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Anti-cancer effects of Tranilast: An update

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ABSTRACT

Tranilast (TRN) or (N-3,4 -dimethoxy cinnamoyl]-anthranilic acid) is an analog of a tryptophan metabolite and is identified mainly as an anti-allergic agent with limited side effects. The anti-cancer effects of tranilast either alone or in combination with chemotherapeutic drugs have been evidenced in several pre-clinical studies. The main mechanism of action of tranilast includes targeting and modulation of various signaling and immune regulatory pathways including Transforming growth factor-beta (TGF-β), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), phosphatidylinositol 3-kinase (PI3K), MAP-Kinase (MAPK), Protein kinase B (ꝑAkt/PKB), c-Jun N-terminal kinase, modulation of cancer stem cells, etc. Most of these pathways are involved in tumor proliferation, invasion, and metastasis and it is postulated that tranilast, with its low toxicity profile and high anti-carcinogenic abilities, can serve as a potential anti-tumorigenic agent. The main aim of this review is to provide updated information on the anti-cancer effects of tranilast and its significance as a therapeutic agent.

1. Introduction

Cancer is a life-threatening disease with a worldwide impact of 19.3 million new cases and 10 million deaths in 2020 [1]. Despite significant advancement in the treatment strategies made to date, life-threatening side effects induced by chemotherapeutic drugs, or the development of chemotherapeutic resistance limit the success of the treatment thereby causing therapeutic failure. [2] In lieu of this, active research is now focused on repurposing existing non-oncology drugs with low toxicity profiles for the clinical management of cancers. A recent study by Corsello et al. [3], has described the use of PRISM molecular barcoding and multiplexing screening method to test 4518 existing drugs against 578 cancer cell lines. This study reported that non-oncology drugs showed an unexpectedly high rate of anticancer potential and direct clinical translation [3]. Accordingly, it is postulated that drugs that target various hallmarks of cancers have better applicability in oncology therapeutics [4]. Since, inflammation is a critical hallmark that fosters multiple functions in cancer development such as immunosuppression, cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis [5]; non-oncology anti-inflammatory drugs may have an essential role in cancer therapeutics.

Tranilast (TRN) or (N-3, 4 -dimethoxy cinnamoyl]-anthranilic acid) is an analog of a tryptophan metabolite and is identified mainly as an anti-allergic agent. It is commonly used in the treatment of inflammatory diseases such as bronchial asthma, atypical dermatitis, allergic conjunctivitis, keloids, and hypertrophic scars [6]. Studies have suggested that TRN could serve as an effective agent in the management of a

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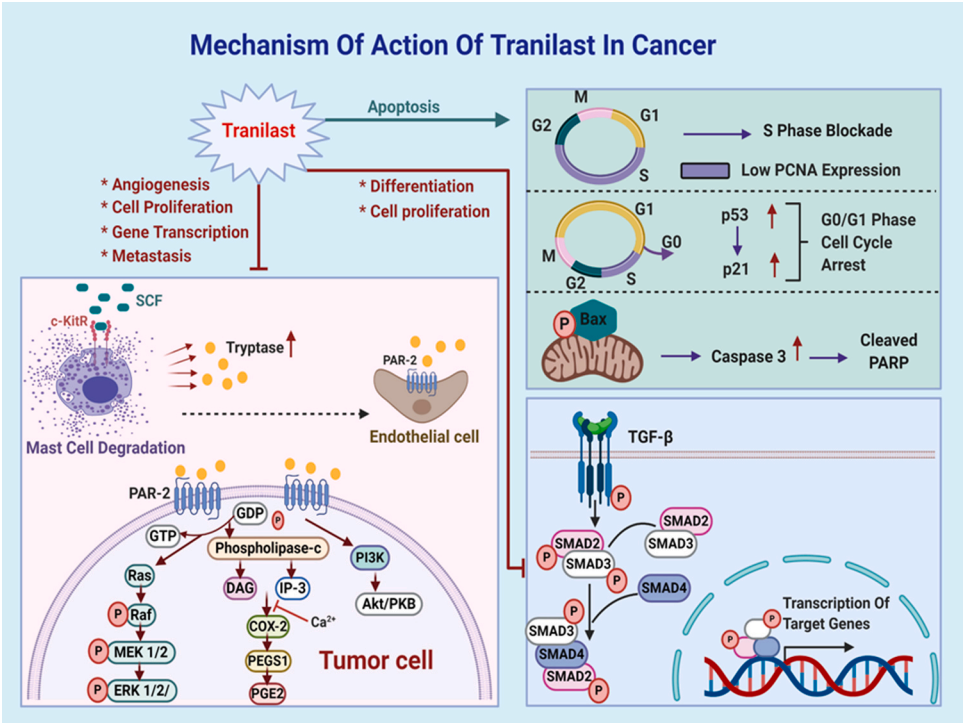

Fig. 1. Mechanism of action of Tranilast in cancers: The figure provides an overview of the cancer-related pathways that are targeted by Tranilast (TRN) in various cancers. TRN modulates a) cell differentiation and proliferation through suppression of TGF-β and cell signaling pathways such as MAPK and PI3K; b) induces apoptosis via caspases and tumor suppressor genes; c) inhibits angiogenesis through targeted angiogenic factors including mast cell degranulation and d) facilitates metastasis and invasion via inflammatory modulators.

Table 1
Effects of Tranilast on cancer pathways in various cancer models.

Tumor type	Model system	Treatment	Effect	Pathway	Reference
Gastric cancer (GC)	Human peritoneal mesothelial cells (HPMCs) Gastric cancer cell lines MKN-7, MKN-45, MKN-74 Human scirrhous gastric cancer OCUM-2MD3 cell line BALB/c-nu/nu mice Xenograft model	Tranilast	Suppression of fibrosis, tumor proliferation	↓ TGF-β/SMAD pathway	[45]
Non-small cell lung cancer cell (NSCLC)	NCSLC A549, PC14 cell lines Mouse Orthotopic lung cancer model	Tranilast	Inhibition of tumor cell invasion	↓ TGF-β/SMAD pathway	[35]
Esophageal cancer (ESCC)	Human ESCC TE8 Spheroids	Tranilast	Inhibition of Cancer stem cells	↓ Transient receptor potential vanilloid 2 (TRPV2)	[41]
Colorectal cancer	CT-26 mouse colon cancer cell Spheroids BALB/C mice Xenograft model	Tranilast + 5 Fluorouracil	Inhibition of tumor fibrosis, growth, density	↓ TGF-β, Thiol, SOD, Catalase ↑ MDA and ROS production	[46]
Ovarian cancer	Cisplatin-sensitive human ovarian cancer IGROV and A2780 cell lines Cisplatin resistant lines IGROV-CP20 and A2780-CP20 cell lines	Tranilast + Cisplatin	Sensitization of resistant tumor cells to Cisplatin	↓ Trafficking of ATP7B ↑ Cisplatin toxicity in Cisplatin resistant cells	[47]
Colon and Lung cancer	Colon and Lung cancer cell lines Colorectal cancer patient tumor explants	TRN + Cisplatin	Inhibition of tumor growth	↑ Apoptosis ↑ Immune cell infiltration	[48]
Breast cancer	Human breast cancer cell lines MCF-7 and MDA-MB-231	TRN + Tamoxifen	Reduction of tumor cell migration/ invasion	↓ CXCR4, CXCL12 mRNA protein expression	[48]
Nasopharyngeal carcinoma (NPC)	Human NPC cell lines, 5-8F, 6-10B, and HK-1	TRN + Radiation	Reduction of tumor proliferation Sensitization of radiation resistant cells to treatment	↓ CAF activation and proliferation ↓ NF-κB pathway activation	[49]

wide range of conditions that include, fibrosis, proliferative disorders, cancers, cardiovascular problems, autoimmune disorders, ocular diseases, diabetes, and renal diseases [7]. Its low toxicity with better patient compliance has been documented in Japan and South Korea where it is already approved for the treatment of allergic conditions and bronchial asthma with a favorable safety profile [7–9].

Several preclinical studies have reported that the main mechanism of action of TRN is its capacity to interfere with transforming growth factor-beta (TGF-β) signaling to inhibit cell proliferation. In addition to this, various other mechanisms such as modulation of inflammatory mediators, cell cycle arrest, promotion of apoptosis, inhibition of invasion, migration, angiogenesis, and targeting of cancer stem-like cells have been reported as well [7,10–12] (see Fig. 1). On the other hand, several studies have also evidenced the synergistic effect of TRN in combination with standard cancer treatment regimen drugs indicating its utility as a potential candidate for a combinatorial therapeutic

approach [13,14] (see Table 1).

Although sufficient information that focuses on the anti-cancer effects of TRN is available, however, these articles lack to cover the mechanistic aspect and clinical utility of TRN as an anti-cancer drug. Therefore, in this review, we aim to contribute updated knowledge on TRN to help the audience to understand the applicability of repurposing TRN for cancer therapeutics.

1.1. Effect of Tranilast on cell proliferation

TRN has been documented as an efficient anti-proliferative drug in various cancer cell lines. Studies have shown that TRN targets various signaling pathways that aid in cancer cell progression. For example, a study by Shime et al. [15], on cultured human leiomyoma cells (derived from Uterine leiomyoma) reported that TRN treatment leads to dose-dependent induction of cyclin-dependent kinase (CDK) inhibitor $p21^{waf1}$ and tumor suppressor gene p53 thus inducing suppression of CDK2 activity. In addition to this, the proliferation of vascular smooth muscle cells and fibrosis was suppressed by TRN via G0/G1 cell cycle phase arrest indicating the anti-proliferative property of TRN. On the other hand, normal cell lines treated with TRN showed negligible toxicity with no apparent morphological changes indicating the low toxicity profile of TRN [15]. Similarly, in vitro study on transient receptor potential vanilloid type 2 channel (TRPV2) in leukemic cells showed that TRN treatment leads to alteration of signaling pathways phosphatidylinositol 3-kinase (PI3K) and MAPK inducing cell death [16]. Interestingly, an in vitro *and in vivo* study on lymphoid tumor cells and murine lymphoid tumor showed that treatment with TRN activates c-Jun N-terminal kinase pathway thereby inducing cell death and decreasing murine lymphoid tumor progression [17]. Such studies allow postulation on the applicability of TRN against lymphoid malignancies.

A recent study on Osteosarcoma cell lines (HOS, 143B, U2OS, and MG-63) and normal fibroblasts (WI-38) as well as in vivo mice xenograft models documented synergistic effect of TRN in combination with standard anti-cancer drugs cisplatin and doxorubicin as an anti-proliferative agent [18]. The study reported that in osteosarcoma cell lines, TRN and cisplatin worked synergistically to increase levels of phospho-cyclin-dependent kinase 1 and increasing the number of cells into the G2/M phase thereby inducing apoptosis via caspase activation and DNA damage. Similar effects were observed in the tumor mimicking the 143B xenograft model. Another study by Kitajima et al. [13] provided evidence on the synergistic effect of TRN with standard anti-cancer drugs wherein effects of TRN in combination with standard chemotherapeutic drug gemcitabine (GEM) in pancreatic cell lines KP-4, PK-8, PK-1, MiaPaca2, and PK-59 were investigated. Interestingly, the authors observed that the combination of GEM with TRN not only increased the apoptotic effect of GEM treatment by inducing the G1 cell cycle arrest phase but also increased the sensitivity of cell lines 15–17-fold to GEM by suppressing the DNA synthesis enzymes ribonucleotide reductase 1 (RRM1) [13]. Thus, the anti-proliferative activity of TRN as a combinatorial drug makes TRN a highly attractive agent for cancer treatment bearing significant utility.

Tranilast leads to apoptosis in cancer cell lines and this mechanism of action has been reported by Subramaniam et al. [14]. The study demonstrated that treatment of the mouse breast cancer cell line 4T1 with TRN modulated cell cycle mediators; cyclin A, B, D1, p27, pRB, and Cdc2 by decreasing ERK1/2 phosphorylation leading to cell arrest beyond the G1/S cell cycle phase. In addition to this, the authors observed that TRN promoted tumor cell apoptosis by up-regulation of p53, induction of Poly (ADP-ribose) polymerase (PARP) cleavage, and increased expression of cleaved caspase 3 indicating that TRN potentiates and induces cellular and molecular changes in apoptotic pathways. Similar effects were observed in the human breast cancer cell lines BT-474 and MDA-MB-231 [19].

The suppressive effects of TRN on prostate cancer growth and osteoclast differentiation were determined in different prostate cancer models [20]. TRN induced apoptosis via upregulation of phospho-GSK3 beta and downregulation of phospho-Akt. Similarly, in vivo, TRN lead to significantly decreased tumor volumes and cranial bone defects in the rat tissues.

1.2. Effect of Tranilast on angiogenesis

Branching of the vascular network and formation of new blood vessels from pre-existing vasculature is known as angiogenesis. The mechanism of angiogenesis is manipulated by tumor cells including tumor-associated stromal cells that secrete pro-tumorigenic factors such as cytokines, growth factors, matrix metalloproteinases, and microvesicles. This facilitates the tumor to attain oxygen and nutrients for its metabolic needs and growth [21]. Therefore, inhibition of angiogenesis is considered a critical target to prevent cancer progression. *In vitro and* in vivo study on human dermal microvascular endothelial cells (HDMEC) and C57BL/6 mice showed that treatment with TRN targeted angiogenic factors including VEGF, mast cell degranulation, proliferative inflammation, and G0/G1 phase of cell cycle indicating its anti-angiogenic potential [22].

Neurofibromatosis type 1 (NF1) caused by germline mutations in the NF1 gene is known to cause benign tumors known as neurofibromas. The therapeutic potential of TRN was tested by Harigai et al. [23] on NF1-mutated sNF96.2 cells and NF1-associated neurofibromas in the patient's sample. TRN effectively downregulated TGF-β, IL-8, VEGF, and matrix metalloproteinase 2 (MMP2). This attenuated the expression of mesenchymal markers and angiogenesis-related genes subsequently inducing an anti-tumor effect. Herbal extract-*Teucrium polium* (TP) in combination with TRN was investigated for its anti-angiogenic potential on Human Umbilical Vein Endothelial cells (HUVECs). Combination treatment successfully inhibited the production of nitric oxide (NO) leading to a significantly increased anti-angiogenic effect. The increased BAX/BCL2 ratio leads to apoptosis in cancer cells indicating that this is a pro-apoptotic drug [24].

Components of the mitochondrial electron transport chain play an important role in the provision of metabolic energy for angiogenic neovascularization in malignant tumors. This energy is supplied in the form of adenosine 5′-triphosphate (ATP) by mitochondrial oxidative phosphorylation (OXPHOS) and is required essentially for both angiogenic and tumorigenic activity [25]. Therefore, anti-angiogenic drugs with a mitochondrial target of action can serve as effective anti-carcinogenic agents. A study by Quayle et al. [26] on TRN and its mechanism of action on mitochondrial components showed interesting results. TRN affected oxygen consumption and membrane potential in intact isolated mitochondria, specific enzyme activities of mitochondrial complex I [EC 1.6.5.3], mitochondrial complex II–III [EC 1.8.3.1], and mitochondrial complex IV [EC 1.9.3.1] in MCF-7, NCI-H460 and rat heart [26]. In rat heart mitochondria, 10 μM to 30 μM concentrations of TRN resulted in small concentration-dependent reductions in complex II-linked mitochondrial membrane potential possibly due to inhibition of tricarboxylic acid cycle (TCA cycle). In the MCF-7 cell line, cell viability was significantly reduced at 100 μM TRN, and the authors postulated that small inhibition of complex I induced changes in the integrated mitochondrial functions leading to significantly decreased ATP production and cell death. However, no significant inhibition of mitochondrial complex was observed in NCI-H460 possibly due to the intrinsic ability of this cell line to adapt to metabolic changes and resist apoptosis. The results clearly showed the ability of TRN to exert anti-angiogenic effects via a reduction in mitochondrial membrane potential and oxygen consumption leading to cell death [26].

1.3. Effect of Tranilast on tumor immune microenvironment

The immune-modulatory effects of TRN have been described in various diseases. The main mechanism of action of TRN is to suppress the production and/or release of inflammatory mediators such as

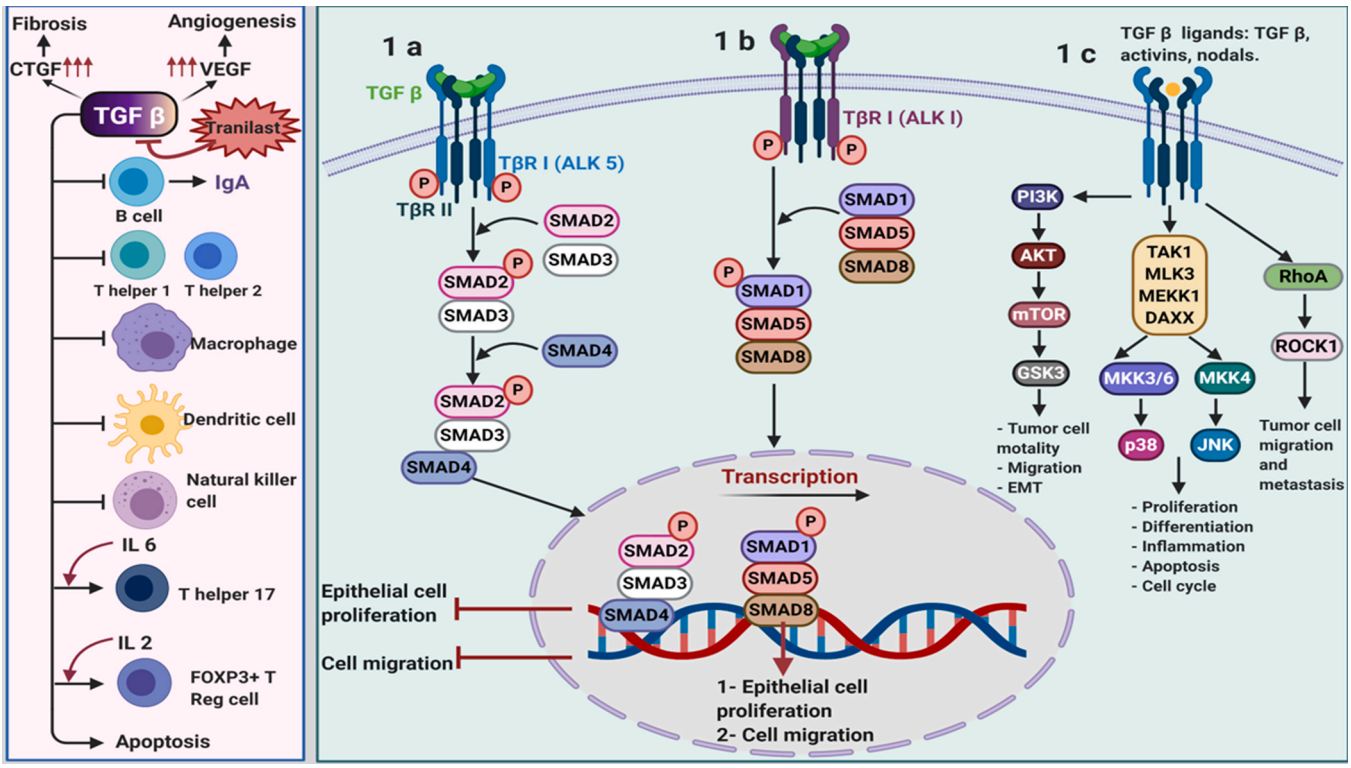

Fig. 2. Mechanism of action of Tranilast on Transforming Growth Factor-β (TGF-β). TGF-β exists in three isoforms: TGF-1, 2 and 3 (1a, 1b, 1c in this figure) and all 3 use the same receptors that include 3 components type I, II, and III. TGF-β signaling pathways are categorized into two types, depending upon the main mediators in the intracellular environment as SMAD-dependent or -independent pathways. Upon ligand binding, TGF-βRII phosphorylates TGF-βRI at the GS domain. Activated TGF-βRI phosphorylates R-SMADs SMAD 2/SMAD 3 which complexes with SMAD 4 and translocate to the nucleus. Here, the complex interacts with DNA-binding cofactors to mediate the regulation of TGF-β-specific gene programs. This differential expression of TGF-β target gene programs is dependent on distinct cofactor binding, transcription factor binding, and DNA/histone modifications. In cancers, TRN targets TGF-β through co-inhibition/reduction of inflammatory mediators, monocytes, and macrophages, fibroblasts subsequently affecting tumor cell proliferation, differentiation, and inflammation.

interleukins, COX-2, iNOS, VCAM-1, ICAM-1, HLA-DR/DQ antigens, NF-κB, MAPK, Nitric Oxides, and TGF-β from macrophages, monocytes, fibroblasts, and neutrophils [7]. Therefore, the anti-carcinogenic effect of TRN about its immune-modulatory effects is an area of immense interest.

Mast cells (MCs) are immune cells of myeloid lineage that play a crucial role in regulatory functions between inflammatory and tumor cells via the release of pro-angiogenic factors such as VEGF and tryptase [27]. In cancers, high MCs density is correlated with tumor angiogenesis, cell invasion, and metastasis. The ability of TRN to block the release of pro-angiogenic mediators from MCs is well established. A study by Isaji et al. [22] on human microvascular endothelial cells observed that TRN induced inhibition of angiogenesis via downregulation of tryptase release. Similarly, a study on pancreatic cells PGHAM-1 cells and the pancreatic cancer model showed that TRN suppressed tumor angiogenesis via inhibition of VEGF [28].

Cancer-associated fibroblasts (CAFs) are dominant components in the tumor microenvironment (TME) that support tumor growth via secretion of several soluble factors which contribute to proliferation, invasion, and metastasis of tumor cells [29]. In addition to this, CAFs secrete TGF-β and immune-suppressive cytokines to impair anti-tumor responses and therefore, drugs that target CAFs can be of immense importance [30]. Several studies have documented the inhibitory effects of TRN on CAFs. E.g. a study by Ohshio et al., demonstrated that treatment in mouse tumor tissue cells E.G7 or LLC1 with low doses (100 μm) of TRN inhibited proliferation of CAFs via reduction of the TGF-β release [31]. Since TGF-β is a known potent inducer of regulatory T cells (Tregs), the authors reported that reduction in TGF-β secretion from impaired CAFs contributed to reduced induction of immune suppressor cells such as Tregs and myeloid-derived suppressor cells (MDSCs). Furthermore, the authors provided robust in vivo evidence on the effect of TRN on CAFs in tumor-bearing mouse models bearing syngeneic E.G7 lymphoma, LLC1 Lewis lung cancer, or B16F1 melanoma. TRN inhibited CAFs function via decreased secretion of stromal cell-derived factor-1, prostaglandin E2 and TGF-β leading to reduced infiltration of Tregs and MDSCs with subsequent activation of tumor-associated antigen-specific $CD8^+$ T cells [31]. Furthermore, TRN, when given in combination with a dendritic cell-based vaccine, was shown to synergistically enhance systemic antitumor immune responses such as cytotoxic $CD8^+$ T cell response, natural killer activity, and antitumor humoral immunity in tumor-draining lymph nodes indicating that CAF targeting by TRN induces anti-tumor immune-modulation [31].

1.4. *Effect of Tranilast on TGF-β*

TGF-β is an instrumental cytokine for the regulation of cellular processes such as cell proliferation, differentiation, apoptosis, motility, invasion, angiogenesis, immune response, and extracellular matrix (ECM) production [32]. TGF-β signaling occurs through ligands TGF-β1, TGF-β2, and TGF-β3 and intracellular SMAD proteins. Several studies have documented the pharmacological activity of TRN through TGF-β signaling interference and inhibition of TGF-β production [33] (Fig. 2). For example, a study by Platten et al. [6] demonstrated that TRN inhibited migration, invasiveness, and chemotactic response of human malignant glioma cells by reducing the release of TGF-β1 and TGF-β2 thus leading to inhibition of matrix metalloproteinase-2 expression and activity. *In vivo* experiments with oral administration of TRN in Fisher 344 rats showed reduced expression of TGF-β2 with inhibition of rat gliomas [6]. Furthermore, studies on human breast cancers and prostate

cancer cell lines showed that TRN induced downregulation of TGF-β signaling thereby inhibiting the proliferation of cancer cells [34]. On the other hand, a study on TRN treatment of the lung cancer cell lines A549, PC14 reported that TRN increased E-cadherin expression via SMAD 4 suppression and inhibited cell invasion in the TGF-β1-stimulated cells. In a mouse orthotopic lung cancer model of the same study, TRN treatment was shown to reduce pleural dissemination of cancer cells, suppression of vimentin, SMAD 4 expression indicating the therapeutic ability of TRN [35].

An important aspect concerning TGF-β is that it is postulated to influence the programmed death ligand-1 (PD-L1) regulation as well. Though the mechanism is unclear, some reports show that expression of TGF-β could increase PD-L1 expression on dendritic cells in the tumor microenvironment (TME) [36]. In addition, TGF-β activation in CAFs is a crucial indicator for ECM dysfunction in cancers thus contributing to immunosuppression. Furthermore, increased PD-L1 expression and CAF-driven ECM dysfunction are identified as important events responsible for the failure of PD-L1/PD-1 immune checkpoint blockade in cancer immunotherapy [37]. As a result, TGF-β targeting is a promising strategy for overcoming immune checkpoint blockade therapy resistance. In lieu of this, Tranilast, with its potent ability to inhibit TGF-β, can also serve as an important drug in cancer immunotherapy. Indeed, it has been demonstrated that a combination of TRN (for TGF-β blockade) with immune checkpoint blockade therapy can downregulate PD-L1 expression, modulate CAF-driven ECM dysfunction, and effectively reversed the immunosuppressive state to achieve significant tumor regression and improve patient survival [38]. A study by Panagi et al. has shown that combining TRN and the cytotoxic chemotherapy drug Doxil significantly inhibited tumor progression and improved the efficacy of anti-PD-1 and anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) treatment in triple-negative breast cancer [39].

1.5. Effect of Tranilast on cancer stem cells

Cancer stem cells (CSC) are known to increase resistance to chemotherapeutic treatment and therefore targeting of CSCs is a valuable strategy for cancer treatment. TRN significantly inhibited mammosphere/colony formation and reduced retinoblastoma protein phosphorylation/stem cell markers Oct4 and CD133 expression [40]. Moreover, Atsushi Shiozaki et al. reported that administration of low doses of TRN in the esophageal squamous cell carcinoma cell line TE-8, led to inhibition of transient receptor potential vanilloid 2 (TRPV2), decreased tumorsphere formation, and a significant decrease in ALDH1A1 expressing CSCs [41]. These studies give insight into the ability of TRN to target CSCs and its potential utility in cancer therapeutics.

2. Role of Tranilast in cancer nanomedicine

As mentioned above TRN bears high potential with diverse antitumor mechanisms. Interestingly, nanomedicine holds a great potential to improve anticancer therapy via modulation of drug biodistribution, increasing tumor (and metastasis) perfusion, permeability, and penetration, as well as delivery to and into target cells [42,43]. Keeping these perspectives in mind, TRN has been experimentally utilized to understand its application in cancer nanomedicine. For example, a study by Mpekris et al., reported interesting results with respect to TRN and its ability to facilitate cancer nanomedicine via TGF-β inhibition [44]. The study showed that treatment with TRN and Doxil as nanomedicine in metastatic triple-negative syngeneic mice models, 4T1 and E0771, and in patients can lead to stroma normalization via an increase in intratumoral blood vessels diameters. This leads to reduction of ECM components causing a significant increase in perfusion in the metastatic lesions allowing the nanoparticles to penetrate the tumor and work effectively. The study provided novel insights and give evidence on the potential utility of TRN in cancer nanomedicine. Several studies on the utility of TRN in cancer nanomedicine are shown in Table 2.

Table 2
Application of Tranilast in cancer nanomedicine.

Tumor type	Treatment	Observed effect	Reference
Triple-negative breast cancer (TNBC) tumor mouse models 4T1 and E0771	Tranilast + Doxil nanomedicine	TME normalized Increased perfusion Enhanced anti-tumor immunity Improved efficacy of anti-CTLA-4 and anti-PD-1	[39]
Orthotropic human breast cancer models MCF10CA1a and 4T1	Tranilast + Doxorubicin, Abraxane and Doxil nanomedicines	Reduced mechanical stresses Improved tumor perfusion Decreased interstitial fluid pressure (IFP) Suppressed TGFβ signaling and expression of extracellular matrix components Significantly enhanced efficacy of nanomedicine drugs	[50]
Breast cancer 4T1 cells and fibroblast 3T3 cells	Tranilast + nanomedicine Docetaxel micelles (DTX-Ms)	Enhanced DTX-Ms' antitumor effect Tumor cell migration blocking Reduced interstitial fluid pressure Inhibiting tumor growth and metastasis Cancer associated fibroblasts (CAFs) ablation Improving DTX-Ms penetration and retention	[51]
U87 human glioblastoma cells in a mouse xenograft model	TRN + anti-angiogenic nanomedicines SU5416, 2-methoxyestradiol, Silibinin	Inhibition of tumor growth Slower, sustained release of drugs	[52]

2.1. Conclusion and future directions

This review provides comprehensive updated information on the therapeutic potential of the anti-allergic drug TRN in cancer. Although many preclinical studies are published, data on clinical trials using TRN in cancer are still lacking. Since TRN is a safe, approved drug for other diseases, it is imperative that large scale studies should be performed to understand its applicability in cancer treatment. Repurposing of such a drug may have advantages such as in combination treatment and may well benefit the patients with its limited adverse events.

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Author contributions

SO and AR wrote the manuscript; LAZ, VP and NA designed the figures; KP, VP, MM, SK and SD revised and provided critical input. All authors read and approved the submitted version.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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