

Protease-activated receptor-1 (PAR-1): a promising molecular target for cancer

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ABSTRACT

PAR-1 is expressed not only in epithelium, neurons, astrocytes, immune cells, but also in cancer-associated fibroblasts, ECs (epithelial cells), myocytes of blood vessels, mast cells, and macrophages in tumor microenvironment, whereas PAR-1 stimulates macrophages to synthesize and secrete thrombin as well as other growth factors, resulting in enhanced cell proliferation, tumor growth and metastasis. Therefore, considerable effort has been devoted to the development of inhibitors targeting PAR-1. Here, we provide a comprehensive review of PAR-1's role in cancer invasiveness and dissemination, as well as potential therapeutic strategies targeting PAR-1 signaling.

INTRODUCTION

PAR-1 was the first member of the PARs (protease-activated receptors) family, which was found simultaneously by both two independent laboratories in 1991, during the process of identifying GPCR (G protein-coupled receptors) that mediate thrombin signal pathway in both human and hamster cells [1–3]. Thrombin-activated PAR-1 is expressed not only in all types of blood cells, but also in epithelium, neurons, astrocytes, and immune cells [3, 4, 5–7]. Furthermore, PAR-1 expression is also expressed in cancer-related fibroblasts, ECs (Epithelial Cells), blood vessels myocytes, mast cells, and macrophages in tumor microenvironment [8, 9]. In macrophages, PAR-1 elevates levels of numerous growth factors including thrombin [9]. More studies had since focused on the role of PAR-1 in biological function of tumor cells, as well as PAR-1 agonists and inhibitors [10–12]. PAR-1 as a target drug has become a hot spot in recent years, of which vorapaxar and atopaxar have entered the phase 3 clinical trial and phase 2 clinical trial, the clinical efficacy evaluation has become the last two years of research hotspots, which is expected to provide new clinical treatment ideas [13–23]. Hence, we review

the role of PAR-1 in tumor development, invasion and metastasis, and discuss the potential therapeutic strategies for targeting PAR-1 signaling.

Biological function of PAR-1

PAR-1 is a G protein-coupled receptor consisting of 415 amino acids, five functional domains: extracellular N-terminal, extracellular loop, 7 hydrophobic transmembrane domain, intracellular loop and intracellular C-terminal (Figure 1). PAR-1 is irreversibly activated by thrombin, tissue factor (TF), endothelial protein C receptor (EPCR), MMPs, and so on. More and more evidence has showed that PAR-1 not only participates in normal biological functions, but also in tumorigenesis.

Activation

The binding of thrombin, principal ligand of PAR-1, to the N-terminus LDPR⁴¹-S⁴² sequence of the receptor cleaves the R⁴¹-S⁴² peptide bond [24]. The new unmasked sequence produced in this manner is used as a tethering ligand, which in turn binds intramolecular to the residue 42SFLLRN⁴⁷ in the conserved region of the receptor second loop to induce transmembrane signaling. Matrix

metalloprotease-1 (MMP-1) cleaves PAR-1 at a novel site (D³⁹-P⁴⁰) resulting in clonal ligands of two amino acids longer (PR-SFLLRN) than the one produced by thrombin, which activate the G12/13, Rho-GTP and MARK signaling to alter platelet shape and motility [3, 25]. EPCR interacts with the N-terminus of activated protein (APC) which induces protease cleavage of PAR-1 [26]. PAR-2 induced gene regulation by TF / FVIIa in glioblastoma cell line is mediated by thrombin-mediated activation of PAR-1 [27]. Of note, PAR-1's activation is irreversible (Table 1).

Regulation

Two main mechanisms that account for activation (cleavage) of PAR-1 are receptor trafficking and desensitization [8]. PAR-1 transports from the cell membrane to the endosome, followed by degradation in lysosomes [28, 29]. PAR-1 internalization requires ubiquitination and is associated with the clathrin / AP2 (adapter protein 2) dimer and dynamin [30]. The transport of PAR-1 to lysosomes was facilitated by protein sorting nexin-1 (SNX-1) [31]. G protein-coupled receptor kinase (GPCRKs, GRKs) directed PAR-1 phosphorylation and protein interaction is fast, within a few seconds, ensued by G-protein dissociation and PAR-1 desensitization.

In contrast to the tight and rapid control of PAR-1 activation in normal tissues, PAR-1 is constitutively activated in cancer cell (Figure 2). Thrombin activates signaling pathways in tumor cells by interacting with PAR-1 [33–35]. Most of the cellular responses are activated by the persistent stimulation of the second messenger ERK^{1/2} [36–37]. In a rat model of benign tumor, PAR-1 mediated silencing of pro-apoptotic genes led to tumor growth and invasion [38]. Repression of PAR-1 activity inhibited *in*

in vivo tumor growth, demonstrating PAR-1's anti-apoptotic effects [36]. Consequently leading to consistent activation of second messenger signaling [36–37], PAR-1 cooperates with growth factor receptor (EGFR) and ErbB / Her2 or MMP-1 derived from fibroblasts to mediate Ca²⁺ pathway in cancer [39–40]. PAR-1 and MMP-1 alone can also up-regulate Galectin-3 [41]. PAR-1 signaling also interacts with the Hippo-YAP pathway to promote tumorigenesis [42].

PAR-1 is also involved in cancer cell invasion and metastasis (Figure 2). Multiple tumor cell lines show that PAR-1 overexpression is closely related to invasive phenotype and distant metastasis [33–34, 36, 37, 43–48]. PAR-1 enhances cancer cell invasiveness via increasing adhesion to extracellular matrix. After thrombin/PAR-1 stimulation, several cancer cell lines demonstrated increased platelets adhesion as well as to aorta and capillaries [32–34, 45, 49–50]. Prothrombin-induced HIF-1 α increases mRNA expression of torsion, whose protein level is also mediated by activated PAR-1: all these can enhance EMT and increase tumor metastasis [42]. The interaction of cancer cells with integrin v5 and cytoskeleton promotes lung cancer and melanoma cell migration, invasion and metastasis [32, 50–51]. On the other hand, the use of anti- $\alpha_{v}b_{3}$ antibodies specifically attenuated PAR-1-mediated invasion[50]. PAR-1 signaling induced expression of integrin IIb3 and P-selectin promoted melanoma cell-EC/platelet interaction, thereby increasing the metastatic potential of cancer cells [33–34, 45, 52–53]. Overexpression of NF- κ B, EGFR can activate PAR-1 signaling, which consequently promotes tumor cell growth and invasion [54]. In contrast to normal tissue, STAT3-dependent transactivation of EGFR and PAR-1 in endothelial cells of

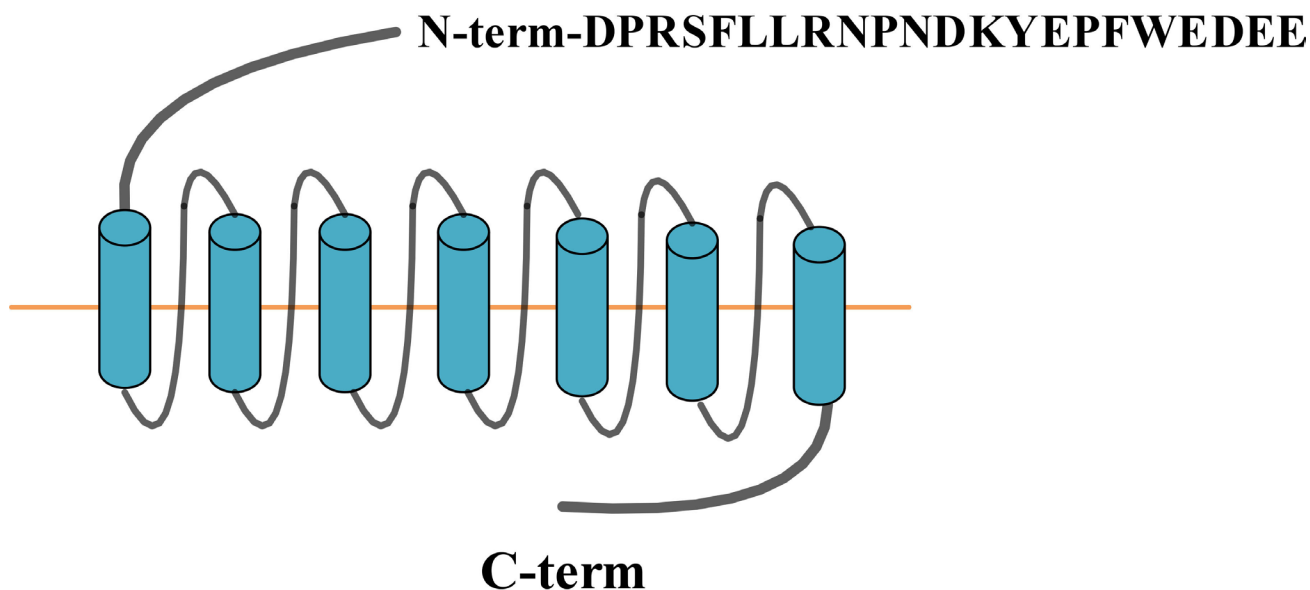


Figure 1: PAR-1 structure.

clear cell renal cell carcinoma was significantly increased [55]. PAR-1 stimulated Akt / PKB signaling pathway, resulting in decreased Bim and Bax expression, and lower caspase-3 and caspase-9 cleavage levels, which induced less apoptosis [56].

PAR-1 plays an important role in angiogenesis (Figure 2). PAR-1 small interfering RNA (siRNA) lowered expression levels of IL-8, MMP-2 and VEGF, causing less vascular density [11]. PAR-1 expression is also directly associated with increased VEGF levels, stimulating angiogenesis [57]. PAR-1-induced effects depend on agonist concentration, allowing low concentrations of thrombin to stimulate the proliferation and growth of tumor cells, whereas high thrombin levels inducing apoptosis [58]. Down-regulation of long non-coding RNA-ncRuPAR resulted in tumor inhibition via modulating PAR-1 and VEGF [59]. Mouse development studies have confirmed the PAR-1-angiogenesis association since half of the mice that deprived PAR-1 perished due to poor blood development [60–62].

In summary, these aforementioned findings demonstrated that PAR-1-dependent promotion of tumor growth and metastasis is mediated by its regulation of adhesion and pro-antigenic factors, suggesting PAR-1 as a potential cancer therapeutic target.

PAR-1 in cancers

Many a study has elucidated PAR-1 regulates several pro-tumorigenic signaling pathways in cancer. PAR-1 overexpression has been found in breast, melanoma, renal, gastric, colon, lung, pancreatic, esophageal, prostate, liver, ovarian, endometrial, head and neck cancers [27, 43, 46–47, 63–69] (Supplementary Table 1, Figure 3).

Breast cancer

While not secreted in normal breast epithelium, benign dysplasia or adenoma, PAR-1 over-expresses *in situ* carcinoma and secreted in invasive breast cancer cell lines [38, 70–71]. PAR-1 signaling is activated by TF, MMPs and thrombin, mediates tumor progression, PAR-1 and PAR-2 cooperate functionally in breast cancer [8, 72]. Tumor growth and invasion in breast cancer gland xenograft models require thrombin-induced interplay between ErbB and EGFR, or by MMP-1-induced fibroblasts derived Ca²⁺ signaling [8]. Sustained activation of ErbB/Her2 and EGFR via thrombin-cleaved PAR-1 signaling was identified in invasive breast cancer but not in normal mammary epithelial cells [8, 36].

Melanoma

PAR-1 is over-expressed in metastatic melanoma cell lines and metastatic melanomas, but not in primary nevus and normal skin [11, 55]. In addition, melanoma cells isolated from patients' metastatic lesions had increased PAR-1 mRNA and protein expression compared to those of non-metastatic disease [73]. Studies also revealed

activated PAR-1 signal pathway in precursor phenotype of melanoma cells [11, 32, 40]. Studies on melanoma cell lines showed that PAR-1 signaling mobilized adhesion, invasion, anti-apoptotic and angiogenic factors to promote the invasion and metastasis of melanoma [11, 32, 40]. The migration capability of melanoma cells is enabled by thrombin- or MMP-1-mediated PAR-1 activation [40, 70, 74–75]. MMP-1 is shown to enhance type I collagen levels through skin to promote melanoma invasion, whereas PAR-1 activation leads to an increase in growth factor activation of EGFR and IGF-1 [40, 55]. In addition, PAR-1 induces metastatic melanoma by modulating tumor suppressor Maspin and the connexin 43 [76]. PAR-1 silencing and inhibiting thrombin decrease dissemination of metastatic melanoma cells [11–12, 77]. PAR-1 siRNA mediated inhibition decreased MMP-2, IL-8 and VEGF, expression levels, subsequently vascular density [78]. Accordingly, studies have shown that by inhibiting PAR-1 function, melanoma cells lost motility, became non-metastatic and less invasive.

Renal-cell cancer

It was reported that PAR-1 was associated with distant metastasis and survival in renal cell carcinoma (RCC). AA genotype of PAR-1 gene variant IVSn-14A>T was associated with an increased risk of RCC metastasis and a poorer prognosis [79]. In contrast to normal tissues, STAT3-dependent EGFR and PAR-1 activation in endothelial cells OF clear cell renal cell carcinoma was significantly increased [55].

Gastric and colorectal cancers

Thrombin-activated PAR-1 induces EMT (epithelial-mesenchymal transition, EMT) in gastric cancer cell lines [80]. Overexpression of NF-κB, EGFR, and TN-C also activated PAR-1 expression, which in turn promoted gastric cancer cell growth and invasion [54]. PAR-1 signaling is involved in multidrug resistance and tumorigenesis by interacting with Hippo-YAP pathway in gastric cancer stem cell-like cells [43]. EPCR activates ERK^{1/2} through PAR-1 to enhance proliferation and migration of MGC803 gastric cancer cells [37]. PAR-1 and MMP-1 up-regulate Galectin-3 in metastatic gastric cancer [41]. LncRNA-ncRuPAR regulates PAR-1 and VEGF in GC patients [59]. ALEX1 inhibits gastric cancer metastasis through dampening PAR-1/Rho GTPase signaling pathway [81]. PAR-1 expression levels are higher in metastatic gastric cancer and have prognostic value [82].

PAR-1 is associated with prognostic factors for colorectal cancer [83]. PAR-1 could promote colorectal cancer growth, local invasion and metastasis [84]. Downregulation of lncRNA-ncRuPAR contributes to tumor inhibition through PAR-1 and VEGF in colorectal cancer patients [85]. PAR-1 induced platelet activation is critical in EMT and migration of colon cancer cells [86]. Thrombin-mediated HIF-1α increases twist mRNA and

Table 1: PAR-1 activators

PAR-1	Activators	The activation point
	Thrombin [3–7, 13]	R ⁴¹ -S ⁴² , S ⁴² -FLLRN ⁴⁷
	MMP-1, MMP-2, MMP-9, MMP-13 [3, 25]	D ³⁹ -P ⁴⁰
	APC [26], Plasmin [26], Factor Xa [26], Granzyme A [26], Gingipains-R [26], TF-FVIIa [27]	Cleave the N-terminus, with the EPCR as a cofactor Gene elicited by TF-FVIIa through PAR-2

protein levels, which is induced by PAR-1 activation and regulation of the HIF-1 α translation, thereby regulating EMT and increasing metastasis [42]. KLK4 induces activated PAR-1 signaling in colon tumorigenesis [87]. Tumor-endothelial cross-talk via an intravascular MMP-1/PAR-1 axis exists in microvascular and macrovascular endothelium [88]. PAR-1 signaling enhances cancer cell invasion via Rho-Rho kinase axis and tumor microenvironment [89]. Activated PAR-1 also promotes colon cancer cell proliferation EGFR transactivation [90].

Lung cancer

The serum levels of PAR-1 might have a diagnostic value in lung cancer patients [91]. PAR-1 in NSCLC (Non-small cell lung cancer) is mainly expressed in cells that constitute the tumor microenvironment, including vascular endothelial cells, macrophages and stromal fibroblasts [92]. According to a survey of 209 patients, PAR-1 polymorphism was associated with tumor stage and median OS (overall survival) of squamous cell lung cancer patients [93]. A study of 63 lung cancer patients showed that continuous activation of platelets and thus exhaustion was involved in cancer-associated venous thromboembolism (VTE) and cancer mortality, through activating PAR-1 [94]. PAR-1 siRNA significantly decreases lung adenocarcinoma cell growth and invasion

[95]. PAR-1 expression was up-regulated by TGF- β and indispensable for A549 lung adenocarcinoma cells [96]. G α q and G α 13, coupled with PAR-1 as well as constitutively active G α qQL and G α 12/13QL mutants to stimulate SCLC (small cell lung cancer) to connect autocrine bombesin (BBS). BBS-induced activation of GPCR/G α q-12/13/Rho-mediated NF- κ B signaling unregulates the activity of NF- κ B response element in the Shh gene promoter [97].

Pancreatic cancer

PAR-1 expression levels are positively associated with disease progression and OS in pancreatic cancer [98–100]. Thrombin-activated PAR-1 can significantly enhance the integrin β 1-specific adhesion of pancreatic cancer cells to vitronectin [101]. Nuclear Ca²⁺ signaling generated by trypsin and thrombin-PAR-1 pathway promote proliferation in pancreatic stellate cells (PSC) [39].

Prostate cancer

It is reported that PAR-1 is overexpressed in prostate cancer, may contribute to the malignant progression of prostate cancer [102–103]. Unregulated PAR-1 expression in peritumoral stroma of prostate cancer patient is associated with biochemical recurrence. MMP-1 and PAR-

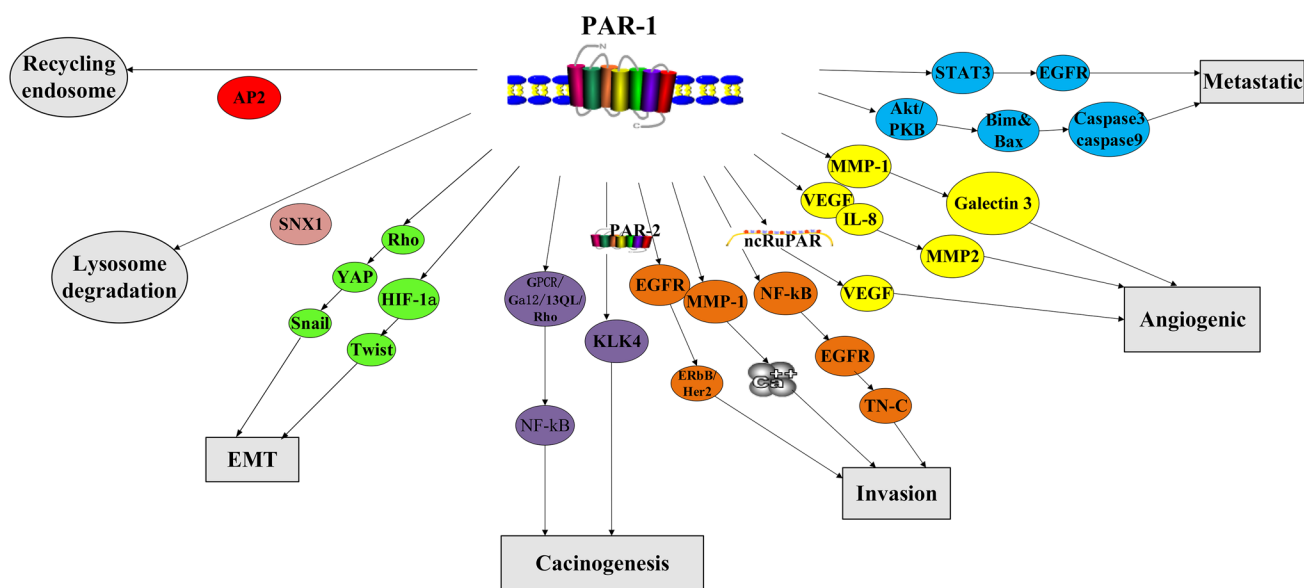


Figure 2: Biological function of PAR-1.

1 coexpression with the clinicopathological characteristics and prognosis of patients with prostate cancer [103]. Tissue kallikrein (TK) promotes keratinocyte migration through activation of PAR-1 and transactivation of EGFR [104]. Evidence also showed for a novel double-paracrine mechanism whereby cancer epithelium produces KLK4 to activate PAR-1 in the surrounding stroma, which in-turn releases cytokines (IL-6) that stimulate cancer cells to proliferate and increase production of KLKs [105].

Others

PAR-1 promotes tumor cell growth and invasion in nasopharyngeal carcinoma [106–107]. Thrombin-induced PAR-1 activation breaks down extracellular matrix and basement membrane to increase MMP-1/-9 levels, which is closely related to nasopharyngeal carcinoma metastasis [106]. PAR-1 enhances acute myeloid leukemia leukemia stem cell activity and aggravates disease progression [108–109]. The expression of PAR-1 in esophageal squamous cell carcinoma was increased [110], to promote glioma cell malignancy and glioblastoma neoangiogenesis [111]. Thrombin activates PAR-1 expression, thus enabling tumor cell seeding and metastasis, giving rise to increased

tumor cell growth and angiogenesis in glioblastoma [112]. Per HIF- α /VEGF pathway, PAR-1 maintains self-renewal and tumorigenicity of tumor-initiating progenitor cells (TPC) in gliomas, whilst inhibition of PAR-1 signaling slows down tumor progression [113–114]. PAR-1 and PAR-4 activate common promigratory signaling pathways in Hep3B liver carcinoma cells including activation of the receptor tyrosine kinases Met and PDGFR, the formation of ROS and the inactivation of PTP1B. However, PAR1/4-triggered Met and PDGFR transactivation seem to be mediated independently from the ROS-PTP1B signaling module [115]. PAR-1 has also been shown to be associated with the pathogenesis of ovarian cancer, which may be associated with PO-14 - tumor expression of coagulation proteases of the APC pathway [116].

Drugs targeting PAR-1 in clinical use

According to the experimental research mentioned above, PAR-1 inhibitors may have the effect of inhibiting tumor cell proliferation, reducing invasion and metastasis, and anti-tumor angiogenesis. The development of drugs targeting PAR-1 has caused widespread concern.

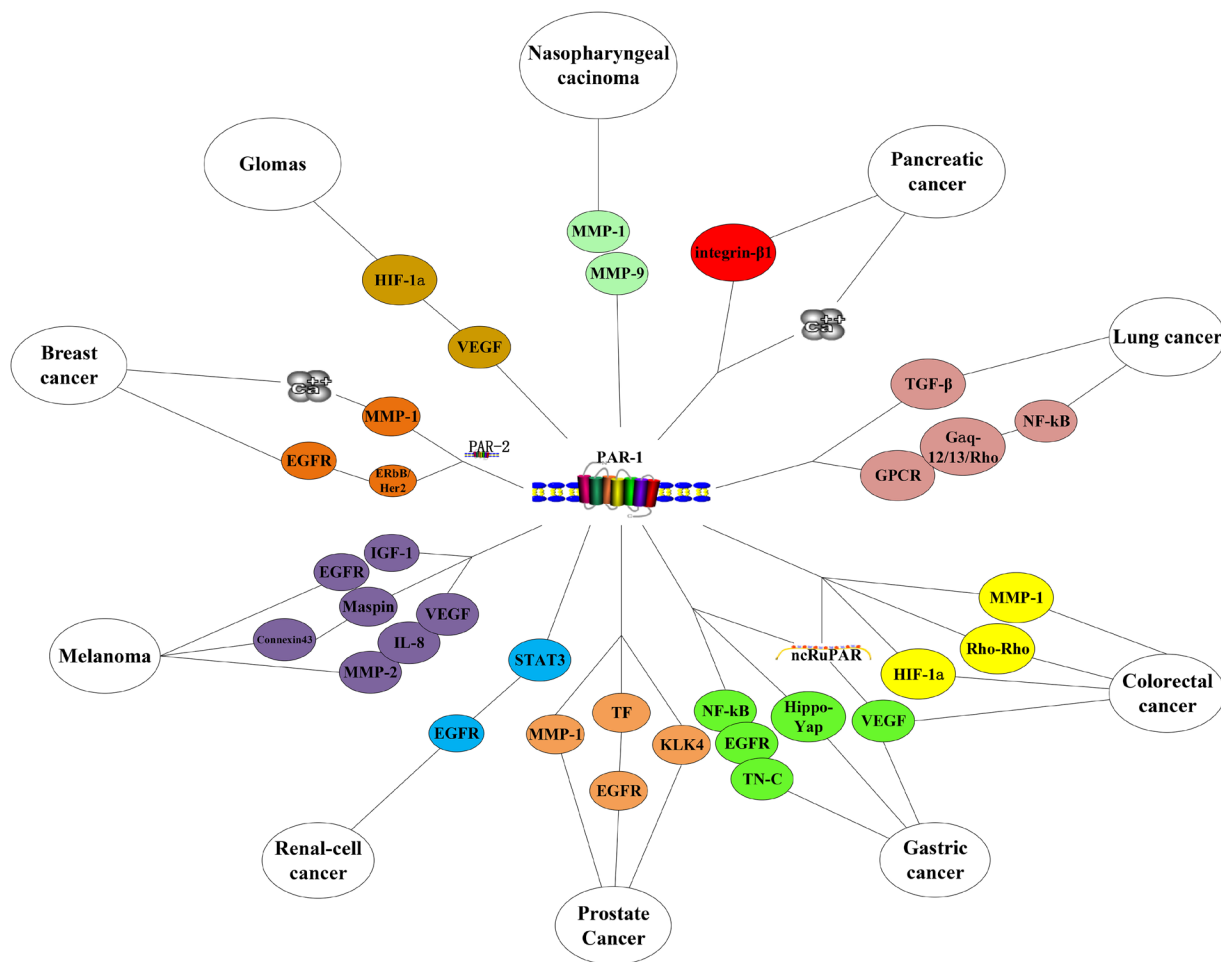


Figure 3: PAR-1 in cancers.

Currently, vorapaxar (SCH530348) and atopaxar (E5555) are the two clinical formulations of PAR-1 inhibitors [13–23], which have undergone extensive clinical development.

Vorapaxar is the first PAR-1 inhibitor approved for clinical use. Regarding vorapaxar, phase 3 clinical trial data has been available since 2012, and the parent drug company Merck has filed for submission of approval to the US FDA, as well as the European Medicines Agency (EMA) [13–14]. Its main indication is the reduction in thrombotic cardiovascular events in patients with previous myocardial infarction or symptomatic peripheral artery disease. Numerous clinical studies have demonstrated that it plays an effective role in peripheral arterial disease, pulmonary hypertension, acute coronary syndrome, and so on [15–18]. It is regarded as a new approach to antiplatelet therapy. Vorapaxar was recently approved in two key jurisdictions: the FDA approved the drug for the reduction of thrombotic cardiovascular events in patients with a history of MI or with PAD, and EMA approved it for the reduction of thrombotic cardiovascular events in those with a history of MI [19]. But vorapaxar in cancer clinical research is still very few. A recent study showed that vorapaxar could inhibit epithelial ovarian cancer (EOC) progression in ovarian cancer [20]. No other researches had been reported of PAR-1's role in other cancers. The most common side effect of vorapaxar is bleeding, which needs careful assessment in treatment.

Atopaxar hydrobromide is the second inhibitor used in clinical. It shows potent inhibitory effects on human platelet aggregation. Phase 2 clinical evidence is available for atopaxar administered in combination with ASA and/or P2Y₁₂ receptor antagonists. These trials reported an increased bleeding risk [21–22]. While, another case of the evidence on atopaxar came from LANCELOT phase 2 trials, which had two target populations, ACS (acute coronary syndrome) and CAD (coronary artery disease) [21–23]. The goals of these two studies were to look at the safety and tolerability of atopaxar in patients with ACS [22–23]. The results showed no increases in any CURE bleeding between the combined (50 mg, 100 mg, 200 mg) atopaxar group and the control group (0.6% versus 3.3%; $P = 0.125$); there was also no statistically significant difference in the rate of TIMI bleeding in the combined atopaxar group versus the control group (19.4% versus 16.4%; $P = 0.61$). As a result, further research is needed to confirm its side effect. Currently, there is no reports in the study of Atopaxar in cancer.

Thus, PAR-1 inhibitors in cancer clinical study is still lacking, to be further enriched and assessed. The potential importance of PAR-1 target in cancer therapy is of concern. Whether it can play a clinical role in the development of tumor invasion and metastasis, angiogenesis, is still our attention and important research direction.

CONCLUSIONS

PAR-1 has far-reaching significance in the mechanism of cancer research, as the earliest and most in-depth molecular of the PARs family. As mentioned above, PAR-1 actively participates in steps of cancer cell proliferation, invasion and metastasis which involve complex mechanisms. Therefore, more PAR-1 centered studies are in dire need, not only for elucidation of its tumorigenic functions, but also for its future use as a promising molecular target for clinical treatment. Although PAR-1 antagonists are known to be potent antiplatelet agents that are also complementary to other antiplatelet therapies, its role in clinical cancer treatment is still a mystery. Once it is demonstrated that PAR-1 targeted drugs play a role in tumor development or invasion and metastasis, it may become a new target for tumor therapy. Drug research and development based on PAR-1 mechanism is still a new potential direction of clinical treatment.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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