, antihyperglycemic drugs	Inhibition of mitochondrial complex I	Increased ADP:ATP and AMP:ATP ratios, resulting in AMPK activation, which regulates glucose metabolism
Metoprolol	74,578,817	angina, heart failure, myocardial infarction, atrial fibrillation, atrial flutter and hypertension	Selective betablocker, Betablockers	Antagonist of the β1-adrenergic receptor and negligible antagonism of	Receptor inhibition results in lowered cardiac output

				β2-adrenergic receptor	
Amlodipine	73,542,114	Hypertension, Coronary artery disease, Chronic stable angina, Vasospastic angina and Angiographically documented coronary artery disease	dihydropyridine calcium channel blockers, calcium channel blockers	Antagonist of calcium channels in vascular smooth muscle and cardiac muscle	Lowered contraction of vascular smooth muscle and cardiac muscle, resulting in lowered blood pressure
Albuterol	60,679,987	Prevention of bronchospasm due to bronchial asthma, chronic bronchitis, reversible obstructive airway disease, and other chronic bronchopulmonary disorders in which bronchospasm is a complicating factor	β2 adrenergic receptor agonist, Anti-asthmatic Agents	Agonist of the β2-adrenergic receptor.	Relaxion of airway smooth muscle.
Omeprazole	52,546,641	gastroesophageal reflux disease (GERD) and drug-induced peptic ulcers	Proton pump inhibitors, Acid secretion inhibitors	Inhibition H+/K+ ATPase of parietal cells	Inhibition of acid secretion
Losartan	51,773,869	Hypertension, diabetic nephropathy and hypertension with left ventricular hypertrophy,	Angiotensin receptor type I antagonist, RAS inhibitors	Antagonist of angiotensin II receptor type I	prevention of angiotensin II binding causes vascular smooth muscle relaxation, lowering blood pressure
Gabapentin	47,149,505	Epilepsy, neuropathic pain	Anticonvulsant	Inhibition of α2δ-1 subunit of voltage-gated calcium channels	Inhibition α2δ-1 which results in less dense pre-synaptic volage-gated calcium channels.

5 Main text

5.1 Statins

Statins are usually prescribed as lipid lowering drugs for patients with hyperlipidemia and/or with a high risk for atherosclerosis[25]. Statins inhibit 3-hydroxy-3-methylglutaryl CoA reductase (HMGCR), the rate limiting enzyme of the mevalonate pathway. This pathway is responsible for cholesterol biosynthesis and therefore, inhibition of this pathway results in lowered cholesterol synthesis accompanied with lowered intracellular cholesterol levels, which in turn activates a negative feedback loop to lower circulating lipid concentrations[25]. Beside its lipid lowering effect, statins also have an effect on other end-products of the mevalonate pathway like farnesyl-diphosphate (FPP) and geranylgeranyl-diphosphate (GGPP) isoprenoids, ubiquinone (coenzyme Q10, CoQ10) and dolichol[26]. In cancer cells, it was shown that inhibition of the mevalonate pathway majorly affected the production of these end-products rather than the production of cholesterol[27–29]. Statin-induced inhibition of the production of isoprenoids, CoQ10 and dolichol has been suggested to be the mechanism underlying anti-cancer activity of statins. The mechanisms of the proposed anti-cancer activity of statins are described below and visualized in Figure 2. These mechanisms suggest that statins affect the cancer hallmarks sustaining proliferative signaling, deregulating of cellular energetics and invasion & metastasis.

Firstly, statins showed to induce apoptosis and reduce invasiveness by targeting isoprenoid synthesis. The isoprenoids FFP and GGP are commonly used for prenylation, a post-translational modification where FFP and GGP are added to cysteine residues of proteins[30]. FFP and GGP function as lipophilic anchors of prenylated proteins, which enables proper localization of the proteins to cell membranes[31–33]. An important class of prenylated proteins is the RAS GTPases superfamily, which includes tumor driver proteins like Ras and Rho GTPases[31,32]. Statins showed previously to reduce protein prenylation of GTPases via inhibition of FFP and GGP[26,34], leading to apoptosis in some cancer cells[35–38]. Cytotoxic effects of statins were rescued by supplementation with GGPP and sometimes with FPP [35–38], providing evidence that anti-cancer effects were established via inhibition of isoprenoid production. Beside cytotoxic effects, statins also showed to decrease invasion via inhibition of prenylation. In aggressive breast cancer cells, it was observed that statin treatment decreased invasion by reduced prenylation of RhoA and RAS[39,40].

In addition, statins have been shown to reduce proliferation, induce apoptosis and deregulate cellular energetics by inhibition of CoQ10 synthesis. CoQ10 is involved as electron carrier in the electron transport chain (ETC) and functions as a cofactor of dihydroorotate dehydrogenase (DHDOH), a rate limiting enzyme in pyrimidine synthesis. Statins have shown to specifically inhibit CoQ10 synthesis in pancreatic ductal adenocarcinoma, multiple myeloma and p53 deficient colon cancer[27–29]. Statin-induced inhibition of CoQ10 resulted in decreased pyrimidine synthesis by inhibition of DHDOH[27] and induced oxidative stress by ETC-mediated inhibition of oxidative phosphorylation (OXPHOS)[27,28]. These processes decreased proliferation and induced apoptosis in the respectable cancer cells.

Finally, statins showed to induce apoptosis and affect the hallmark resisting cell death by targeting dolichol synthesis. Dolichol is involved in N-linked protein glycosylation as a carrier of oligosaccharides[41]. Inhibition of dolichol synthesis by statins can therefore affect N-linked protein glycosylation[42]. Statins showed anti-glioblastoma effects by affecting glycosylation of multi-drug resistance protein (MDR-1)[43], which made the tumor cells more sensitive to irinotecan. A comparable mechanism was found in FMS-like tyrosine kinase 3/ internal tandem duplication ((FLT3)/(ITD))

positive AML cells. These cells are hard to treat, but were sensitive for statins which was accompanied with decreased glycosylation of FLT3[44].

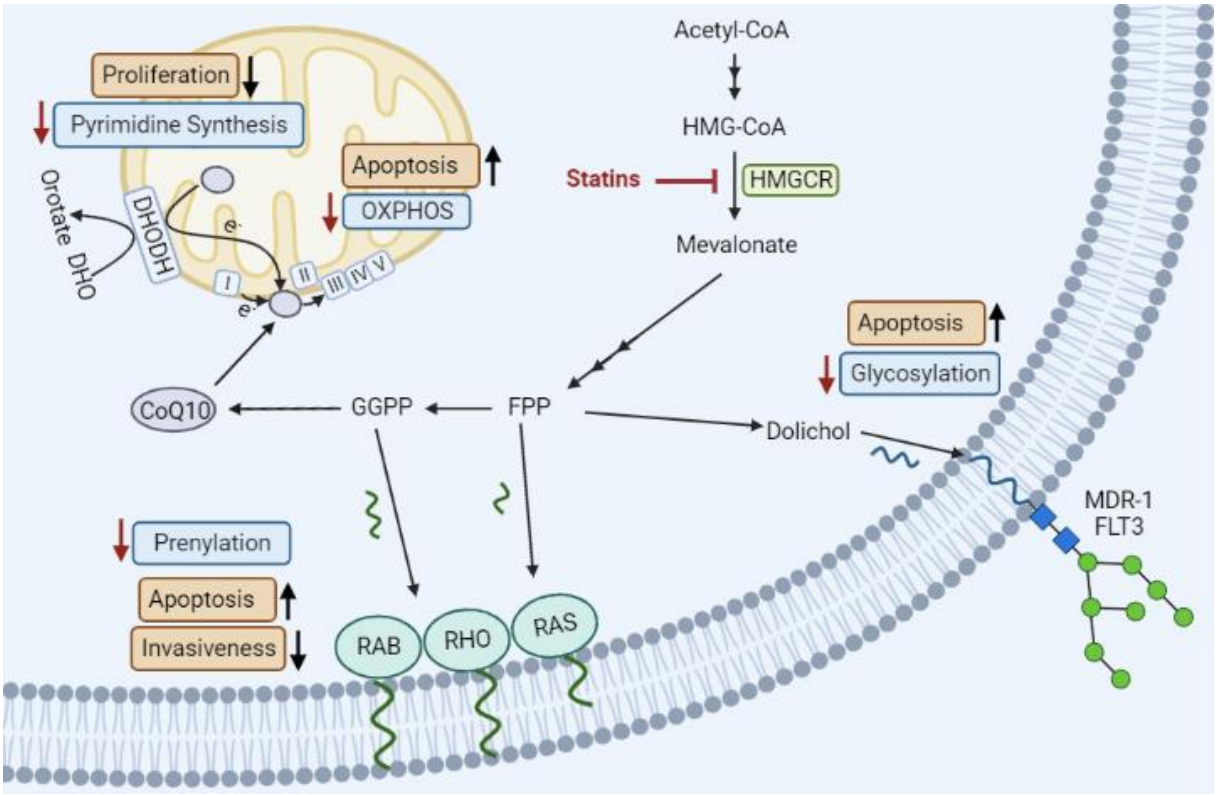

Figure 2. Proposed anti-cancer mechanisms of statins. Statins inhibit the mevalonate pathway by inhibition of HMGCR. This results in a decrease in the synthesis of isoprenoids, CoQ10 and dolichol, which affects prenylation, pyrimidine synthesis, OXPHOS and glycosylation. The following cancer hallmarks are targeted by statin treatment: sustaining proliferative signaling by decreased pyrimidine synthesis, deregulation of cellular energetics by inhibition of OXPHOS, invasion & metastasis by reduced prenylation of GTPases and resisting cell death by decreased glycosylation of MDR-1 and FLT3. Square boxes on the mitochondrion represent the complexes (I-V) of the electron transport chain (ETC). Blue boxes represent biological key processes that are affected upon statin treatment. Orange boxes represent effects of statins on relevant anti-cancer endpoints.

5.2 Renin angiotensin system inhibitors

The renin angiotensin system (RAS) regulates blood pressure homeostasis[45], which makes it an frequently used target to treat hypertension. The two most used RAS inhibitors are angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). ACEIs inhibit angiotensin converting enzyme (ACE) which reduces the conversion of biological inactive angiotensin I to biological active angiotensin II. ARBs are antagonists of the angiotensin II receptor type I (AT1R) and therefore evade binding of angiotensin II to this receptor. Components of the RAS system like AT1R and ACE are expressed on tumor cells and on several cells of the tumor microenvironment (TME)[46]. Therefore, it is suggested that RAS signaling is involved in tumor progression and that RAS inhibitors could reverse these effects[19,20,47,48]. Indeed, RAS inhibition showed to affect the cancer hallmarks activating invasion & metastasis, inducing angiogenesis and avoiding immune destruction. In addition, it was shown that RAS inhibitors increased the drug delivery of chemotherapeutics. The mechanisms that clarify these effects are discussed below and visualized in Figure 3.

RAS signaling influences invasion and metastasis via multiple mechanisms. One suggested mechanism is by supporting epithelial to mesenchymal transition (EMT), which is a known driver of invasiveness of cancer cells[49]. In colorectal cancer, it was observed that induction of AT1R signaling using angiotensin II resulted in increased migration and increased expression of the EMT marker

ZEB1. Treatment with the ARB irbesartan reversed both migration and ZEB1 expression[50], showing that RAS inhibitors successfully can be used to target migration and EMT in colorectal cancer. Beside EMT, metastasis can be modulated by increasing invading capabilities. RAS signaling was suggested to increase invasiveness in breast cancer cells by inducing the expression of metalloproteinase (MMP)-2, MMP-9 and intercellular adhesion molecule 1 (ICAM-1)[51]. Especially MMP-2 and MMP-9 play a role in invasion and migration by enzymatically degrading extracellular matrix (ECM)[52].

Angiogenesis is as well modulated by RAS signaling. In AT1R positive ovarian carcinoma cell lines, it was observed that angiotensin II resulted in increased vascular endothelial growth factor (VEGF) excretion and that this effect was successfully reversed by AT1R blockade with the ARB candesartan[53]. When these cells were grown in a mice model, it was again observed that angiotensin II induced angiogenesis. In addition, increased invasiveness was observed upon angiotensin II exposure. Candesartan treatment reversed both angiogenesis and invasiveness in the mice model, which provided extra evidence that RAS signaling modulates angiogenesis and invasiveness.

Beside the effects of RAS inhibitors on cancer hallmarks, it was also found that RAS inhibitors affected drug delivery. Losartan showed to increase the delivery of chemotherapeutic drugs to cancer cells by decompression of the tumor vasculature in the TME and by reducing solid stress (i.e., accumulation of solid structural components in the TME[54])[55]. Losartan reduced solid stress by decreasing collagen I production in cancer associated fibroblast (CAFs)[55]. In a study of the same authors, it was shown that this collagen I production was a result of AT1R-mediated secretion of transforming growth factor β1 (TGF-β1) activators like thrombospondin-1 (TSP-1)[56], which shows that cross-talk between AT1-R and TGF-β1 signaling is responsible for the effect on solid stress.

Finally, RAS inhibitors showed to affect the cancer hallmark avoiding immune destruction. Immune cells can either be pro-tumorigenic by suppressing the immune system or anti-tumorigenic by increasing the anti-tumor immune response. Examples of pro-tumorigenic immune cells include regulatory T-cells and M2 macrophages which both suppress the anti-tumor immune response. Anti-tumorigenic immune cells include pro-inflammatory M1 macrophages and cytotoxic T-cells. Nanoconjugated valsartan showed a synergistic effect with anti-PD1 and anti-CTLA4 checkpoint inhibitors[57]. This effect was associated with increased cytotoxic T-cells to Treg ratio and an increased M1 macrophage to M2 macrophage ratio. These effects can be declared by the previously indicated effects of RAS inhibitors on solid stress, TGF-β and VEGF since these factors are known mediators of immune invasion[48].

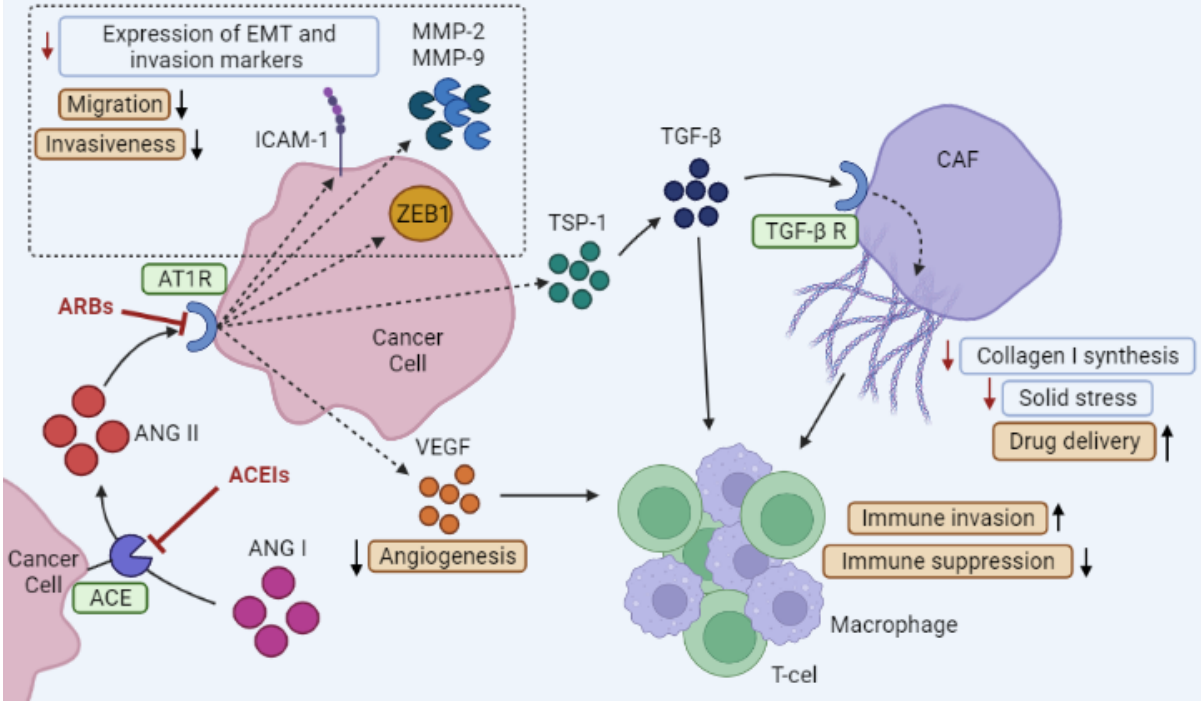

Figure 3. Anti-cancer mechanisms of RAS inhibitors. RAS inhibitors directly or indirectly antagonize AT1R resulting in decreased expression of EMT marker ZEB1, decreased expression of invasion markers MMP-2, MMP-9 and ICAM-1, decreased secretion of VEGF and decreased secretion of TSP-1. Reduced secretion of TSP-1 results in a reduction of available TGF-ß1 levels which decreases collagen I synthesis by cancer associated fibroblast (CAFs). Ras inhibitors affected the cancer hallmarks invasion & metastasis by decreased expression of EMT marker ZEB1 and decreased expression of MMP-2, MMP-9 and ICAM-1, angiogenesis by reduced expression of VEGF and avoiding immune destruction by decreasing VEGF and TGF-ß levels and by decreased collagen I synthesis accompanied with reduced solid stress. In addition, RAS inhibitors showed to induce drug delivery by decreasing collagen I synthesis which reduced solid stress. Blue boxes represent biological key processes that are affected by RAS inhibitors. Orange boxes represent effects of RAS inhibitors on relevant anti-cancer endpoints. Green boxes represent important receptors and enzymes.

5.3 Selective betablockers

There is growing evidence that chronic stress, inflammation and accumulation of catecholamines stimulates cancer progression[58]. In line with this, it was shown that accumulation of catecholamines and increased density of β-adrenergic receptors (β-AR) promoted carcinogenesis of breast, pancreas and ovary cancers[18]. β-ARs can be targeted with betablockers (BBs) and showed anti-tumor activity previously[58]. BBs can be subdivided in non-selective and selective BBs. Non-selective BBs target both the β1-AR and the β2-AR while selective BBs solely target the β1-AR. As reviewed elsewhere, anti-cancer effects of BBs are majorly established by targeting β2-AR using non-selective BBs[15,47,59,60]. However, the goal of this review was to declare anti-cancer effects of the most used drugs. Since the prescription of selective BBs is higher than non-selective BBs[24], the potential anti-cancer effect of selective BBs was further investigated.

Some studies suggest that the selective BB nebivolol induces apoptosis in cancer cells and affects the cancer hallmarks deregulation of cellular energetics and angiogenesis[61,62]. The mechanisms that clarify these effects are discussed below and visualized in Figure 4.

Nebivolol was suggested to induce apoptosis by β1-AR dependent targeting of the mitochondria. It was shown that β1-AR inhibition using Nebivolol resulted in upregulation of ATPase inhibitory factor I (IF1), which inhibited ATP synthase (also known as complex V of the ETC)[61]. In addition, nebivolol prevented phosphorylation of complex I of the ETC. As a result, OXPHOS was impaired resulting in apoptosis.

The effect of nebivolol on angiogenesis was established by targeting of human umbilical vein endothelial cells (HUVEC). It is known that decreased proliferation of these cells results in decreased formation of new blood vessels[63]. Nebivolol showed anti-angiogenic activity by decreasing proliferation of HUVECs[61]. Mechanistically, nebivolol prevented the phosphorylation of ERK, which subsequently reduced glycolysis and finally lead to cell cycle arrest.

Together, the anti-proliferative and anti-angiogenic effects of nebivolol resulted in decreased cancer growth in colon and breast cancer mice models[61]. Furthermore, nebivolol showed to reduce angiogenesis and proliferation *in vitro* and synergized with vincristine *in vivo* in neuroblastoma[62].

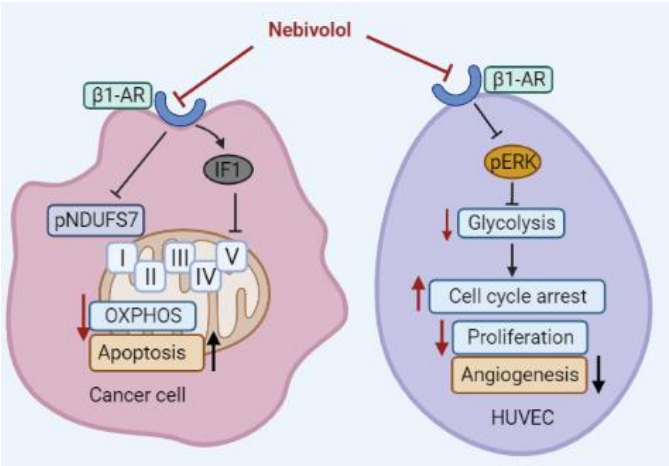

Figure 4. The proposed anti-cancer mechanism of nebivolol. Nebivolol targets the cancer hallmark deregulation of cellular energetics by β1-AR-dependent inhibition of complex I and complex V of the ETC resulting in decreased OXPHOS and induction of apoptosis. Nebivolol also targets angiogenesis by β1-AR dependent inhibition of the proliferation of human umbilical vein endothelial cells (HUVECs). Square boxes on the mitochondrion represent the complexes (I-V) of the ETC. Blue boxes represent biological key processes that are affected upon nebivolol treatment. Orange boxes represent effects of nebivolol on relevant anti-cancer endpoints.

5.4 Dihydropyridine calcium channel blockers

Calcium signaling is a complex signaling network that plays a key-role in multiple cellular processes[64]. Disruption of calcium homeostasis has been shown to affect multiple functions including proliferation, gene expression, cell death, and protein phosphorylation and dephosphorylation[65]. Interestingly, expression of calcium channels/pumps and calcium regulating proteins is altered in cancer[66], which makes targeting of calcium signaling a potential cancer drug target. Since dihydropyridine calcium channel blockers (CCBs) block L-type voltage gated calcium channels, these drugs might have an anti-cancer effect by modulating calcium signaling. Indeed, some studies suggest anti-cancer activity of CCBs by affecting the cancer hallmark sustaining proliferation[67,68]. The proposed anti-cancer mechanisms of CCBs are discussed below and visualized in Figure 5A.

Disruption of calcium regulation by the dihydropyridine CCB Amlodipine showed anti-proliferative effects on uveal melanoma and epidermoid carcinoma cell lines[67,68]. For both uveal melanoma and epidermoid carcinoma, it was observed that anti-proliferative effects were established by induction of cell-cycle arrest. This effect could be clarified by changed intracellular calcium signaling. Intracellular calcium will bind to calmodulin and calcineurin, which subsequently upregulate p21 expression and cyclin D1 synthesis[23,69]. These both processes are involved in cell cycle progression and it is known that inhibition of calmodulin results in cell cycle arrest[70]. Therefore, the proposed anti-cancer mechanism of amlodipine in uveal melanoma and epidermoid carcinoma is decreasing of calcium influx, which subsequently down regulates calcium signaling and results in cell cycle arrest.

Conflicting data were found for dihydropyridine CCBs. While the dihydropyridine CCB amlodipine showed anti-proliferative effects in uveal melanoma and epidermoid carcinoma, nifedipine, another

dihydropyridine CCB, showed to increase proliferation in breast cancer cells[71,72]. Therefore, it is debatable whether all dihydropyridine CCBs have anti-cancer activity.

A clarification of these opposing results might be that the anti-cancer effect of dihydropyridine CCBs is dependent on the expressed calcium channel isoform. Anti-cancer activity of dihydropyridine CCBs was observed for uveal melanoma and epidermoid carcinoma which both arise from the skin. In melanoma, another form of skin cancer, it was observed that majorly the Cav1.3 calcium channel isoform was expressed[73]. Interestingly, it was shown that silencing of Cav1.3 resulted in a decrease in proliferation in breast cancer cells[74]. This study is in contrast with the study where targeting of calcium channels with nifedipine in the same form of cancer resulted in an increase in proliferation[71]. Therefore, it might be possible that the anti-cancer effect of dihydropyridine CCBs is dependent on expression of specific calcium channel isoforms e.g. Cav1.3.

5.5 Gabapentin

Gabapentin is a structural analogue of gamma-aminobutyric acid (GABA), which is a inhibitory neurotransmitter. The drug was originally developed as anti-epileptic drug to treat certain types of seizures, but nowadays it is as well used for treatment of neuropathic pain including cancer-induced pain[75,76]. Interestingly, two studies suggest that gabapentin also has anti-cancer activity by affecting the cancer hallmark sustaining proliferative signaling[22,77]. The mechanism behind this proposed effect is discussed below and visualized in Figure 5B.

Likely to CCBs, gabapentin could modulate calcium signaling. Gabapentin affects calcium signaling as it is a ligand of α2δ1 and α2δ2 subunits of voltage gated calcium channels[78]. Both studies that discovered anti-proliferative activity in cancer, suggested that this effect was established by inhibition of the α2δ2 subunit of calcium channels[22,77]. In prostate cancer cells, it was shown that up- and downregulation of the α2δ2 subunit resulted in in- or decreased cell proliferation by in- or reducing cell cycle arrest[22]. In this study, it was shown that gabapentin reduced cell proliferation both *in vitro* and *in vivo*. The anti-proliferative effect was suggested to be caused by targeting of the calcineurin/nuclear factor of the activated T cell (NFAT) pathway. It was shown that α2δ2 overexpressing cells had an increased calcium influx. The subsequently increased cytosolic calcium levels can activate calcineurin, which in turns increases NFAT activity resulting in increased proliferation. Due to increased calcium influx, α2δ2 overexpressing cells indeed showed increased NFAT activity. In addition, calcineurin inhibitors showed to decrease proliferation in these α2δ2 overexpressing cells. Together these data show that α2δ2 regulates proliferation using the calcineurin/NFAT pathway. In melanoma, gabapentin also reduced proliferation *in vitro* and *in vivo*[77]. In this study it was shown that gabapentin reduced calcium influx, which also links the anti-proliferative effect of gabapentin to calcium signaling.

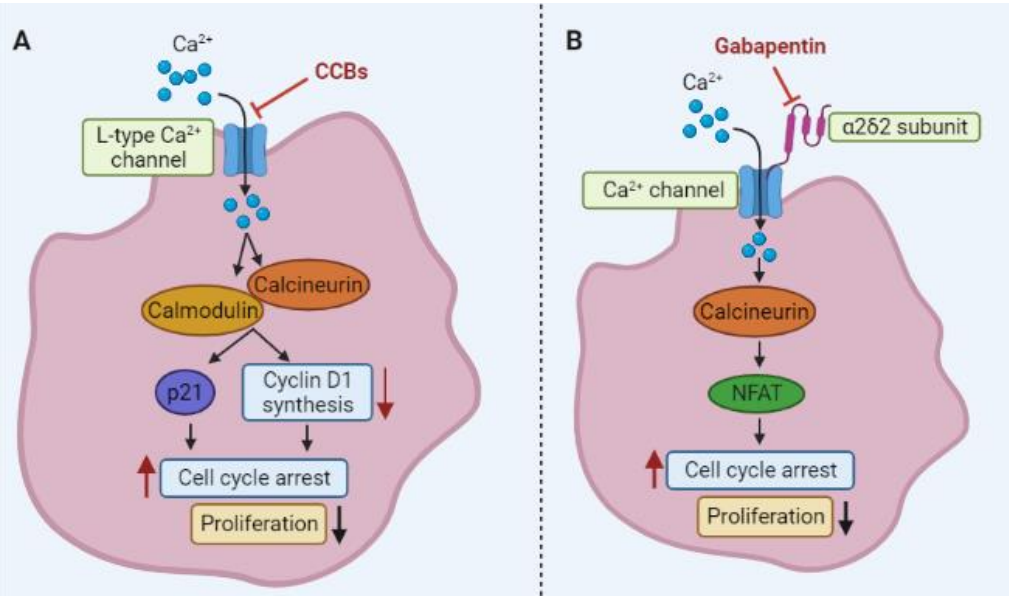

Figure 5. The proposed anti-cancer effects of dihydropyridine CCBs and gabapentin. A) CCBs affect the cancer hallmark sustaining proliferative signaling by reducing the calcium influx resulting in decreased activation and downstream synthesis of cyclin D1 which eventually induces cell cycle arrest. B) Gabapentin affects the cancer hallmark sustaining proliferative signaling by inducing cell cycle arrest. Gabapentin reduces calcium influx by inhibition of the α2δ2 subunit of calcium channels which results in decreased binding to calcineurin and downstream activation of NFAT which eventually induces cell cycle arrest. Blue boxes represent biological key processes that are affected by the drugs. Orange boxes represent effects of the drugs on relevant anti-cancer endpoints. Green boxes represent important channels or subunits of channels.

5.6 Metformin

Metformin is a biguanide that is typically prescribed as a first line therapy for type II diabetes[79]. Metformin decreases circulating glucose levels by inhibition of hepatic gluconeogenesis[80]. In addition, metformin is suggested to induce insulin sensitivity by increased expression of the insulin receptor[81]. Beside this, some studies suggest that metformin also has anti-cancer activity. Metformin is suggested to have anti-cancer activity by targeting the cancer hallmarks invasion & metastasis, sustaining proliferative signaling and deregulation of cellular energetics. The mechanisms that declare these anti-cancer effects are discussed below and visualized in Figure 6.

Direct and indirect anti-cancer mechanisms of metformin are described[12]. Direct anti-cancer mechanisms are direct effects of metformin on cancer cells. Indirect effects are effects that are established via the insulin lowering effect of metformin. The direct anti-cancer mechanisms will be discussed first.

Firstly Metformin affects the cancer hallmarks sustaining proliferative signaling and deregulating cellular energetics. Metformin inhibits complex I of the ETC and subsequently reduces OXPHOS, resulting in decreased ATP production and relative high AMP levels. These elevated AMP levels induce AMP-activated protein kinase (AMPK), which is in an important mediator of (cancer) metabolism[82]. Beside AMPK activation via AMP, it was shown that low doses of metformin activates AMPK by binding to the lysosomal protein PEN2[83]. Metformin-induced AMPK activation showed to inhibit mTOR which resulted in cell cycle arrest in multiple myeloma cells[84]. This caused inhibition of proliferation, but did not initiate apoptosis. This is in line with other studies that as well showed that metformin alone does not induce apoptosis in tumor cell lines, but does decrease proliferation by inducing cell cycle arrest[85–87].

In another study, metformin did show an apoptotic effect. It was shown that metformin induced apoptosis in p53 deficient colon cancer cell lines, but not in cells with functioning p53[88]. In a later study, it was found that the apoptotic effect in p53 deficient colon cancer cells was established by

the inhibition of complex I and subsequent impaired OXPHOS[89]. However, conflicting data were found in another type of cancer. In breast cancer, cells with functioning p53 showed metformin-induced apoptosis while mutated p53 cells were resistant to metformin.[90] Therefore, it might be possible that the apoptotic effect on p53 deficient cells is specific for colon cancer cells.

Beside the effect of metformin on proliferation and apoptosis, it has also been shown that metformin reduces invasion and migration in some cancers[90–92]. The effect of metformin on invasion in multiple myeloma was dependent on AMPK activation and subsequent activation of p53[93]. In addition, this study showed that metformin effectively reduced metastasis of multiple myeloma cells in a mice model. In hepatocellular carcinoma cell lines, metformin reduced both migration and invasion in a p53 dependent manner, which supports the anti-metastatic potential of metformin[91]. Finally, it was shown in cholangiocarcinoma that metformin reduced invasion and synergized the anti-migratory effect of cisplatin[92]. This effect was again accompanied with increased activation of p53 which provided additional evidence that metformin affects migration and invasion by regulating p53 activation.

Indirect anti-cancer effects of metformin are related to insulin-modulating activity of metformin. Metformin decreases insulin-like growth factor (IGF) levels in hyperinsulinemic patients, by decreasing the IGF binding protein 1 (IGFBP-1) levels[94]. The indirectly lowering effect on circulating insulin and insulin growth factor is proposed as an anti-neoplastic effect of metformin[95]. It was observed in a lung cancer mice model that metformin indeed decreased circulating IGF levels with subsequent decreased phosphorylation of the IGF receptor (IGFR)[96]. This affected downstream AKT signaling which resulted in inhibition of mTOR. This inhibition of mTOR was not accompanied with increased activation of AMPK, which confirmed an alternative mechanism of metformin to inhibit mTOR. Again it was shown that inhibition of mTOR resulted in decreased cell proliferation, but did not result in apoptosis.

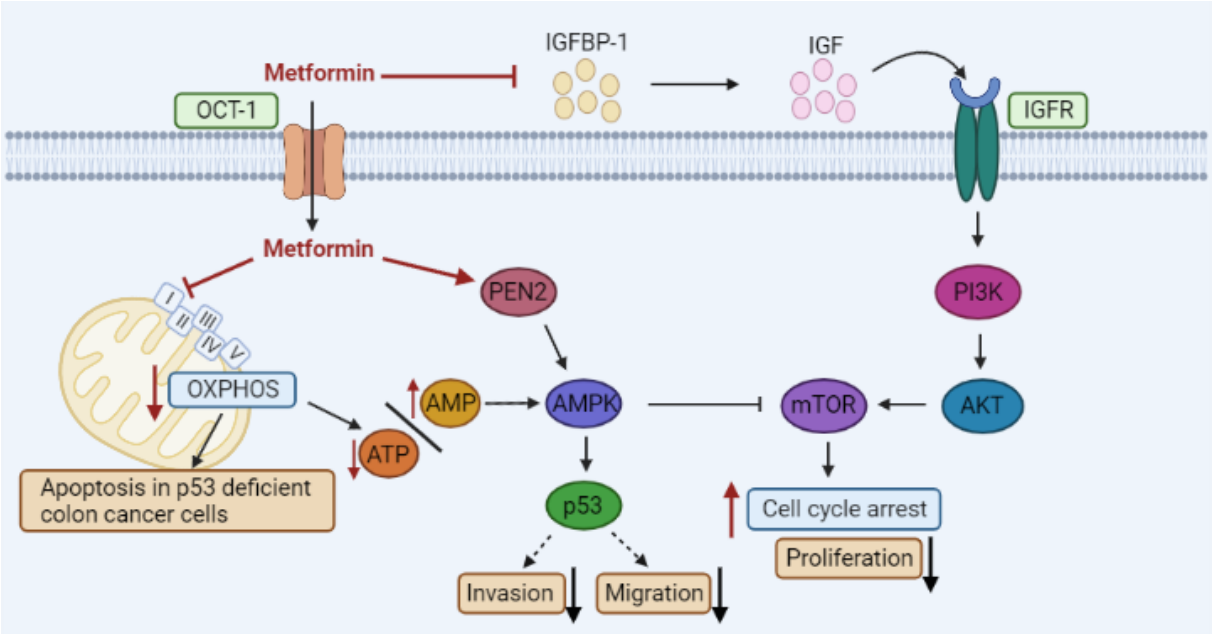

Figure 6. Proposed anti-cancer mechanisms of Metformin. Metformin directly targets the cancer cell by inhibition of complex I of the ETC or by binding to PEN2 and subsequent downstream effects. In addition, metformin targets cancer cells indirectly by decreasing the circulating IGF levels. The affected cancer hallmarks are deregulating cellular energetics by inhibition of complex I of the ETC and subsequent decreased OXPHOS, invasion & metastasis by activation of p53 and sustaining proliferative signaling by inducing cell cycle arrest. Blue boxes represent biological key processes that are affected by metformin. Orange boxes represent effects of metformin on relevant anti-cancer endpoints. Green boxes represent important receptors or transporters.

5.7 Protein pump inhibitors

Proton pump inhibitors (PPIs) reduce acidification of the stomach by inhibiting H^+/K^+ ATPase of parietal cells[97]. Because of its anti-acid effect, PPIs are prescribed for treatment of gastroesophageal reflux disease (GERD) and drug-induced peptic ulcers. Beside its effect on H^+/K^+ ATPase, PPIs can inhibit the vacuolar-type ATPase (V-ATPase)[98] and fatty acid synthase (FASN)[99]. Some studies suggest anti-cancer activity by PPI-induced inhibition of these two targets[100–104]. PPIs were suggested to affect the cancer hallmarks migration & invasion and genome instability. In addition, it was shown that PPIs induced the delivery of weakly basic drugs[105106]. The mechanisms that clarify the suggested anti-cancer effects of PPIs are discussed below and visualized in Figure 7.

Firstly, PPIs induce apoptosis in cancer cells and increase drug delivery by inhibition of V-ATPase and subsequent pH modulation. V-ATPase is expressed on cancer cells and is involved in regulation of the intra- and extracellular pH[107]. The extracellular pH is acidic while the intracellular pH is neutral to alkaline[108]. PPIs successfully induced apoptosis in melanoma *in vitro* and *in vivo* by inhibition of V-ATPase, which was related with elevated extracellular pH levels and decreased intracellular pH levels[100]. This pH modulation can also affect the delivery of chemotherapeutic drugs. It is known that the activity of weakly basic chemotherapeutic drugs is decreased by the low pH in the TME[109]. PPIs induce the extracellular pH by targeting V-ATPase on tumor cells and therefore could reverse this effect[100]. In line with this, it was shown that pre-treatment with omeprazole and esomeprazole improved the drug response of the weakly basic chemotherapeutics cisplatin, 5-fluorouracil and vinblastine in multidrug resistant cells[106]. In addition, it was shown that omeprazole and lansoprazole induced the drug delivery of the weakly basic anticancer drug doxorubicin in 3D breast cancer spheroids[105].

Secondly, several studies showed that PPIs target the cancer hallmark migration and invasion in gastric cancer, breast cancer and glioma[101,102,104]. The effect of PPIs in these studies was accompanied with decreased expression of EMT markers like vimentin, n-cadherin and snail. However, these studies did not provide a direct link between the mechanism of action of PPIs and the observed effects on EMT markers. Potentially, the effects on migration and invasion were established by PPI-induced inhibition of FASN. Knockdown of FASN showed decreased migration in gastric cancer cells accompanied with decreased expression of the EMT marker vimentin[110], which was as well affected in PPI-treated cells. Therefore, it is hypothesized that the effect of PPIs on migration, invasion and EMT is established by inhibition of FASN.

Finally, PPI-induced inhibition of FASN is suggested to affect the hallmark genomic instability. It is mechanistically known that FASN can regulate nonhomologous end-joining(NHEJ) pathways[111]. These pathways are involved in DNA repair and are therefore useful to protect the cancer cells from chemotherapeutics and ionizing radiation[112]. FASN regulates NHEJ by suppression of NF-κβ and induction of specificity protein 1 (SP1) expression. Both suppression of NF-κβ and increased expression of SP1 result in induction of the poly(ADP-ribose) polymerase 1 (PARP-1) promotor. Finally, PARP-1 recruits Ku proteins to induce chromatin and DNA repair resulting in increased DNA repair by NHEJ[111]. Palmitate, the fat molecule which is produced by FASN, modulated the activation of PARP1 and SP1. This showed that the effect on NHEJ is dependent on the production of palmitate by FASN. Inhibition of FASN using PPIs showed to induce apoptosis in breast cancer cells[103]. In this study, it was observed that FASN inhibition was accompanied with reduced PARP1 expression and decreased DNA repair, which is in line with the effect of FASN on NHEJ. In addition, it was found that PPIs synergized with doxorubicin. In a follow up study, PPIs were tested for their potential to synergize with chemotherapeutics in a phase II clinical trial with patients with triple negative breast cancer (TNBC)[21]. This study population was selected since FASN is overexpressed in 70% of the TNBC

cases. In the clinical trial, it was observed that addition of high dose omeprazole improved the pathologic complete response of neoadjuvant chemotherapy[21].

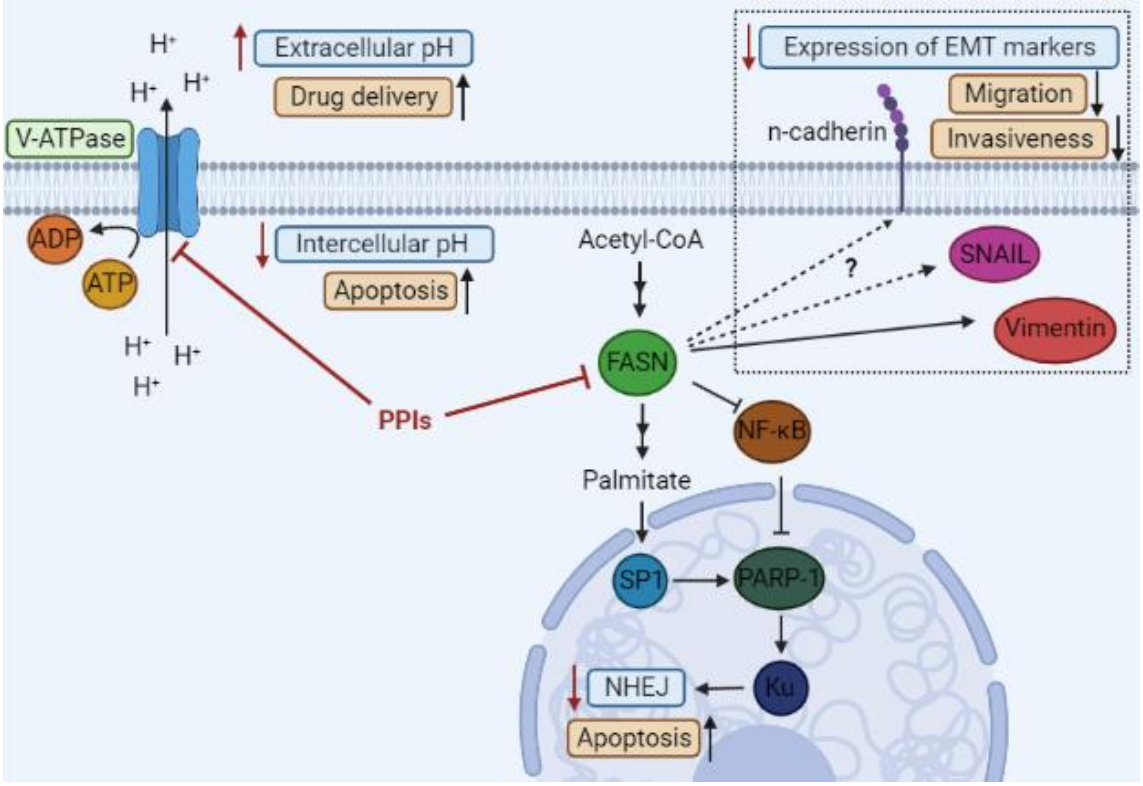

Figure 7. Proposed anti-cancer mechanisms of PPIs. PPIs target V-ATPase which affects the inter- and extracellular pH homeostasis and results in increased delivery of drugs and/or cancer cell apoptosis. In addition, PPIs target FASN which is involved in NHEJ and is hypothesized to be involved in the expression of EMT markers. The affected cancer hallmarks are invasion & metastasis by inhibition of the expression of EMT markers and genomic instability by decreasing NHEJ. Blue boxes represent biological key processes that are affected by metformin. Orange boxes represent effects of metformin on relevant anti-cancer endpoints. Green boxes represent important transporters.

6 Discussion

Drug repurposing is an attractive approach to develop novel cancer treatments since it is less time consuming, has lower costs and has higher changes to get marketing authorization compared to development of new drugs[13,14]. Potential candidates for drug repurposing are extensively used drugs since their high utilization provides a lot of safety data and insight in potential side effects. Therefore, mechanistical evidence that supports anti-cancer activity of (the drug classes of) eight of the ten most used drugs worldwide was investigated in this literature review. Data from experimental *in vitro* and *in vivo* studies suggested anti-cancer activity for all of the investigated drugs. The anti-cancer effects were established by targeting of several cancer hallmarks including: sustaining proliferation, induction of invasion and metastasis, avoiding immune destruction, induction of angiogenesis, deregulation of cellular energetics, genome instability and resisting cell death. Mechanistical evidence that clarified anti-cancer effects were found for all drugs. These mechanisms support suggested anti-cancer activity of the investigated drugs.

Targeting of cancer with single compounds is challenging since hallmarks of cancer are clearly not regulated by single signaling pathway[4,113]. Drug combinations that target multiple hallmarks can therefore be superior compared to monotreatment since they may target supporting pathways that are not targeted by single treatments, ultimately resulting in reversion of drug resistance and increased effect of the drug[4,114]. Therefore, combining of drugs is an effective approach to develop novel cancer treatments. In addition, combining of drugs is an attractive approach for drug repurposing since drugs are more likely to get authorized as repurposed drugs if they are combined with other drugs[115]. Since combining of drugs is an attractive and effective approach for cancer drug repurposing, the drug classes statins[43], RAS inhibitors[55], selective BBs[62], biguanides[92] and PPIs[103] which showed combinational effects with conventional treatments in this literature review, were considered as potential candidates for drug repurposing.

Repositioning of RAS inhibitors, selective BBs and CCBs could be challenging as these drugs decrease systemic blood pressure. Therefore, there is a risk of hypotension when these drugs are administered to patients with normotension. Because of this, clinical trials to test the efficacy of these drugs might be restricted to patients with existing hypertension. A novel approach to avoid unwanted hypotension is targeted delivery of the drugs to the TME. For ARBs, several approaches were already tested. Encapsulation of losartan in liposomes effectively improved the efficacy of liposomal paclitaxel without affecting the blood pressure[116]. In addition, the ARB valsartan conjugated to a pH sensitive polymer showed effective delivery of valsartan to the TME and synergism with immune-checkpoint inhibitors in a breast cancer mice model[57]. These data show that targeted delivery could avoid side effects of blood pressure lowering drugs. Furthermore, it was shown that the investigated drugs might have the potential to be used as active agents for novel nanomedicines.

Interestingly, the compounds pitvastatin and amlodipine were identified as potential anti-cancer drugs by high-throughput screening[43,67]. The drugs showed effects on uveal melanoma and glioblastoma, which are both orphan diseases with limited treatment options[117–119]. Drug repurposing holds a great promise for these orphan diseases, since the low incidence of these diseases makes it relatively expensive to develop novel drugs for such a small population[120]. Especially the results of pitavastatin on glioblastoma were promising since this drug showed anti-cancer effects both *in vitro* and *in vivo*. Therefore, these two studies show that high-throughput screening could be an effective approach to identify compounds for drug repurposing in orphan diseases.

Overall, anti-cancer mechanisms were identified for all the investigated drugs. These mechanisms support suggested anti-cancer activity of the investigated drugs and therefore it was concluded that

the drug gabapentin and the drug classes statins, RAS inhibitors, selective betablockers, dihydropyridine CCBs, biguanides and PPIs have the potential to be used for cancer drug repurposing. Since the drug classes statins, RAS inhibitors, selective BBs, biguanides and PPIs showed combinational effects with conventional treatments, these drug classes were especially considered as potential agents for cancer drug repurposing.

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