

# DPP-IV Inhibition in Anticancer Treatment

Subjects: **Oncology**

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Dipeptidyl peptidase IV (DPP-IV, CD26) is frequently dysregulated in cancer and plays an important role in regulating multiple bioactive peptides with the potential to influence cancer progression and the recruitment of immune cells. Therefore, it represents a potential contributing factor to cancer pathogenesis and an attractive therapeutic target. Specific DPP-IV inhibitors (gliptins) are currently used in patients with type 2 diabetes mellitus to promote insulin secretion by prolonging the activity of the incretins glucagon-like peptide 1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). Nevertheless, the modulation of the bioavailability and function of other DPP-IV substrates, including chemokines, raises the possibility that the use of these orally administered drugs with favorable side-effect profiles might be extended beyond the treatment of hyperglycemia.

gliptin

cancer

tumor microenvironment

immune response

chemokine

stromal cell-derived factor

drug repurposing

stem cells

## 1. Introduction

There is a growing appreciation that the tumor microenvironment represents a critical parameter for the development and progression of malignancies. During the course of tumorigenesis, a tumor niche defined by and specific for the tissue in which the tumorigenic process was initiated is established and contributes to the tumor's development and growth <sup>[1]</sup>. The recruitment of immune and other cell types into this niche and their interactions within it are dependent upon a complex display of chemokines and other signaling mediators. Concomitantly, a number of these mediators are involved in the maintenance of niches that are critical for tissue homeostasis and recovery after the stress induced by conventional anticancer treatments. Consequently, the researchers' knowledge of the control of the expression and activity of these mediators may open up novel or complementary avenues for intervention in malignant diseases.

## 2. DPP-IV Inhibition and Cancer Initiation and Progression

Currently, more than ten potent and relatively selective dipeptidyl peptidase IV (DPP-IV) inhibitors (gliptins) are used in clinical practice worldwide. The systemic inhibition of DPP-IV enzymatic activity with the ensuing increased bioavailability and signaling of various DPP-IV substrates, including those that may affect cell proliferation and migration, has raised concerns in two areas.

The first is its possible impact on diverse processes in premalignant niches, resulting in their more rapid evolution into cancer. The increased risk of pancreatic cancer ranks among the most frequently discussed and controversial topics related to the use of DPP-IV inhibitors. DPP-IV expression is upregulated in pancreatic adenocarcinoma, which may be linked to the impaired glucose homeostasis frequently associated with this type of cancer [2]. In a transgenic rat model of type 2 diabetes mellitus, DPP-IV inhibition by sitagliptin increased ductal cell proliferation and induced ductal cell metaplasia as a precursor of pancreatic ductal adenocarcinoma, possibly due to the increased availability of GLP-1 [3]. In line with these findings, an autopsy study in patients treated with sitagliptin reported a marked expansion of the exocrine and endocrine compartments of the pancreas [4]. By contrast, an independent study revealed no pronounced histological abnormalities in the pancreatic tissues of diabetic patients treated with incretins compared to diabetic patients not receiving incretins [5]. In addition, three different studies on rodents failed to reveal changes in ductal proliferation or evidence of pancreatitis, ductal metaplasia, or neoplasia with gliptin treatment lasting for up to two years [6][7][8]. Conflicting data on pancreatic cancer were also reported in clinical studies and meta-analyses, some of which showed no increase or even a numerical decrease in risk [9][10][11][12][13], while others reported increased risk [14][15]. A large population-based cohort study has also demonstrated an increased risk of cholangiocarcinoma in patients using gliptins [16], but mechanistic studies in this serious but relatively rare cancer type are lacking.

The second area of concern is that DPP-IV inhibition may support the growth/invasive spread of cancer cells in patients with a preexisting malignancy. A case study reported that a patient with a recurrent metastatic carcinoid tumor that was stable for several years experienced an almost twofold increase in plasma serotonin levels after the initiation of saxagliptin, suggesting tumor progression. Upon the discontinuation of the medication, the values quickly returned to their previous levels, implying causality [17]. A study in a mouse model of breast cancer suggested that the inhibition of DPP-IV may promote the epithelial–mesenchymal transition, proliferation, and metastasis of cancer cells through the CXCL12–CXCR4 axis [18]. Although the inhibitor utilized in this research had a rather low potency [19] and is not used in clinical practice, this report raises a concern that other DPP-IV inhibitors may have a similar effect. In another study, using a mouse model of prostate cancer, sitagliptin administration led to a more rapid restoration of tumor growth after castration, suggesting that DPP-IV inhibition may decrease the efficacy of androgen deprivation therapy [20]. Saxagliptin and sitagliptin further promoted the migration and invasion of various cancer cell lines in vitro without affecting their proliferation or sensitivity to chemotherapeutics and promoted metastatic dissemination in vivo. This was linked to the reduced oxidative stress caused by the decreased ubiquitination and resulting activation of the nuclear factor E2–related factor 2 (Nrf2) antioxidative pathway in the cancer cells [21]. A similar Nrf2-mediated promigratory and proinvasive effect, and a more rapid growth of lung metastases, was observed for thyroid cancer cells [22]. DPP-IV inhibition is highly likely to be responsible for these effects, since several structurally diverse gliptins activated Nrf2. Nevertheless, the underlying molecular mechanism is currently unclear and the responsible DPP-IV substrate(s) remain(s) to be identified. The increased metastatic spread of a preexisting tumor, as observed in preclinical models, has so far not been reported in clinical studies analyzing the development of metastatic disease in type 2 diabetes patients treated with DPP-IV inhibitors. An observational German study with a 3–4 year follow-up did not reveal an increased risk of metastases in DPP-IV-inhibitor-treated patients with breast, prostate or digestive-organ cancers [23]. Similarly, a study with a

5.6-year follow-up in Korean diabetic patients with preexisting primary cancer did not reveal an association between the use of DPP-IV inhibitors and new metastatic disease. A possible exception was a subgroup of patients with thyroid cancer, but the overall frequency of metastatic disease in this small subgroup was low [24]. These studies in two different populations provide reassurance, but caution is advisable in interpreting the results given the inherent limitations of such studies and their relatively short follow-up.

In contrast to the worrying reports mentioned above, several epidemiological studies suggest that gliptin use is associated with a reduced risk of breast [25], prostate [26], and HCV infection-associated hepatocellular cancer [27]. In addition, a small study reported improved outcomes in tyrosine-kinase-inhibitor-treated patients with renal cell cancer using gliptins [28]. DPP-IV is upregulated in hepatocellular carcinoma [29][30] and high serum DPP-IV activity is associated with worse patient survival [31]. In animal models, gliptins ameliorated chemically induced liver fibrosis [32][33][34][35][36], a known risk factor for hepatocellular carcinoma. In addition, vildagliptin prevented diethylnitrosamine-induced hepatocarcinogenesis in rats fed a high-fat diet. Increased vascularization and macrophage, but not the T- or NK-cell infiltration of hepatic nodules, together with lung metastases, were observed in animals fed a high-fat diet, and these effects were suppressed by vildagliptin. Interestingly, vildagliptin normalized the high-fat diet-induced elevation of plasma CCL2, a potential contributor to the proangiogenic effects. Similar results were obtained in DPP-IV knockout animals, suggesting a critical role of DPP-IV enzymatic activity in these processes [31]. Hepatoprotective effects were also observed for saxagliptin in a rat model of hepatic injury induced by thioacetamide [37]. Saxagliptin reduced the serum levels of the markers of hepatocellular injury and alpha-fetoprotein, diminished the histopathological changes induced by thioacetamide, and deferred the occurrence of hepatocellular carcinoma, possibly by suppressing Wnt/Hedgehog/Notch1 signaling. Of note, the protective effects were observed even when DPP-IV inhibition was initiated several weeks after exposure to hepatotoxic treatment [37]. However, whether and which of these effects are mediated by DPP-IV substrates affecting hepatocytes, immune cells [38], or both remains unknown.

Nonalcoholic steatohepatitis (NASH) is an increasingly prevalent disease, which leads to liver cirrhosis and predisposes patients to hepatocellular carcinoma. DPP-IV may participate in the pathogenesis of NASH by regulating the levels of bioactive GLP-1, but also through its auto and paracrine effects on hepatic insulin signaling [39]. In a genetically obese melanocortin 4 receptor (MC4R)-deficient mouse model of NASH, anagliptin ameliorated fibrosis and reduced the number of liver tumors that developed after the mice were fed a Western-type diet. Anagliptin had no effect on body weight, systemic glucose and lipid metabolism, hepatic steatosis, or adipose tissue inflammation, but its protective effects were proposed to be mediated by the GLP-1-mediated suppression of macrophage activation [40]. Concordantly, sitagliptin mitigated hepatic steatosis and reduced the number and size of hepatic tumors developing in a STAM mouse model of NASH. The authors proposed that these effects may be linked to the inhibition of the pentose phosphate pathway in the tumor tissue, possibly resulting from the suppression of the p62–Keap1–Nrf2 pathway [41]. Two studies utilizing a choline deficiency-induced steatohepatitis rat model [42][43] demonstrated that gliptins may reduce the development of liver fibrosis and preneoplastic lesions; this is likely to occur through their inhibition of activated stellate cells, through their role in reducing oxidative stress, and through their inhibition of angiogenesis. The combination with either a sodium-glucose cotransporter-2

(SGLT2) inhibitor [42] or an angiotensin II receptor type 1 (AT1) antagonist [43] was synergistic and led to more pronounced protective effects.

The chemopreventive effects of gliptins were also reported in colorectal cancer, about which DPP-IV inhibition has raised concerns because of its potential to enhance the intestinotrophic effects of GLP-2 [44][45]. Despite this, no association was observed between gliptin use and the incidence of colorectal carcinoma [46]. In fact, diabetic patients with colorectal carcinoma treated with gliptins seem to have improved outcomes compared to those treated with other hypoglycemic medications [47][48][49]. In addition, several models emulating various aspects of intestinal tumorigenesis show rather protective effects of gliptins. High-fat diet-fed rats exposed to the carcinogen 1,2-dimethylhydrazine developed lower numbers of precancerous lesions with sitagliptin administration [50]. Lower blood plasma levels of hydrogen peroxide in animals receiving sitagliptin were reported in this research [50], but whether and how this related to DPP-IV inhibition is currently unclear. A similar study with sitagliptin in leptin-deficient mice, in which intestinal carcinogenesis was initiated using 1,2-dimethylhydrazine together with chemically induced colitis, reported a lower number of aberrant crypt foci and lower intestinal IL6 expression [51]. Further, rather than an increase, a statistically nonsignificant decrease in tumor number was described for sitagliptin in a model of high-fat diet-induced carcinogenesis in mice carrying a heterozygous mutation in the adenomatous polyposis coli (*Apc*) tumor suppressor gene (C57BL/6J-*Apc*<sup>Min/J</sup>) [52]. Somewhat counterintuitively, the long-term sitagliptin administration in this research lowered the high-fat diet-induced increase in GLP-2, CXCL5, and CXCL12 in the blood plasma [52].

Preclinical data on other types of cancer are scarce. A study using a model of chemically induced renal cell carcinoma showed that, probably by improving the defense against oxidative stress and ameliorating inflammation, sitagliptin decreased the occurrence of neoplastic foci in the kidney cortex and improved renal functions [53]. Sitagliptin further reduced tumor growth in transgenic mice that expressed oncogenically activated MAPK kinase 1 in non-dividing, differentiating epidermal cells, in which skin wounding induced tumor formation. Nevertheless, the onset, formation, and number of tumors were similar, and there was no effect of sitagliptin on angiogenesis or cancer cell proliferation [54].

Collectively, current evidence from clinical studies regarding the effect of gliptins on cancer development and progression is rather conflicting [25][26][27][46][47][48][49][55][56][57][58], possibly due to the long period during which most malignancies develop before they are diagnosed and the complexity of the pathogenetic mechanisms determining their growth, invasion, and metastatic spread. Preclinical studies suggest that gliptins may impede the development of certain tumors, such as hepatocellular carcinoma. On the other hand, there may be a risk that DPP-IV inhibition may encourage the progression of some preexisting malignancies by enhancing the spread of cancer cells.

## 3. DPP-IV Inhibition in Anticancer Treatment

### 3.1. Direct Cytotoxic Effects of DPP-IV Inhibition on Cancer Cells

Vildagliptin has been shown to decrease the growth of colorectal cancer cells in vitro [59]. In addition, it inhibited the growth of lung metastases in a mouse model, possibly by promoting cancer cell apoptosis and decreasing autophagy [59]. In a series of three closely related in vitro studies, the cytotoxic effects of a highly selective DPP-IV inhibitor, gemigliptin, were evaluated in thyroid cancer cells by Kim et al. The authors reported that gemigliptin exhibited a dose- and time-dependent cytotoxic effect, accompanied by the activation of Akt, ERK1/2, and AMPK, elevated levels of the apoptosis regulator Bcl-2, and a reduction in cellular ATP and mitochondrial membrane potential. The effects of gemigliptin were synergistic with those of the histone deacetylase inhibitor PXD101, the heat-shock protein 90 inhibitor, AUY922, and metformin [60][61][62]. Similarly, sitagliptin has been shown to inhibit the migration, invasion and, at higher concentrations, the growth of thyroid cancer cells in vitro and attenuated tumor growth in a mouse model, possibly by interfering with TGFβ signaling [63]. In another in vitro study, sitagliptin blocked the growth and clonogenic capacity of gastric cancer cells [64] by inhibiting the YAP transcriptional co-activator. In breast cancer models, DPP-IV has been shown to promote tumorigenesis by enhancing EGF-induced MEK/ERK signaling, leading to AP-1 activation and the expression of the peptidylprolyl cis/trans isomerase encoded by *PIN1*. Sitagliptin suppressed these effects, inhibited colony formation, and induced cytotoxicity by activating apoptotic signaling in vitro [65]. In vitro, sitagliptin also suppressed the growth and migration of endometrial cancer cells [66] and the growth, motility, and invasion of colorectal cancer cells [67].

A general caveat applies to several of the aforementioned studies due to the high gliptin concentrations used and the very limited in vivo data supporting their conclusions. Gliptins effectively inhibit DPP-IV in nanomolar concentrations. The mean tissue concentrations in mice fed sitagliptin are approximately 40 nM [54], the maximum plasma concentrations in humans are below 2 μM with usual dosing, and, in a study using repeated doses of up to eight times the usual dose of sitagliptin, maximum plasma concentrations of 11 μM were reported [68]. This contrasts with the millimolar concentrations for which cytotoxicity was reported in most studies. While micromolar gliptin concentrations were—by inhibiting DPP-IV—sufficient to enhance the promigratory effect of CXCL12 in chronic myeloid leukemia (CML) cells [69], there was no effect on the growth of DPP-IV-expressing CML cells [69][70]. Similarly, several studies observed no cytotoxicity in DPP-IV-expressing hepatocellular carcinoma cells at concentrations of up to 100 μM [21][38][43][71][72][73], and a recent study using DPP-IV<sup>+</sup> renal cell carcinoma stem cells demonstrated that sitagliptin had no effect on the growth of these cells, but enhanced their sensitivity to the tyrosine kinase inhibitor, sunitinib, in vitro and in vivo [28].

The inhibition of DPP-IV-related proteases may contribute to some of the observed cytotoxic effects. Vildagliptin enhanced the cytotoxicity of a sesquiterpene parthenolide in acute myeloid leukemia cells [74] and was toxic for multiple myeloma cell lines [75]. Similar cytotoxic activity in multiple myeloma was observed for saxagliptin, but not for the more selective DPP-IV inhibitors sitagliptin, alogliptin, and linagliptin. In both studies in hematological malignancies, the anti-tumor effect of vildagliptin was mediated by the inhibition of DPP8 and 9 and not DPP-IV, as demonstrated by knockdown approaches and the use of DPP8 inhibitors [74][75]. Similarly, high concentrations of sitagliptin (above 2 mM) compromised the integrity of the plasma membrane, as evidenced by the LDH release and decreased viability of various cervical carcinoma cell lines, including cells not expressing DPP-IV [76], further supporting the conclusion that these effects are not related to DPP-IV.

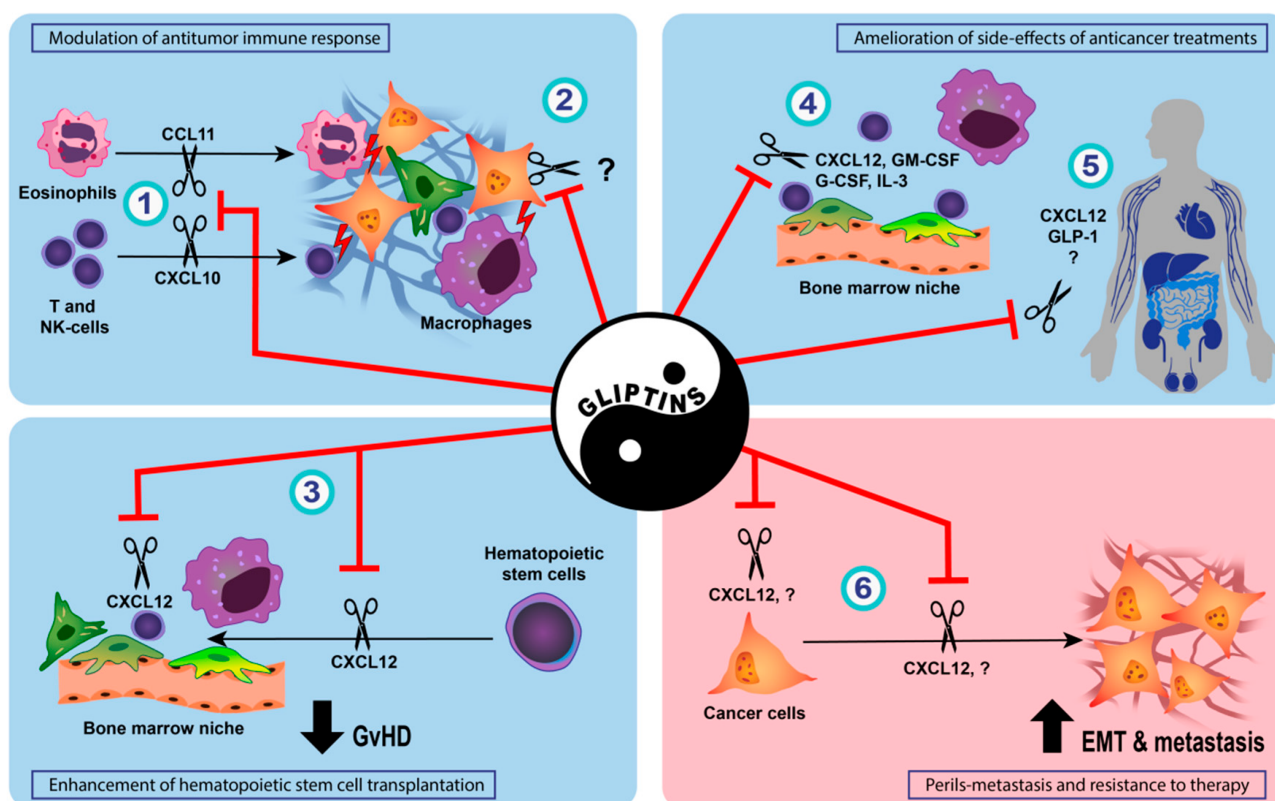
The mechanisms responsible for these non-DPP-IV-associated effects of gliptins in cancer cells are currently unknown. Nevertheless, several potential off-target effects were observed for individual gliptins. For example, nanomolar concentrations of linagliptin attenuated cardiac remodeling in DPP-IV-deficient rats, possibly by reducing the TGFβ-1 and MMP2 expression in cardiac fibroblasts [77]. Another study showed that at clinically relevant concentrations, linagliptin, but not sitagliptin, alogliptin, or saxagliptin, enhanced cardiac recovery after ischemia reperfusion, most likely by stimulating the Akt/eNOS in the endothelial cells, leading to the cyclic guanosine monophosphate (cGMP)-mediated activation of phospholamban, the pivotal regulator of cardiomyocyte contractility [78]. In an ex vivo study, vasodilatory effects mediated by the activation of Kv channels and SERCA pumps were reported for trelagliptin [79]. Further, high concentrations of sitagliptin may affect cells by activating AMPK, as demonstrated in gastric cancer cells [64]. Whether and how these effects of gliptins, seemingly unrelated to DPP-IV inhibition, impact cancer cells remains to be established.

In summary, the evidence for the direct cytotoxic effect of DPP-IV inhibition by gliptins in cancer cells is not convincing.

### 3.2. Effect of DPP-IV Inhibition on Anti-Tumor Immune Response

Anti-tumor immune responses are largely dependent on the infiltration and effector functions of activated T cells. Indeed, subpopulations of CD4<sup>+</sup> DPP-IV/CD26<sup>high</sup> T cells seem to have strong anti-tumor activity, possibly due to the fact that DPP-IV/CD26 is a marker of T-cell activation and a co-stimulatory molecule. These cells exhibit a phenotype similar to, but distinct from, Th17 cells, and express several chemokine receptors, cytokines, and anti-apoptotic genes that allow them to migrate, survive, and persist in tumors [80][81]. Since chemokines are key factors driving the infiltration of T cells into the tumor microenvironment, DPP-IV inhibition may modulate anti-tumor immune responses (**Figure 1**). For example, DPP-IV cleaves CXCL10 (IFN-γ-induced protein-10, IP-10), a chemoattractant for various immune cells, and the truncated chemokine acts as an antagonist on its receptor CXCR3 [82]. In a syngeneic melanoma mouse model, tumor growth and the establishment of metastases after the intravenous application of melanoma cells were diminished in DPP-IV knockout animals and after sitagliptin administration. The mechanism of this anti-tumor activity involved higher levels of intact CXCL10 and the increased infiltration of CXCR3-positive lymphocytes into the tumors [83]. As a possible contributing factor, sitagliptin enhanced the recruitment of type 1 conventional dendritic cell precursors (pre-cDC1), which express CXCR3 and are critical for the cross-presentation of exogenous antigens to CD8<sup>+</sup> T cells [84]. Sitagliptin also delayed tumor growth in a syngeneic colorectal cancer mouse model, which was accompanied by the enhanced infiltration of T and NK cells and improved the response to immunotherapies, including a CpG oligodeoxyribonucleotide, the adoptive transfer of tumor-targeting T cells, and an anti-CTLA-4 immune-checkpoint inhibitor. The combination of sitagliptin with a dual anti-CTLA-4 and anti-PD-1 blockade resulted in tumor rejection in all the experimental animals, whereas a combination therapy with anti-CTLA-4 and anti-PD-1 cured only 42% of the animals [83].





**Figure 1.** Potential utility and pitfalls of DPP-IV inhibition by gliptins in anticancer treatment. (1) By preventing DPP-IV-mediated cleavage of chemokines, gliptins may support the recruitment of immune cells with anti-tumor activity into the tumor microenvironment [38][71][83][85]. (2) In addition, changes in cancer cells induced by gliptins may activate macrophages and NK cells [86]. (3) In patients undergoing hematopoietic stem cell transplantation, attenuated cleavage of CXCL12 facilitates the homing and engraftment of donor cells [87][88][89] and result in lower incidence of acute graft-versus-host disease (GvHD) [90]. By reducing the DPP-IV-mediated cleavage of various mediators supporting tissue regeneration, gliptins may increase the resilience of healthy tissues to chemotherapy-induced damage, resulting in (4) accelerated hematopoietic recovery after chemotherapy [91], (5) decreased nephrotoxicity [92][93][94][95][96], cardiotoxicity [97][98], neurotoxicity [99], hepatotoxicity [100], testicular toxicity [101], and reduced mucositis [102]. (6) On the other hand, increased bioavailability of CXCL12 resulting from DPP-IV inhibition, together with gliptin-induced activation of nuclear factor E2-related factor 2 (Nrf2), carries the risk of accelerated epithelial–mesenchymal transition (EMT) and metastatic dissemination of cancer cells [18][21][22][103][104].

A follow-up study [71] by the same group suggests that, at least in certain tumor types, DPP-IV inhibition may also support innate anti-tumor immune responses. In preclinical models of liver and breast carcinoma, the anti-tumor effects of sitagliptin were preserved, even when T cells were depleted. Increased intratumoral concentrations of CCL11, IL4, IL5, and IL33 were observed in sitagliptin-treated animals, and the beneficial effects of sitagliptin were mediated by eosinophils and CCL11, a DPP-IV substrate. Sitagliptin enhanced CCL11-mediated eosinophil infiltration, and the anti-tumor effects seemed to be particularly relevant for tumors producing IL33, a known eosinophil activator and inducer of CCL11 expression. Indeed, anti-IL33 neutralizing antibodies eliminated the beneficial effect of DPP-IV inhibition in liver and breast carcinoma models [71]. The anti-tumor effect of DPP-IV inhibitors in hepatocellular carcinoma was supported by another report, which showed that high intratumoral DPP-

IV expression was associated with lower numbers of tumor-infiltrating NK and T cells in patients with hepatocellular carcinoma [38]. In addition, tumor xenotransplant growth was decreased by alogliptin and vildagliptin due to the CXCR3-mediated increase in infiltration by NK cells. Similarly, sitagliptin increased tumor infiltration by NK and T cells in a mouse model of non-alcoholic steatohepatitis-induced hepatocellular carcinoma. Gliptins prevented the degradation of CXCL10 by DPP-IV-expressing cancer cells and preserved its chemotactic activity for NK cells, suggesting that in these models, chemokine-mediated lymphocyte trafficking contributes to the anti-tumor activity of gliptins. Interestingly, the tumors in gliptin-treated animals were also less vascularized [38]. The CXCR3 ligands, CXCL10, CXCL9, and CXCL11, are known to inhibit angiogenesis, but their DPP-IV-mediated truncation seems—in contrast to the effect of truncation on lymphocyte trafficking—not to interfere with their angiostatic properties [105]. The decreased conversion of NPY by DPP-IV to a pro-angiogenic NPY(3-36) Y2/Y5 receptor agonist [106] may be an alternative mechanism, but this remains to be established in future studies.

A study using a syngeneic mouse model of ovarian carcinoma further supports the role of gliptins in enhancing the anti-tumor immune response. Sitagliptin improved animal survival and decreased tumor dissemination in parallel with an increase in intratumoral CD8<sup>+</sup> T cell/Treg ratio, a decrease in the plasma levels of immunosuppressive cytokines, and an improvement of intratumoral lymphocyte activation and proliferation [85]. The infiltration of the tumors by CXCR3<sup>+</sup> T lymphocytes suggested a similar mechanism of immune system activation by sitagliptin, involving the increased bioavailability of chemokines.

A different mechanism through which vildagliptin leads to the stimulation of the innate anti-tumor immune response was described in lung cancer models. Jang et al. [86] demonstrated that tumor growth was hampered in a syngeneic and xenograft mouse model upon the administration of vildagliptin. However, the T- and B-cell infiltration of the tumors was not substantially different between the treated and untreated animals. By contrast, the macrophages and activated NK cells were much more abundant in the mice receiving vildagliptin, which was accompanied by an increased expression of proinflammatory cytokines, perforin, FasL, and TRAIL. Importantly, the growth-inhibiting effect of vildagliptin was suppressed by macrophage ablation or NK cell depletion, and vildagliptin enhanced TRAIL-mediated lung cancer cell killing by NK cells in vitro. The mechanism behind this immunostimulatory effect proposed by the authors involves the rapid upregulation of surfactant proteins in cancer cells exposed to vildagliptin, which increases the inflammatory activity of macrophages [86].

Although the clinical implications of the aforementioned animal studies remain unclear, a case study reported the rapid regression of hepatocellular carcinoma in a hepatitis C virus-infected patient with poorly controlled diabetes mellitus after sitagliptin was initiated. The residual tumor tissue was heavily infiltrated by CD8<sup>+</sup> T cells, suggesting the likelihood of an immune-mediated mechanism [107].

Overall, the emerging evidence suggests that, at least in certain tumor types, gliptins may enhance the anti-tumor activity of both the innate and the adaptive immune system, and may act synergistically with currently available immunotherapeutic approaches. Nevertheless, these encouraging preclinical results need to be validated in clinical studies.



### 3.3. Enhancement of Hematopoietic Stem Cell Transplantation and Prophylaxis of Acute Graft-Versus-Host Disease by DPP-IV Inhibition

Hematopoietic stem cell transplantation is currently an important and potentially curative approach in leukemia and lymphoid malignancies and may also be beneficial for some patients with solid tumors [108]. Umbilical cord blood represents an important source of hematopoietic stem/progenitor cells for patients without a HLA-matched sibling or unrelated adult donor. However, delayed engraftment due to a low number of progenitor cells constitutes a significant obstacle.

Human hematopoietic stem cells express CXCR4, which helps transplanted stem cells to localize to bone marrow niches that actively produce the CXCL12 (SDF-1 $\alpha$ ) ligand [109][110]. Further, it is now established that the CXCR4–CXCL12 axis is critical in maintaining the bone marrow niche that nurtures HSC, where the disruption of the chemokine signaling pathway results in reduced HSC numbers and reduced ability to repopulate on transplantation [109]. The DPP-IV-processed CXCL12(3-68) has a significantly reduced ability to induce signaling through CXCR4 [111]. Although it has not been observed unequivocally in all studies [112], the genetic or pharmacologic ablation of DPP-IV enzymatic activity both in transplanted cells and in bone marrow enhanced CXCL12-induced responses and improved transplantation efficiency [87][113], implicitly suggesting that the lifetime of CXCL12 was enhanced. In patients with hematological malignancies receiving umbilical cord blood transplants, high-dose sitagliptin was shown to enhance engraftment compared to historic controls at the same institution, and a more sustained inhibition of DPP-IV was associated with improved results [88][89]. An unexpected and intriguing observation from these studies was the very low incidence of graft-versus-host disease, a frequent and significant cause of morbidity and mortality in transplanted patients. This finding stimulated a recently published phase 2 nonrandomized clinical trial on patients who had received myeloablative allogeneic peripheral-blood stem cell transplantation [90]. High-dose sitagliptin (600 mg every 12 h for 15 days) was added to a standard prophylactic regimen consisting of tacrolimus and sirolimus, and the incidence of acute grade II–IV graft-versus-host disease by day 100 was evaluated. None of the 36 patients had toxic side-effects attributable to sitagliptin, all achieved engraftment, and acute graft-versus-host disease developed in two (5.6%) of them, a frequency substantially lower than the 30% incidence reported in similar patient cohorts in the past. The incidences of relapse and chronic graft-versus-host disease were comparable to those in previous studies.

### 3.4. Amelioration of Side-Effects of Conventional Anticancer Treatments by DPP-IV Inhibition

The side-effects of cytotoxic anticancer therapies frequently impact on quality of life and lead to dose reduction or treatment discontinuation in a considerable proportion of cancer patients. Various endogenous DPP-IV substrates, such as glucagon-like peptides, CXCL12, human GM-CSF, and human IL3 [114][115][116][117][118], may have protective effects on the chemotherapy-induced damage to healthy tissues. Combined with the favorable safety profile of gliptins, this was an impetus for several, so far mostly preclinical, studies examining the potential of DPP-IV inhibition to mitigate the side-effects of chemotherapy (**Figure 1**).

In addition to the importance of DPP-IV in modulating the CXCL12–CXCR4 axis, studies on the role of DPP-IV in hematopoietic stem cell engraftment revealed that DPP-IV may cleave GM-CSF, G-CSF, IL3, and erythropoietin and decrease their activity [91]. Furthermore, mice receiving sitagliptin prior to and shortly after 5-fluorouracil administration had higher cellularity in the bone marrow and greatly accelerated hematopoietic progenitor cell recovery, as evidenced by the increased colony formation and number of immunophenotypically defined long-term and short-term hematopoietic stem cells. The enhancement of the recovery in the peripheral blood by sitagliptin was modest and was not seen in mice that received sitagliptin only after the administration of 5-fluorouracil, hinting that the timing, dosing, and duration of gliptin administration plays an important role. Similar, albeit more pronounced effects were seen in DPP-IV knockout mice, supporting the conclusion that the absence of DPP-IV enzymatic activity facilitates the recovery of hematopoiesis after chemotherapy [91].

Various gliptins seem to have nephroprotective effects. In a rat model, the administration of teneligliptin attenuated cisplatin-induced acute kidney injury and accelerated the recovery of renal functions [92]. A histopathological analysis of the kidney tissues of animals treated with a DPP-IV inhibitor revealed the decreased apoptosis of the proximal tubule epithelial cells in the early stages and, subsequently, increased proliferation at a later stage, decreased tubulointerstitial fibrosis, and increased infiltration with reparatory M2 macrophages. In vitro, teneligliptin increased the proliferation of proximal tubule epithelial cells mediated by CXCL12–CXCR4 signaling, suggesting a possible mechanism for its beneficial effects on cisplatin-induced nephrotoxicity [92]. Another DPP-IV inhibitor, alogliptin, has been shown to have protective effects in a rat model of cyclophosphamide-induced nephrotoxicity [93]. The coadministration of alogliptin improved the functional and histopathological markers of renal injury. An analysis of the possible mechanisms underlying these protective effects revealed that alogliptin diminished the renal levels of TNFalpha and TGFbeta and the activation of JNK1 and SMAD signaling, and improved the markers of oxidative stress. In addition, the activation of caspase-3 and the Bax/Bcl-2 ratio were significantly reduced by alogliptin. It remains to be confirmed whether the increased bioavailability and signaling of GLP-1 proposed by the authors [93] represent a unifying molecular mechanism of these effects of DPP-IV inhibition. The anti-inflammatory effects of gliptins were proposed to contribute to their ability to diminish doxorubicin nephrotoxicity in rats. Sitagliptin and linagliptin decreased tubulointerstitial injury and interstitial fibrosis, possibly by reducing the activation of the NOD-like receptor containing pyrin domain 3 (NLRP3) inflammasome [94]. In line with these findings, an independent study reported similar beneficial effects of vildagliptin and saxagliptin on kidney function, the kidney expression of TNF-alpha, IL1beta, neutrophil gelatinase-associated lipocalin (NGAL), and NLRP3 and morphological alterations induced by doxorubicin [95].

The protective effect of GLP-1 and GLP-2 in chemotherapy-induced alimentary mucositis [119] led to the hypothesis that gliptins may prevent this common complication of chemotherapy. Indeed, the administration of vildagliptin attenuated the severity of 5-fluorouracil-induced diarrhea, morphological changes in the small intestine, and TNF-alpha expression [102] in a mouse model. GLP-1 and gliptins were also proposed as neuroprotective agents [120] [121]. Alogliptin ameliorated oxaliplatin-induced mechanical allodynia and axonal degeneration in rats and prevented neurite shortening in vitro [99]. Interestingly, these effects were selective for platinum-based chemotherapeutics, as there were no effects on paclitaxel- or bortezomib-induced neuropathy. The molecular mechanism remains to be established, but the in vitro results of this research suggested that GLP-1 receptor signaling was not involved [99].

Another study on rats demonstrated that a 10-day treatment with sitagliptin prior to the administration of doxorubicin ameliorated ECG changes, lowered the level of serum markers of cardiotoxicity, and improved histopathological alterations in the heart. This was accompanied by decreased lipid peroxidation, increased levels of superoxide dismutase and reduced glutathione, and decreased markers of inflammation and apoptosis in cardiac tissue [97]. Similarly, linagliptin treatment ameliorated the cardiotoxicity induced by the repeated administration of lower doses of doxorubicin and reduced lipid peroxidation [98]. An improved antioxidant status after gliptin administration was also observed in methotrexate-induced hepatic injury [100]. The pretreatment of mice with sitagliptin for five days before methotrexate administration reduced the elevation of the serum transaminases, ALP and LDH, improved histopathological changes in the liver, and was accompanied by the alleviation of lipid peroxidation and the preservation of the antioxidants superoxide dismutase and glutathione. The expression of Nrf2, a transcription factor regulating the expression of antioxidant enzymes [122], was preserved in animals pretreated with sitagliptin, whereas methotrexate suppressed it. Sitagliptin also counteracted the activation of NF-kappaB signaling and the expression of proinflammatory mediators in the liver and reduced the hepatocyte apoptosis induction caused by methotrexate administration [100]. A recent study further demonstrated that linagliptin substantially alleviates testicular injury after the administration of cisplatin. Increased intratesticular levels of CXCL12 and the abrogation of the beneficial effects of linagliptin by a CXCR4 antagonist suggested enhanced CXCL12–CXCR4 signaling as the underlying mechanism [101].

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