Journal of Research in Pharmacy

Review Article

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The Role of Endothelin Axis in Cancer Treatment and Its Position in Therapeutic Strategies

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Received: 01 January 2023 / Revised: 31 January 2023 / Accepted: 31 January 2023

ABSTRACT: Endothelin and its two different cognate receptors have been implicated in a wide variety of pathophysiological conditions since it was first identified as a vasoactive local hormone.

Especially in the last decade, the studies revealed that the aberrant expression of endothelin axis has critical importance in the cancer biology involving in neovascularization, cellular survival, metastasis as well as drug resistance, by taking part in different signalling mechanisms within the cell.

This situation has attracted the attention of many scientists to investigate not only reveal the molecular mechanistic role of endothelin axis in cancer pathophysiology but also design new drugs targeting the endothelin axis. Further studies suggest that utilizing endothelin axis as a new diagnostic parameter to define malignant features and monitor the prognoses of cancer

This study, which was compiled from both preclinical and clinical studies, was prepared to provide an overview of the potential role of the endothelin axis in cancer biology, as well as an overview of the drugs developed against the endothelin axis

KEYWORDS: Endothelin 1; Endothelin Receptor A; Endothelin Receptor B; Endothlin Antagonists; Cancer

1. INTRODUCTION

Endothelin 1 (ET-1) is a short 21-amino-acid polypeptide with a wide range of physiological functions, including cell proliferation [1], migration and invasion [2], apoptosis resistance [3] and angiogenesis besides its function in cardiovascular homeostasis.

ET-1 has a half-life of one minute in circulation. As a result, its swift influence is local in autocrine or paracrine manner. Accordingly, its regulation take places at the transcriptional level. The ET-1 gene's initial translation product is the prepro-ET-1 (212 amino acids), which is cleaved by an endothelin converting enzyme (ECE) into the big ET-1 (38-amino acids), which is subsequently converted into the physiologically active ET-1 (21 amino acids) that is structurally characterized with a single a-helix and two disulphide bridges [4,5].

ET-1 exerts its effects by binding to two G-protein coupled receptors (GPCR). The receptors, endothelin A receptor (ETAR) and endothelin B receptor (ETBR), have seven hydrophobic transmembrane domains, an intracytoplasmic C terminus, and an extracellular N terminus. Due to differences in their C terminus sequences, which are essential for G protein coupling, each receptor has divergent intracellular actions.

GPCRs interact with heterotrimeric G proteins that are formed of α,β,γ subunits. G protein α subunit is classified into four subfamilies: Gαs, Gαi, Gαq, and Gα12. Each G-protein triggers numerous downstream effectors to be activated. Gαs interaction results in adenylyl cyclase activation, whereas Gαi interaction results in adenylyl cyclase inhibition and Ca2+ channel activation. Gq, on the other hand, activates phospholipase C (PLC) [6], while $G\alpha_{12}$ regulates the activity of mitogen-activated protein kinase (MAPK) as well as the stimulation of other essential genes [7].

ET-1 binds with equal affinity to its cognate receptors and activates a multifaceted signalling cascade rather than a linear intracellular signalling pathway. Hence, ETAR activation leads angiogenesis, cell death inhibition [8], cell proliferation via signal cross-talk with Epidermal Growth Factor Receptor (EGFR) [9,10], and invasion in many cells, whereas ETBR activation leads to apoptotic processes [11] and ET-1 clearance [12] (illustrated in Figure 1)

How to cite this article: Gul N. The Role of Endothelin Axis in Cancer Treatment and Its Position in Therapeutic Strategies. J Res Pharm. 2023; 27(2): 481-492.

ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.331

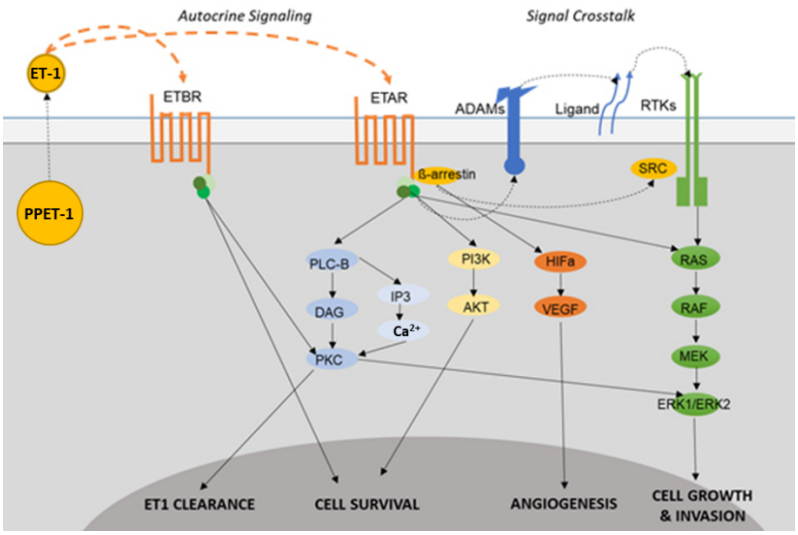


Figure 1: Physiological impact of **ET-1** and its axis. **ET-1**-induced activation of multiple and coordinated signalling pathways governs pleiotropic functions just like tumour growth, survival, angiogenesis, and invasion. Abbreviations : Preproendothelin 1 (PPET-1), A Disintegrin And Metalloproteinases (Adams),: Receptor Tyrosine Kinases(RTK), Phospholipase C (PLC-B), Diacylglycerol (DAG), Protein Kinase C (PKC), Inositol Trisphosphate (IP3), Phosphoinositide 3-Kinases (PI3Ks), Protein Kinaz B (AKT), Hypoxia-Inducible Factor A (Hifa), Vascular Endothelial Growth Factor (VEGF), RAF (Rapidly Accelerated Fibrosarcoma Gene), Mitogen-Activated Protein Kinase Kinase (MEK), Extracellular Signal-Regulated Kinases (ERK 1-2) (Illustrated by Nadir Gül)

The pattern of expression reveals that ET receptor mRNA is likely to be identified in all tissues or organs accessing a blood flow, indicating the ubiquitous expression of ETAR on vascular smooth muscle and ETBR on endothelial cells. These expression patterns, however, are not present at the same level in most tissues and organs. For example, when compared to other peripheral organs, the lungs have the largest density of ET receptors [9600 fmol/g protein], with ETAR receptors predominating, whereas the brain has [5000 fmol/g protein]. 13,14] a high density of ET receptors, with ETBR accounting for 90% of total ET receptors in the cerebral cortex [15,16]. Hence, the relative ratio of ET receptors in human tissues assessed by the competitive saturation binding assays, as shown in Figure 2, suggest that they should be addressed in diagnostic and therapeutic methods. [17]

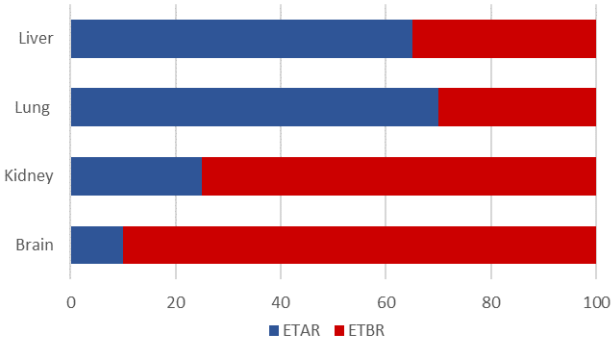


Figure 2 Ratio of ETAR to ETBR densities in the human brain, kidney, lung, and liver. The figure is adapted from [17]

2. ROLE OF ET-1 AXIS IN CANCER

Due to its versatile physiological effect on cells, abnormal regulations of members of the endothelin axis suggest a critical importance in the pathogenesis and clinical progression of various human diseases such as cancer. High expression of ET-1 has therefore been a notable feature in many malignancies, such as prostate, ovarian, colorectal, bladder, breast, and lung cancers (Table 1) Further, studies imply that high ET-1 expression may be an early process in carcinogenesis [10,19,20]. ET-1 acts as a local hormone in the tumour microenvironment, contributing to cancer pathophysiology in proliferation [1], apoptosis resistance [3], migration and invasion [2], as well as angiogenesis, extracellular matrix degradation, and chemoattraction of macrophages [21].

Table 1: Altered expression patterns of endothelin axis in cancer

Type of Cancer	ET-1	ETAR	ETBR	Reference
Bladder Cancer	increased			22
	increased	increased	increased	23
	increased	increased		24
Breast Cancer	increased			25
	increased	increased	increased	26
	increased			27
	increased	increased	increased	20
	increased	increased		28
Colorectal Cancer	increased	increased	normal	29
	increased	increased	decreased	30
	increased	increased	decreased	31
	increased	increased		32
Gastric Cancer			decreased	33
		increased		34
Glioblastoma			increased	35
	increased	increased	increased	36
			increased	37
Head and Neck Squamous Carcinoma	increased			38
Hepatocellular Carcinoma			decreased	39
	increased			40
	increased	increased		41
	increased	increased		42
Lung Cancer	increased		decreased	43
	increased	increased	normal	44
Nasopharyngeal carcinoma		increased	decreased	45
Osteosarcoma	increased			46
Ovarian Cancer	increased	increased		47
	increased	increased		48
		increased		49
Pancreas Cancer	increased	increased	increased	50
	increased		increased	51
	increased			52
Prostate Cancer		increased	decreased	53
Renal Cell Carcinoma	increased	normal	normal	54
	increased	increased	increased	55
			increased	56
Skin Cancer		increased	increased	57
			increased	58
Thyroid Cancer	increased	increased		59
	increased	increased		60
Uveal Melanoma			decreased	61

Cancer progression is determined by the intrinsic properties of the malignant cells as well as their interactions with benign cells and stromal components. Unlike normal tissues, the tumour microenvironment is hypoxic [62] and its vascular systems are remarkably permeable and tend to be leaky [63], which may line the vascular

canal with neoplastic cells "Mimicry" or cancer cells and endothelial cells "Mozaisizm" [64]. Such vascular deformations are more aggressive and prone to metastasis. The tumour is in a hypoxic microenvironment, which elevates ET-1 expression [8, 65]. ET-1 boosts the hypoxia stimulation by enhancing the levels of hypoxia inducible factor-1 (HIF1a) and vascular endothelial growth factor (VEGF) production, further secretion as well as activation of the HIF-1 transcription complex. [66,67]. in this context, HIF1a expression is widespread surrounding cancer cell-lined vessels, suggesting that hypoxia is involved in the formation of cancer cell-lined vascularization. [68,69]

As shown in Table 1, two distinct ET axis patterns emerge depending on the tissue or organ where the cancer is located. In the first pattern, increased ET-1 expression is associated with higher ETAR and ETBR expression, as documented in bladder, breast, glioblastoma, pancreas, and skin cancers, whereas in the second pattern, increased ETAR but decreased ETBR expression in colorectal, lung, prostate, uveal melanoma, and gastric malignancies draw attention.

According to studies, hypermethylation of the promoter region of the ETBR gene leads to a reduction in ETBR expression [70-73]. Although it could not be determined at which stage ETBR expression begins to be downregulated, the downregulation of ETBR, which affects ET-1 clearance and induces apoptosis, leads cancer to evolve into a more aggressive phenotype, such as uveal melanoma and lung cancers. [61].

Studies suggest that the differential expression levels of the ET axis in various cancer types may be affected by the propensity of the originating cell type [59]. When we evaluate Figure 2 and Table 1 together from this perspective, we can emphasize that the origin of the cell has a role in the regulation of the ET axis. For example, the expression of ETBR is downregulated in liver and lung cancers (Table1), where ETBR is expressed at a relatively lower rate in healthy organs (Figure 2). Similarly, ETBR expression is upregulated in malignant states involving organs such as the brain and with lymphatic invasion. [74], where ETBR is found to be relatively more expressed than ETAR.

Another conclusion that can be inferred from Table 1 is that in cancer, ETAR expression increases in accordance with high ET-1 expression. Overexpression of ETAR, which promotes tumour progression and correlates with poor survival, is more common in cases with distant metastases [45,59,75].

To understand the underlying mechanism, a study on the liver metastasis of colon cancer demonstrated that increased ET-1 mediated ETAR signalling exhibits an increase in matrix metallo protease 2 (MMP2) expression and manages cell survival and invasion via phosphoinositide 3-kinase (PI3K) mediation [30]. Another study indicated that enhanced ET-1-ETAR signalling is an important component promoting epithelial to mesenchymal transition (EMT) and cell invasion in ovarian cancer [76]

The EMT arises when tumour cells lose their polarity and cell–cell junctions and acquire a mesenchymal phenotype, therefore gaining the ability to invade the extracellular matrix, and spread to distant sites [77,78]. The endothelin axis contributes to the suppression of E-cadherin and beta catenin expression and, concomitantly, increases the expression of mesenchymal N catenin [79]. Sustained ET-1 signalling is essential for this molecular and molecular transformation maintenance in tumour cells [48,76]. Inhibition or knockdown of ET axis signalling exhibited a phenotypical reversion of EMT and blocked invasive behaviour [80]. The invasive behaviour and EMT phenotype is frequently seen in chemotherapy resistance in malignant cells [81]. This suggests that ETAR activation are also crucial in drug resistance. Following this hypothesis, an immunohistochemical study of human ovarian cancer tissues revealed ETAR overexpression in chemo-resistant tumours, implying that ETAR expression levels can be utilized to predict chemo resistance in cancer therapy [81].

In addition to the above-mentioned signalling mechanisms and physiological consequences triggered by the ET-1 axis, the ET-1 GPCR receptor can activate Epidermal Growth Factor Receptor (EGFR) through an unconventional signalling process known as signal crosstalk [9,82,83].

The tumorigenicity of the EGFR activation and signalling pathway has been long studied in depth in ovary cancer head and neck cancer, colorectal cancer and breast cancer [38, 83-85].

EGFR and its signalling are key regulators of cellular activities such as proliferation, differentiation, apoptosis, and migration [86,87]. There is also evidence that ET-1 exerts an additive proliferative effect on EGFR transactivation, even in the presence of EGF ligands. As a consequence of, unremitted activation of the Shc/Grb-2 complexes and the ras/MAPK pathway, the proliferation signal is maximized [88,89].

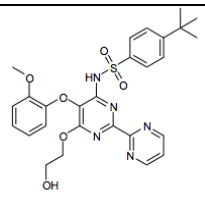
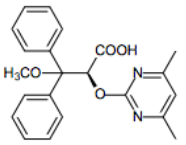
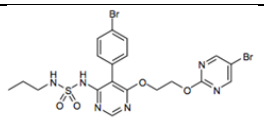
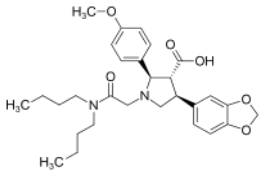
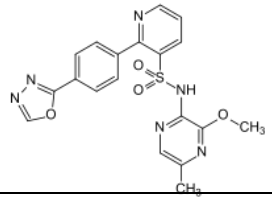
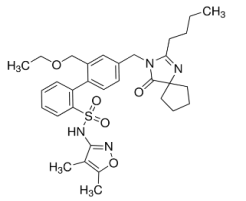
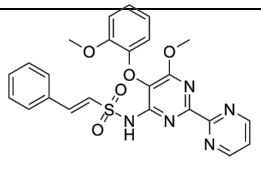
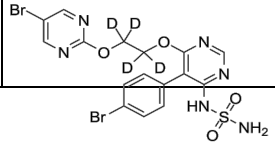
Another signal cross talk mechanism is mediated by B-arrestin, which recruits SRC and stimulates EGFR. B-arrestin may propagate as a hotspot for ETAR downstream signalling in the nucleus, involving the activity of various transcription factors such as B-catenin [47,90] and nuclear factor B [NF-B] [91]. B-arrestin governs the dynamics and remodelling of the cytoskeleton through this signalling, which ends up making cancer cells more aggressive. All of these data indicate that ET-1's versatile network encompasses cell survival, angiogenesis, cell growth and malignant cell behavior.

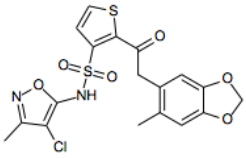
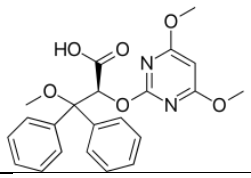
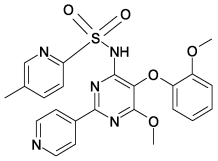
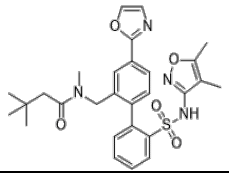
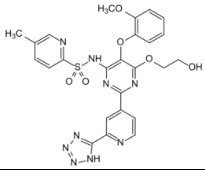
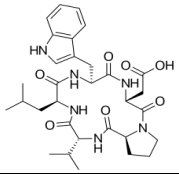
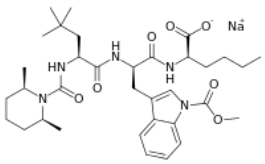
3. ROLE OF ET AXIS IN CANCER TREATMENT

In the previous section, we tried to summarize the versatile effects and significance of the ET axis on cancer biology, which makes it a potential target in cancer therapy. This has paved the way for the development of many approaches targeting the ET axis in the treatment of cancer, including ECE [92] inhibitors, neprilysin transfection [93] and receptor antagonists.

Among these strategies for limiting ET-1 pleiotropy activity, endothelin receptor blockade is the most potential option. Table 2 summerizes prominent ET receptor antagonists. These blockers act either selectively or specifically on the receptor.

Table 2: Endothelin receptor antagonists (Chemical formulations were obtained from pubchem [94]). Abbreviations: European Medicines Agency (EMA), Food and Drug Administration (FDA), pulmonary arterial hypertension (PAH)

Generic Name	Structure	Selectivity	Approval Status	Indications	Reference
Bosentan ATC C02KX01 [Tracleer		*Dual	FDA: 2001 EMA: 2002	» PAH » Systemic sclerosis » Metastatic melonoma	95,96
Ambrisentan ATC C02KX02 [Tadalafil, Volibris]		Only ETAR	FDA: 2007 EMA: 2008	» PAH	97
Macitentan ATC C02KX04 [Opsumit]		Dual	FDA: 2013 EMA: 2013	» PAH	98
Atrasentan L01XX *[Xinlay]*		Only ETAR	Clinical Trial Phase III	» Prostate Cancer » Breast cancer »Colorectal cancer » Ovarian Cancer » Malignant Glioma » Kidney cancer	99
Zibotentan [ZD4054]		Only ETAR	Clinical Trial Phase III	» Prostate Cancer » Breast cancer »Colorectal cancer » Ovarian Cancer » Lung cancer » Heart failure	100,101
Sparsentan		Dual	Clinical Trial Phase III	» Alport syndrome » Focal segmental glomerulosclerosis	102,103
Nebentan YM 598		Only ETAR	Clinical Trial Phase II	» Prostate cancer	104
Aprocitentan ACT 132577		Dual	Clinical Trial Phase III	» PAH	105,106

Sitaxentan ATC C02KX03 *[Thelin]*		Only ETAR	Withdraw		107
Darusentan *[LU-135252; HMR-4005]*		Only ETAR	Clinical Trial Phase III Terminated	» Uncontrolled hypertension.	108
Avosentan		Dual	Clinical Trial Phase III Terminated	» Overt diabetic nephropathy	109
Edonentan		Only ETAR	Clinical Trial Phase II Terminated	» Heart failure	110
Clazosentan [Pivlaz]		Only ETAR	Experimental	» Aneurysmal subarachnoid bleeding	111,112
BQ-123		Only ETAR	Experimental		113
BQ-788		Only ETBR	Experimental		114

Bosentan, Macitentan and Ambrisentan, have all been proven beneficial in PAH treatment by alleviating symptoms and slowing the progress of the disease. Although Bosentan has been reported to induce cell death in human melanoma cells [115], phase 2 clinical studies for metastatic melanoma did not yield the desired result.

Macitentan acts on both receptors like bosentan, while it is one-step ahead of other antagonists due to slow receptor dissociation [116]. An oral cancer research study has reported that Macitentan had no effect on survival when administered alone in oral cancer trials, but when combined with paclitaxel, cancer cell division is significantly reduced [117]. Importantly, this study reveals that Macitentan possesses an analgesic effect, making it useful in relieving cancer pain.

Unlike other Bosentan and Macitentan antagonists, Ambricentan exclusively affects ETAR. Treatment with Ambrisentan reduced metastases in the lungs and liver in a pre-clinical animal model of metastatic breast cancer with a significant increase in animal survival [118].

Atresentan and Zibotentan, developed for cancer treatment, specifically bind to ETAR to suppress the proliferation of cancer cells and malignancy. When these antagonists were combined with cytotoxic medications like paclitaxel or molecular inhibitors like gefitinib, the tumour growth dramatically suppressed.

Furthermore, they have been examined in randomized, placebo-controlled clinical trials for prostate cancer, and the outcomes have also shown that they are safe [119,120].
Another ETAR blocker, Clazosentan, has been shown to be effective in preventing severe cerebral vasospasm and in delaying neurologic ischemia and new ischemic attacks [121]. However, to the best of our knowledge, no scientific papers involving this antagonist for the treatment of cancer have been published.
The remaining antagonists in Table 2 were either withdrawn or their clinical studies were stopped because of severe adverse effects. Flushing, nausea, headache, nasal congestion and peripheral oedema, which develop in a dose-dependent manner, as well as hypotension and palpitation, are among the common side effects [122]. Principally, endothelin receptor antagonists are excreted from the body by biliary excretion or renal/fecal excretion after being metabolized by the hepatic system, involving cytochrome p450. It is therefore dangerous to use it in patients with liver problems. So that the severe side effects that occurred during the clinical studies of sitaxsentan led to the discontinuation of the drug in 2010 [123]. Similarly, Zibotentan, one of the most promising endothelin receptor antagonists in preclinical studies, was pulled from prostate cancer treatment in phase III clinical trials because it did not exhibit a significant difference in overall survival compared to placebo-treated patients [120].
These antagonists are anticipated to have some clinical benefit that has not been fully proven in the currently completed clinical trials.

4. CONCLUSION

Although multiple preclinical and clinical investigations have shown that the ET axis is significant in cancer biology, the underlying mechanism by which this occurs is elusive. More investigation into ET antagonists' biological events and therapeutic outcomes should be encouraged.
Moreover, the endothelin axis' altering expression patterns provide crucial information about cancer phenotype and prognosis. From this perspective, treatment can be tailored more precisely, which is especially useful for diagnosing risky and rapidly progressing diseases.

Acknowledgements: This review was formed by fusing the knowledge and experiences I gathered through my Doctoral dissertation at Humboldt University with recent information. I appreciate the help from my renowned professor Franz Theuring.

Author contributions: Concept – NG.; Design – NG.; Supervision NG.; Resources – NG.; Materials – NG.; Data Collection and/or Processing – NG.; Analysis and/or Interpretation NG.; Literature Search – NG; Writing – NG.; Critical Reviews – NG.

Conflict of interest statement: The author declares there are no competing interests

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