

Review

Trefoil Factor 1 (TFF1) in Retinoblastoma: A Biomarker, Mediator, or Therapeutic Target?

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Abstract

Retinoblastoma is a prevalent pediatric malignant tumour of the retina, primarily caused by biallelic inactivation of the *RB1* gene or, less commonly, amplification of the *MYCN* oncogene. It has a global incidence of approximately 1 in 15,000–18,000 live births and predominantly affects children under five years of age. Trefoil factor 1 (TFF1) is a small, secreted peptide from the trefoil family, mainly expressed in the gastrointestinal mucosa, where it plays an essential role in mucosal protection, repair, and cellular differentiation. Beyond its physiological functions, aberrant TFF1 expression has been implicated in tumour progression and oncogenic signalling across several cancers. TFF1 is not expressed in healthy human retina but is significantly expressed in retinoblastoma tissues, with higher levels correlating with advanced disease stage, high-risk histopathologic features (HRPFs) and metastasis, poor differentiation, and unfavourable prognosis, suggesting a potential role of TFF1 in the pathogenesis and progression of retinoblastoma. Furthermore, in addition to tumour biopsy, its detection in the aqueous humour indicates its potential utility as a non-invasive biomarker for tumour activity and treatment monitoring. Although the precise molecular mechanisms underlying TFF1's function in retinoblastoma remain unclear, evidence suggests that it may modulate tumour aggressiveness through effects on cell proliferation, apoptosis, and tumour microenvironmental signalling, supporting its promise as a prognostic biomarker and potential therapeutic target. This review consolidates the current advances in the role of TFF1 in retinoblastoma and critically examines its emerging significance as a potential clinical biomarker, molecular mediator, and novel therapeutic target for retinoblastoma.

Keywords: trefoil factor; retinoblastoma; biomarker; pediatric ocular cancer; therapeutic target



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1. Introduction

Retinoblastoma is a pediatric intraocular malignancy that arises from cone cells in retinal tissue, caused by the biallelic inactivation of *RB1*, located on chromosome 13q14 [1]. Discovered as the first tumour suppressor gene in 1986 [2], *RB1* forms pRB, a cell-cycle regulatory protein that exerts its function by binding to E2F. *RB1* mutations cause a lack of functional pRB, leading to uncontrolled cell divisions [3]. According to Knudson's two-hit hypothesis, both copies of the *RB1* gene must be inactivated for retinoblastoma to develop [4]. These two "hits" can occur in different ways, heritable and non-heritable.

In heritable retinoblastoma, one RB1 mutation is inherited and is present in all cells of the body. A second mutation occurs in a retinal cell during eye development, leading to cancer. Heritable retinoblastomas constitute 30–40% of all cases and predispose to bilateral (80%) and multifocal (67%) retinoblastomas with an earlier age of onset. In non-heritable retinoblastoma (60–70% of all cases), both RB1 mutations occur only in a retinal cell. The mutation is not inherited and leads to unilateral and unifocal tumours with a later age of onset [3]. In a small subset of retinoblastoma cases, no RB1 mutations are found ($RB1^{+/+}$), but there is a high MYCN oncogene amplification ($MYCN^A$). $RB1^{+/+}MYCN^A$ tumours comprise 1.4% of unilateral retinoblastomas and are nonhereditary [5]. Yet, in other incidences, both RB and MYCN genes are normal, but 13q chromothripsis is found as a causative agent [6,7].

Though retinoblastoma cases are constant across all populations, ranging one in every 15,000 to 18,000 live births [2,8,9], both incidence and mortality are higher in lower- and middle-income countries (LMICs), compared to high-income countries (HICs). LMICs like India witness 1600–2000 cases every year, with 49.1% displaying extraocular retinoblastoma and 18.9% showing metastasis, with notably poorer prognosis [10]. In LMICs, the survival rate can be 30% to 50% due to social stigma, delays in diagnosis, and advanced disease stages [11]. It can be attributed to socioeconomic factors, such as inadequate nutrition during pregnancy, inaccessible healthcare and high treatment costs, etc., that eventually lead to delayed presentation and worse prognosis [3,9]. Various grouping and tagging systems are used for the classification of retinoblastoma, such as the Reese and Ellsworth system (1963), the International Intraocular Retinoblastoma Classification (IIRC, 2005), the International Classification of Retinoblastoma (ICRB, 2006), the International Retinoblastoma Staging System (IRSS, 2006), and the eighth edition of the American Joint Committee on Cancer (AJCC, 2017), as reviewed by Nag and Khetan, 2024 [3].

Advanced retinoblastoma is characterized by intraocular or extraocular signs, along with high-risk pathological factors such as anterior chamber seeding, iris infiltration, ciliary body infiltration, extensive choroidal infiltration, invasion of the lamina cribrosa of the optic nerve, retrolaminar optic nerve invasion, optic nerve transection invasion, scleral infiltration, and extrascleral extension [12,13]. Current treatments for retinoblastoma include cryotherapy, transpupillary thermotherapy, plaque brachytherapy, external beam radiotherapy, systemic chemotherapy such as carboplatin, vincristine, etoposide, and ultimately, enucleation [14]. Children diagnosed with advanced retinoblastoma often show poor responses to chemotherapy, metastasis, and recurrence [15,16]. Therefore, the molecular mechanisms that drive retinoblastoma to advanced stages need to be identified, which will assist in prognostication and risk stratification of high-risk patients to improve outcomes.

Trefoil Factor 1 (TFF1) is a small, highly conserved secretory peptide belonging to the trefoil factor family, identified in healthy gastric mucosa, where it protects, repairs, and maintains the integrity of the gastric epithelium [17–19]. It has been found in the central nervous system, conjunctiva, and lacrimal gland, but not in retinal cells. TFF1 functions as a tumour suppressor gene in gastric cancer and is also dysregulated in breast cancer, ovarian cancer, lung cancer, prostate cancer, and colorectal cancer. Recently, in retinoblastoma, TFF1 has been studied as a biomarker for the cancer [20–24]. This review summarizes the role of TFF1 in different human cancers, with a specific focus on its potential as a biomarker, mediator, or therapeutic target in retinoblastoma.

A narrative review was conducted to synthesize experimental, translational, and clinical studies (published between 1971 and 2025) examining the role of TFF1 across cancers, with particular emphasis on retinoblastoma, encompassing biological functions, regulatory mechanisms, clinical relevance, and therapeutic implications. The literature search was conducted in PubMed using relevant keywords and MeSH terms related to

TFF1, cancer, retinoblastoma, and biomarker potential, supplemented by manual screening of reference lists. Studies addressing TFF1 expression, regulation, signalling pathways, epigenetic control, tumour progression, and therapeutic targeting were prioritized, while non-English articles, those lacking full text or sufficient methodological detail, and studies unrelated to ocular oncology were excluded. Data on experimental models, patient cohorts, methodologies, molecular pathways, and clinical associations were manually extracted and integrated across in vitro, in vivo, patient-based, and transcriptomic studies. As a narrative review, this work does not follow PRISMA guidelines or include meta-analysis, allowing for integrative interpretation while acknowledging potential selection bias.

2. Key Molecular Signatures in Retinoblastoma

Recent advancements in next-generation sequencing, transcriptomics, and proteomics studies have uncovered crucial molecular information about different cancers, including retinoblastoma. Besides *RB1* mutation and *MYCN* amplification, various other key molecular signatures have been identified that directly or indirectly contribute to the initiation, progression, or suppression of retinoblastoma. Mayra Martínez-Sánchez et al. (2021) have reviewed around 200 proteins that interact with RB, such as E2F family members, and chromatin modifiers, e.g., HDAC 1, 2, and 3, DNMT1, SIRT1, the DNA polymerase α , the replication factor CDMX and MDM2, among many others, and enlisted potential invasive (such as RASSF1A, p16INK4A, LncRNA, CCAT1, CRABPs, APOA1, GFAP, RBP3, LMNB1, and TFRC), and non-invasive biomarkers (such as p16INK4A, Sox2, miR-17, miR-18a, miR-20a, miR-103, Survivin, TGF- β 1, miR-320, miR-21, miR-let-7e, p53, MDM2, MDMX, and LDH) for retinoblastoma [25]. Xiangyi Ma et al. (2024) have summarized different dysregulated genes/proteins and epigenetic modifiers in retinoblastoma [26]. Some of these genes include DNA-binding oncogene DEK, transcription factor E2F3, cyclin-dependent kinase regulatory subunit 2 (CKS2), Ubiquitin E2 ubiquitin-conjugating enzyme 2T (UBE2T), cadherin 11 (CDH11), claudin-1, Matrix metalloproteinase (MMP) 1, 2, and 9, vascular endothelial growth factor (VEGF), Centromere protein E (CENPE), and BCL6 corepressor (BCOR). Among epigenetic players, levels of DNA methyltransferase 1 (DNMT1), histone methyltransferases, and non-coding RNAs have been identified to be modified in retinoblastoma [26]. Rathore et al. (2023) [27] have recently presented the developments in the genetic, epigenetic, transcriptomic, and proteomic landscapes of retinoblastoma and discussed their clinical relevance and potential implications for future therapeutic development. Among various markers include the overexpression of *KIF14* and *E2F3*, *UBE2C*, *MDM2*, *OTX2*, *NEK7*, *SKP2*, *DEK*, *CRB1*, *MIR181*, *NUP205*, *IL8*, *IL6*, *MYC*, and *SMAD3* and downregulation of *RPTOR*, *ARHGAP9*, *DRAIC*, *TERT*, *ARID1A*, *MSH3*, *TSC2*, *CREBBP*, *HIST1H4H*, *RELN*, *CDK4*, *BRAF*, *JAK1*, and *ROCK1*. Proteomic profiling of retinoblastoma has identified various potential protein markers, such as upregulated IGF2BP1, B7H3, nucleolin, chromogranin A, Rac GTPase-activating protein 1, fetuin A, midkine, LRP1, COMP, TGB3, TLN, FLNA, OGN, A1BG, Serpin A1, ORM2, LRG1, CHI3L1, apolipoprotein A1, transferrin, alpha-crystallin A, and CRABP2. Corson and Gallie (2007) have reviewed the epigenetic changes in aberrant methylation of genes involved in retinoblastoma, particularly *MGMT*, *RASSF1A*, *CASP8*, and *MLH1*, and the roles of microRNAs [28].

In 2021, Lie et al. [23] published a landmark study using a multi-omics approach, dividing retinoblastoma into two subtypes: subset 1, the early onset, and subset 2, dedifferentiated or high risk. Both types present distinct clinical and pathological features and significantly different gene expressions. Among the most differentially expressed genes were the Cone markers (such as *ARR3*, *GUCA1C*, *GUCA1A*, *GUCA1B*, *GNAT2*, *GNGT2*, *PDE6H*, *PDE6C*, and *OPN1SW*) and neuronal/ganglion markers (such as *EBF3*, *ROBO1*, *DCX*, *GAP43*, *SOX11*, *STMN2*, *PCDHB10*, *NEFM*, *EBF1*, and *POU4F2*). Cone

markers were overexpressed in subtype 1 tumours, whereas neuronal/ganglion markers were overexpressed in subtype 2 tumours. The identification of two molecular subtypes of retinoblastoma, i.e., cone-like and cone/neuronal, represents a major advancement in the understanding of retinoblastoma that would help to design and develop better therapeutics [23].

Recently, a plethora of such genomic, transcriptomic, proteomic, and epigenomic molecular signatures have been identified and studied in cases of retinoblastoma that are envisaged to provide a better understanding of the disease and the potential development of diagnostic and therapeutic targets. Among many such molecules is the trefoil factor 1 peptide, which has very recently been identified as a potential biomarker of retinoblastoma [20,21,23,24].

3. Trefoil Factor Family

The mammalian trefoil factor family (TFF) consists of three peptides: TFF1 (formerly, breast cancer-associated peptide pS2), TFF2 (formerly, pancreatic spasmolytic polypeptide SP), and TFF3 (formerly, intestinal trefoil factor or hP1.B), which are predominantly found as secreted molecules in the mucous covering normal epithelium. Human TFF1 was the first mammalian TFF member to be discovered. It was identified in 1982 through the cDNA cloning of an estrogen-responsive gene [29]. TFF2 was found independently in the porcine pancreas around the same time, and its first sequence was reported in 1985 [30]. TFF3 was identified later in the rat intestine in 1991, with the human sequence reported in 1993 [31,32]. The present nomenclature is based upon an agreement reached at the Conférence Philippe Laudat in Aix-les-Bains in 1996 [33].

All three TFF genes are clustered on chromosome 21q22.3 in humans in a head-to-tail arrangement in the order telomer-TFF1-TFF2-TFF3-centromer and are characterized by a common structural motif, the TFF domain (formerly, P-domain or trefoil domain), which contains six conserved cysteine residues with three intramolecular disulfide bonds at Cys^{I-V}, Cys^{II-IV}, and Cys^{III-VI}. Human TFF1 (60 amino acids) and TFF3 (59 amino acids) contain a single TFF domain, and an additional free 7th cysteine (Cys^{VII}) resides outside the TFF domain. TFF2 (106 amino acids) contains two TFF domains with N- and C- terminals disulfide-linked via two additional cysteine residues outside the TFF domain, possesses circular structure, and is N-glycosylated (in humans) [34]. The amino acid sequence and structure of the three TFF members in humans are represented in Figure 1. TFF1 and TFF2 are predominantly synthesized in the stomach, with TFF2 being additionally synthesized in the Brunner's gland of the duodenum [18]. TFF3 shows a wider distribution and is mainly found in the intestine, salivary glands, lung, uterus, and vagina [18]. Importantly, a minute amount of TFF peptides is also secreted by the immune system and central nervous system in an endocrine manner [18]. Minor amounts of different TFF peptides are secreted by various other tissues as well, which is why all three TFF peptides are detectable in serum. A summary of the secretion of TFF1, TFF2, and TFF3 by different organs/tissues is represented in Figure 2.

The TFF performs various physiological roles in different organs, most prominently in gastrointestinal mucosal defence. The distribution pattern of the three members of TFF differ across the gastrointestinal tract, with TFF1 being primarily present in surface epithelial cells of gastric mucosa [35–37], TFF2 in Brunner's glands in duodenum and pyloric glands of stomach along with mucous neck cells [37], and TFF3 in mucous-secreting goblet cells in the small intestine and colon [38]. The TFF promotes cell migration, thereby enhancing epithelial repair [39]. Also, TFF1 suppresses *Helicobacter pylori*-induced inflammation [40–42] and carcinogenesis both in vivo and in vitro [43–45]. TFF2 and 3 also play a role in *Helicobacter pylori* infection [46]. Besides this, the TFF acts as an immune modulator and protects

the gastrointestinal tract by regulating proliferation, migration, angiogenesis and cell death, the dysregulation of which can lead to TFF-mediated oncogenesis [47,48]. Altered TFF expression has been linked with various pathological disorders in the gastrointestinal tract, ocular system, urinary tract, respiratory tract, and nervous system, as reviewed by Emidio et al. (2020) [19]. The TFF performs this wide array of biological functions by interaction with membrane receptors, mucins, integrins, carbohydrate moieties and gastrophilins. Some of these validated interactors of the different TFF members are listed in Table 1 and are represented as a protein–protein interaction network in Figure 3, as rendered by IntAct, the EMBL-EBI’s molecular interactions database.

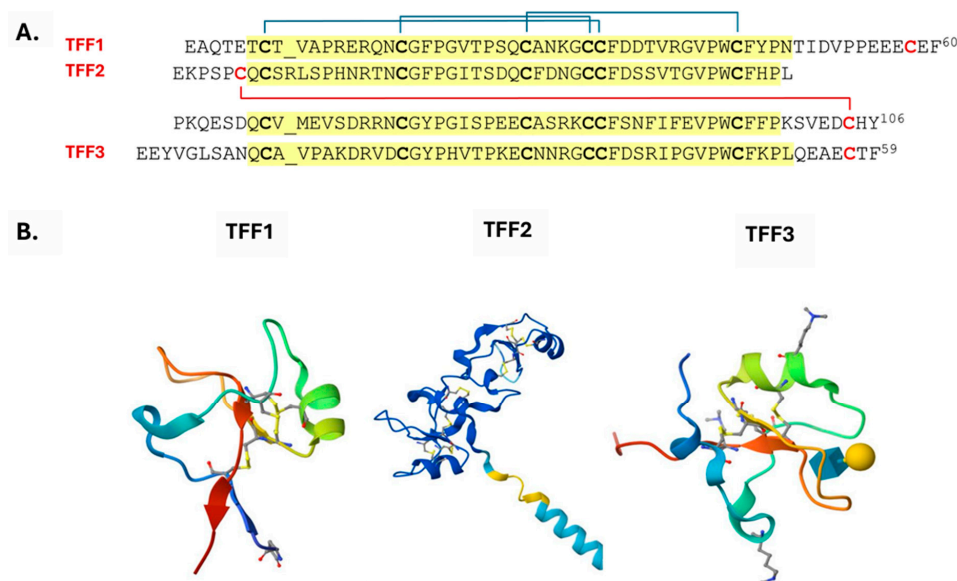


Figure 1. Sequence and structure of the TFF: (A) Amino acid sequence of TFF1 (60 amino acids), TFF2 (106 amino acids), and TFF3 (59 amino acids) showing the trefoil domain (highlighted yellow) and cysteine bridges (with blue lines indicating within the trefoil domain and a red line indicating outside the trefoil domain). Cysteines within the trefoil domain are shown with bold fonts, and outside the trefoil domain are shown with red font colour. (B) Crystal structures of human TFF1 (pdb_00006v1d) and TFF3 (in complex with its cognate ligand) (pdb_00006v1c) and computed structure of TFF2 (AF_AFQ03403F1).

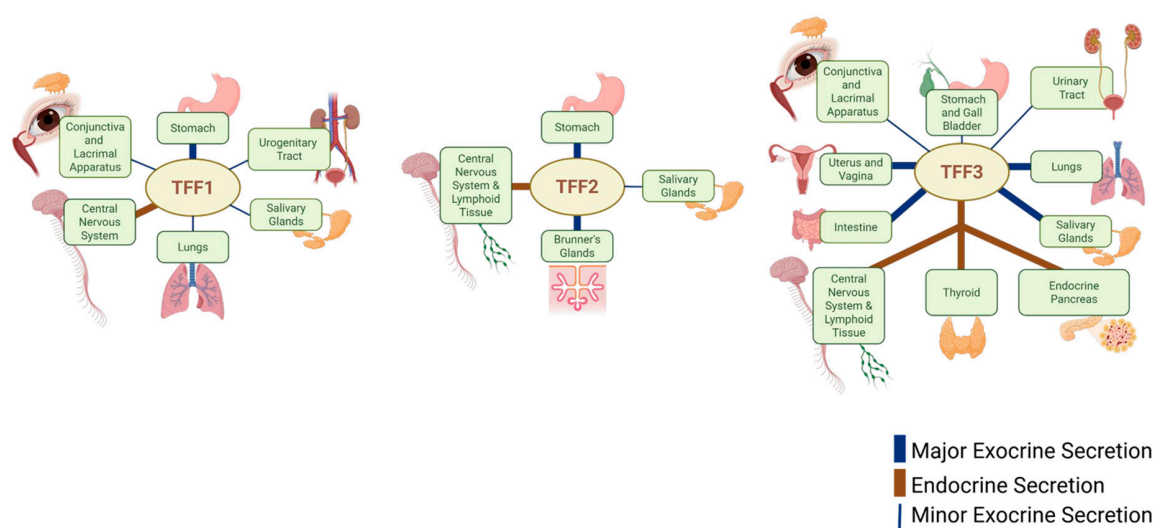


Figure 2. Secretion of human TFF1, TFF2, and TFF3 in different organs/tissues: thick blue connections indicate major exocrine secretion, thin blue connections indicate minor exocrine secretion, and thick red connections indicate endocrine secretion.

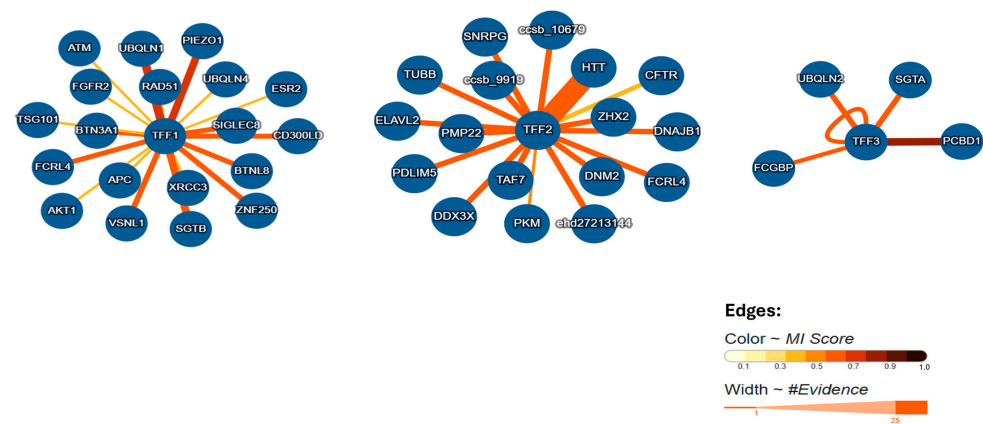


Figure 3. Protein–protein interaction network of TFF1, TFF2, and TFF3 as obtained from the IntACT database of EMBL-EBI (<https://www.ebi.ac.uk/intact/home>, accessed on 20 December 2025).

Table 1. Various trefoil factor family (TFF)-interacting proteins.

TFF	Interacting Protein	Reference
TFF1	Ubiquilin 1 (UBQLN1)	[49–54]
	Piezo-type mechanosensitive ion channel component 1 (PIEZO1)	
	Small glutamine-rich tetratricopeptide repeat-containing protein beta (SGTB)	
	Visinin-like protein 1 (VSNL1)	
	Zinc finger protein 250 (ZNF250)	
	Butyrophilin subfamily 3 member A1 (BTN3A1)	
	Butyrophilin-like protein 8 (BTNL8)	
	CMRF35-like molecule 5 (CD300LD)	
	Fc receptor-like protein 4 (FCRL4)	
	Sialic acid-binding Ig-like lectin 8 (SIGLEC8)	
	RAC-alpha serine/threonine-protein kinase (AKT1)	
	Serine-protein kinase ATM (ATM)	
	Estrogen receptor beta (ESR2)	
	Fibroblast growth factor receptor 2 (FGFR2)	
	DNA repair protein RAD51 homolog 1 (RAD51)	
	Adenomatous polyposis coli protein (APC)	
	Tumour susceptibility gene 101 protein (TSG101)	
TFF2	Ubiquilin-4 (UBQLN4)	[52,55–57]
	DNA repair protein XRCC3 (XRCC3)	
	ccsb_10679	
	ATP-dependent RNA helicase DDX3X (DDX3X)	
	DnaJ homolog subfamily B member 1 (DNAJB1)	
	ELAV-like protein 2 (ELAVL2)	
	Huntingtin (HTT)	
	PDZ and LIM domain protein 5 (PDLIM5)	
	Peripheral myelin protein 22 (PMP22)	
	Small nuclear ribonucleoprotein G (SNRPG)	
	Transcription initiation factor TFIID subunit 7 (TAF7)	
	ccsb_9919	
	Dynamin-2 (DNM2)	
	ehd27213144	
	Tubulin beta chain (TUBB)	
	Zinc fingers and homeoboxes protein 2 (ZHX2)	
	Fc receptor-like protein 4 (FCRL4)	
	Pyruvate kinase PKM (PKM)	
	Cystic fibrosis transmembrane conductance regulator (CFTR)	

Table 1. Cont.

TFF	Interacting Protein	Reference
TFF3	■ Pterin-4-alpha-carbinolamine dehydratase (PCBD1)	[49,51,58]
	■ IgGfc-binding protein (FCGBP)	
	■ Small glutamine-rich tetratricopeptide repeat-containing protein alpha (SGTA)	
	■ Ubiquilin-2 (UBQLN2)	

4. TFF1 in Various Cancers

Trefoil Factor 1 (TFF1) has been identified as a putative molecular marker for prognostication, diagnosis, and theragnostics in various cancers. Its expression varies across different tumour types and their grouping, which can influence both clinical outcomes and prognosis. Beyond its physiological repair function and epithelial restitution, it has a dual role; it can be a tumour suppressor or an oncogenic driver. In the present section, we present the role of TFF1 in different cancers and summarize this information in Table 2.

4.1. Breast Cancer

TFF1 is a typical marker of estrogen expression and is found in the ductal lumen of the mammary gland. Amiry et al. (2009) showed that TFF1 overexpression promotes oncogenicity by increasing cellular proliferation in mammary carcinoma cells both in vitro and in vivo [59]. A study by Pelden et al. (2013) revealed that 74% of breast cancer tissues had high TFF1 expression, which is closely linked with the estrogen response and can cause drug resistance to doxorubicin in ER-positive cases [60]. Another study by Elnagdy et al. (2018) reported that TFF1 mRNA was detected in 34% of metastatic breast cancer samples, suggesting that TFF1 has metastatic potential [61]. Furthermore, Prest et al. (2002) demonstrated that TFF1 functions as a pro-migratory factor, helping breast cancer to migrate and spread; therefore, blocking estrogen and TFF1 may reduce cancer metastasis [62]. On the other hand, using mammary epithelial cells and TFF1 knockout mice, Buache et al. (2011) demonstrated that TFF1 does not exhibit oncogenic properties, but rather reduces tumour development [63]. Similarly, Yi et al. (2020) showed that TFF1 was highly expressed at both the mRNA and protein levels in luminal breast cancer patients and lower in triple-negative breast cancer (TNBC), which is an aggressive form of breast cancer. TFF1 correlated with breast cancer survival. They also showed that TFF1 inhibited cell proliferation, migration, and invasion in vitro [64]. Spadazzi et al. (2021) showed that high TFF1 expression in estrogen receptor-positive breast cancer can predict bone metastasis, as patients with high TFF1 mRNA and protein expression (62%) later developed bone metastasis. The in vivo model demonstrated that TFF1 knockdown can modulate cancer growth, suggesting involvement in metastasis development [65]. Thus, TFF1 can be used as a prognostic marker. Physiological TFF1 expression indicates a differentiated, less invasive tumour state. However, experimental overexpression can enhance proliferation, migration, and metastasis, highlighting its context-dependent behaviour. Together, these findings position TFF1 as both a prognostic indicator and a potential therapeutic target in hormone-driven breast cancer.

4.2. Gastric Cancer

Superficial and foveolar epithelial cells mainly secrete TFF1 in the gastric mucosa to protect against insults. Its deficiency leads to malignant cancer development. Ge et al. (2012) demonstrated in vitro that TFF1 downregulation reduces apoptosis and inhibits proliferation; TFF1 is an integral part of gastric cell differentiation [66]. Loss of TFF1 causes gastric carcinogenesis in both mice and humans by triggering the NF-κB pathway cascade [67].

Further, TFF1 plays an anti-inflammatory role in regulating the NF- κ B pathway, whereas TFF1 reduces cancer cell proliferation via the β -catenin cascade [68]. The pro-apoptotic function of TFF1 is executed through the activation of p53 and the downregulation of microRNA 504 [69]. An in vivo and ex vivo analysis revealed that IL6R α -GP130 complex formation is blocked by TFF1, which induces STAT3 activity, clarifying TFF1's role in inhibiting gastric tumourigenesis [70]. Taken together, TFF1 works as a tumour suppressor in gastric cancer and maintains mucosal integrity by inhibiting pro-inflammatory signalling, being pro-apoptotic, and suppressing EMT, inhibiting malignant progression and metastasis.

4.3. Ovarian Cancer

TFF1 is either not expressed or expressed at low levels in normal ovarian tissues, while it is highly expressed in mucinous ovarian cancer and is associated with poor prognosis. Unlike gastric cancer, where TFF1 plays a suppressive role, in mucinous ovarian cancer, it elevates the malignant phenotype through Wnt/ β -catenin signalling [71]. Ronnerman et al. (2023) demonstrated that TFF1 is a specific diagnostic marker for the mucinous-invasive ovarian carcinoma histotype [72]. Another study by Lutz et al. (2024) found high TFF1 positivity (76.4%) in mucinous ovarian carcinoma among 149 different tumour samples [73]. These findings suggest that TFF1 functions as an oncogenic driver in specific mucinous ovarian carcinoma histotypes, promoting proliferation, migration, and invasion.

4.4. Colorectal Cancer

TFF1 is highly expressed in colorectal cancer compared to normal mucosa [74]. Yusup et al. (2017) demonstrated TFF1 expression in colorectal cancer via immunohistochemistry and suggested its pro-invasive and oncogenic features, but no correlation with survival. Additionally, it is found in well and moderately differentiated tissues rather than poorly differentiated ones [75]. A study by Sugai et al. (2022) revealed that the high expression of TFF1 is associated with sessile serrated lesions (SSLs) compared to traditional serrated adenoma (TSA) and tubular adenoma (TA) at the mRNA and protein levels. Therefore, it serves as a prognostic marker for SSLs, as SSLs are precursors of colorectal carcinoma [76]. Hyperplastic polyps (HPs) are benign, but traditional serrated adenomas (TSAs) and sessile serrated adenomas/polyps (SSA/Ps) can lead to CRC. Immunohistochemical expression of TFF1 was observed in SSA/Ps compared to HPs, indicating the potential of TFF1 as an early prognostic marker [77].

4.5. Pancreatic Cancer

Arumugam et al. (2015) investigated the expression of TFF1 in pancreatic cancer and found that TFF1 expression in preneoplastic cells, compared to human pancreatic stellate cells, increases cell invasion rather than proliferation. Its ectopic expression increases metastasis, thus enhancing the aggressiveness of the cancer [78]. TFF1 is suggested as a urinary prognostic marker for the early detection of pancreatic adenocarcinoma [79]. TFF1 is expressed in PanIN lesions in familial pancreatic cancer, as revealed by transcriptomic analysis [80]. A study by Jahan et al. (2019) found that TFF1 was the highly expressed gene in a publicly available cancer genome dataset and was found to be upregulated compared to benign and chronic pancreatitis control groups in genomic datasets, IHC protein levels, and serum levels [81]. In another study, Yamaguchi et al. (2024) revealed that the TFF1 acts as a tumour suppressor and inhibits EMT and cancer stemness, which enhances chemosensitivity. This indicates that TFF1 therapy can be a promising therapy for pancreatic cancer [82]. Both in vitro and in vivo studies have revealed that TFF1 increases sensitivity to gemcitabine, enhances stemness, migration, and induces anti-apoptotic genes. It also promotes proliferation via the pAkt/pERK pathway and binds to CXCR4, which

in turn increases resistance [83]. Taken together, TFF1 functions as a dual sword; it increases PanIN tumourigenesis while also suppressing epithelial–mesenchymal transition and chemosensitivity.

4.6. Prostate Cancer

TFF1 is not expressed or expressed at low levels in normal prostate tissues [84]. Recent in vitro studies have revealed that TFF1 promotes the migration and invasion of prostate cancer cells. Furthermore, TFF1 expression suppresses E-cadherin, an epithelial marker, thereby promoting epithelial to mesenchymal transition and leading to metastasis in vivo [84]. Another study by Radloff et al. (2011) validated the expression and found that prostate intraepithelial neoplasia shows higher TFF1 expression than normal prostate tissue, although this does not correlate with stage-specific carcinoma. They showed that TFF1 is necessary for tumour growth in vivo and reported that TFF1 promotes tumourigenesis by suppressing oncogene-induced senescence [85]. Abdou et al. (2008) reported that TFF1 is highly expressed in prostate carcinoma (91.4%) and serves as a prognostic marker for metastatic prostate carcinoma with 74.19% accuracy, 91.48% sensitivity, and 78.18% positive predictive value [86]. Thus, TFF1 can potentially serve as a prognostic and/or diagnostic marker for prostate cancer and metastasis.

4.7. Lung Cancer

TFF1 has a protective role in the lungs, but its expression in lung cancer is context-dependent. Minegishi et al. (2021) studied the role of TFF1 in 12 lung cancer cell lines and found that TFF1 decreased proliferation, increased caspase-3/-7 mediated cell death, and suppressed invasion and migration, which shows TFF1 serves as a tumour suppressor in this context [87]. In another study, they evaluated serum and urine levels of TFF1 and found that TFF1 was highly expressed in the early pathological T stage and can serve as a marker for human lung cancer [88]. Fan et al. (2024) demonstrated that knocking down TFF1 suppresses cell proliferation, induces apoptosis in vitro, and suppresses tumour growth in vivo [89]. These findings suggest that TFF1 could serve as a prognostic marker in lung cancer.

Table 2. Role(s) of trefoil factor family (TFF) in different cancers.

Cancer Type	Sample Type	TFF1 Role	References
Breast Cancer	In vitro (MCF7 and T47D cell lines)	Oncogenic driver	[59]
	In vitro (MCF7 cell line)	Oncogenic driver	[60]
	26 metastatic and 24 non-metastatic breast cancer patients, 14 healthy controls	Oncogenic driver	[61]
	In vitro (MCF-7 and MDA MB231 cell lines)	Oncogenic driver	[62]
	In silico database, in vitro (TNBC, MDA-MB-231, and the ER+BC cell line, MCF-7 cell line), serum samples from 35 patients with TNBC, 35 patients with non-TNBC, and 32 healthy controls	Tumour suppressor	[64]
	In vitro (MCF7, ZR75.1, MDA-MB-231, and MCF10A cell lines) and mice model	Tumour suppressor	[63]
	In silico, in vitro (MCF7 cell line), patients, tumour xenograft mouse models	Oncogenic driver	[65]

Table 2. Cont.

Cancer Type	Sample Type	TFF1 Role	References
Gastric Cancer	Gastric adenocarcinoma cell lines (BGC823 and SGC7901), normal gastric epithelial cell line (GES-1 cells)	Tumour suppressor	[66]
	In vivo (mice), AGS cell line, tissue microarrays containing cores from paraffin-embedded stomach tissue samples (39 normal mucosa, 43 gastritis, 88 intestinal metaplasia, 27 dysplasia, and 102 adenocarcinoma)	Tumour suppressor	[67]
	In vitro (AGS cell line), in vivo (mice)	Tumour suppressor	[68]
	In vitro (AGS cell line)	Tumour suppressor	[69]
	TMA108 paraffin-embedded gastric cancer tissue samples, in vitro (AGS, STKM2 cell line), in vivo (mice)	Tumour suppressor	[70]
Ovarian Cancer	In vitro (OMC-3, MCAS, and CaOV-3 cell lines)	Oncogenic driver	[71]
	95 stage I-II OCs, 206 stage I-II ovarian cancers stratified by histotype: (high-grade serous carcinoma (HGSC), endometrioid carcinoma (EC), clear cell carcinoma (CCC), and mucinous carcinoma (MC)	Oncogenic driver	[72]
	149 tumour types and 76 normal human tissue (TMA) samples	Oncogenic driver	[73]
Colorectal Cancer	75 tumour samples, 47 matched normal controls, 30 metastatic lymph nodes, and 10 metastatic livers, in vitro (HIEC cell line)	Tumour suppressor	[75]
	Cohort 1: 12 sessile serrated lesions (SSLs) and 5 traditional serrated adenoma (TSAs), and 15 tubular adenomas (TAs); cohort 2: 24 serrated tumours (15 SSLs and 9 TSAs) and 15 TAs; cohort 3: 72 colorectal tumours	Tumour suppressor	[76]
	20 SSLs, 17 TSAs, 23 TAs, and 12 hyperplastic polyps (HPs)	Tumour suppressor	[77]
Pancreatic Cancer	In vitro (HPAF II, HPAC, Capan-I, Capan-II, SUR 99, BxPc3, Mpanc-96, CFPAC-1, Panc-1, HPDE, MOH, OSN-1, and SU 86.86 pancreatic cancer cell lines), primary tumours and normal and pancreatitis tissues, in vivo (mice)	Oncogenic driver	[78]
	Publicly available cancer datasets, human tissue microarray, in vivo (mice), pancreatic cancer patient serum	Oncogenic driver	[81]
	Pancreatic cancer samples, in vitro (pancreatic cancer cell lines), in vitro (mice)	Tumour suppressor	[82]
	In vitro (SW1990, COLO357, PDAC cell lines), TCGA and GTEx databases of pancreatic adenocarcinoma (PAAD)	Oncogenic driver	[83]
Prostate Cancer	In vitro (DU145 and PC3 cell lines), in vivo (mice)	Oncogenic driver	[84]
	In vitro (PC3 cell line), in vivo (mice)	Oncogenic driver	[85]
	15 benign prostate hyperplasia (BPH) and 47 prostate carcinomas	Oncogenic driver	[86]
Lung Cancer	In vitro (H1650, H1975, SQ5, H1299, A549, PC-3, SBC-3, SBC-5, SmCC, LK2, EBC-1, and Lu-99 cell lines)	Tumour suppressor	[87]
	Serum and urine samples of 199 patients with lung cancer and 198 healthy individuals	Tumour suppressor	[88]
	In vitro (LEWIS and TE1 cell lines), TCGA database analysis, in vivo (mice)	Oncogenic driver	[89]

5. TFF1 in Retinoblastoma and Its Possible Role as Biomarker, Mediator, or Therapeutic Target

The complexity of retinoblastoma arises from its genetic, clinical, and biological heterogeneity. Genetically, the disease is driven by the inactivation of the *RB1* tumour suppressor gene, which can occur as germline (heritable) or sporadic (non-heritable) mutations. Besides *RB1*, many other genomic alterations, such as chromosomal instability and chromothripsis, are also involved. Additionally, it can be bilateral or unilateral. Clinically, retinoblastoma ranges from early localized tumours to advanced, aggressive disease with optic nerve invasion, choroidal infiltration, and metastatic spread. Biologically, tumours vary in aggressiveness. Such high heterogeneity contributes to variable outcomes and underscores the need for risk-adapted and targeted treatment strategies.

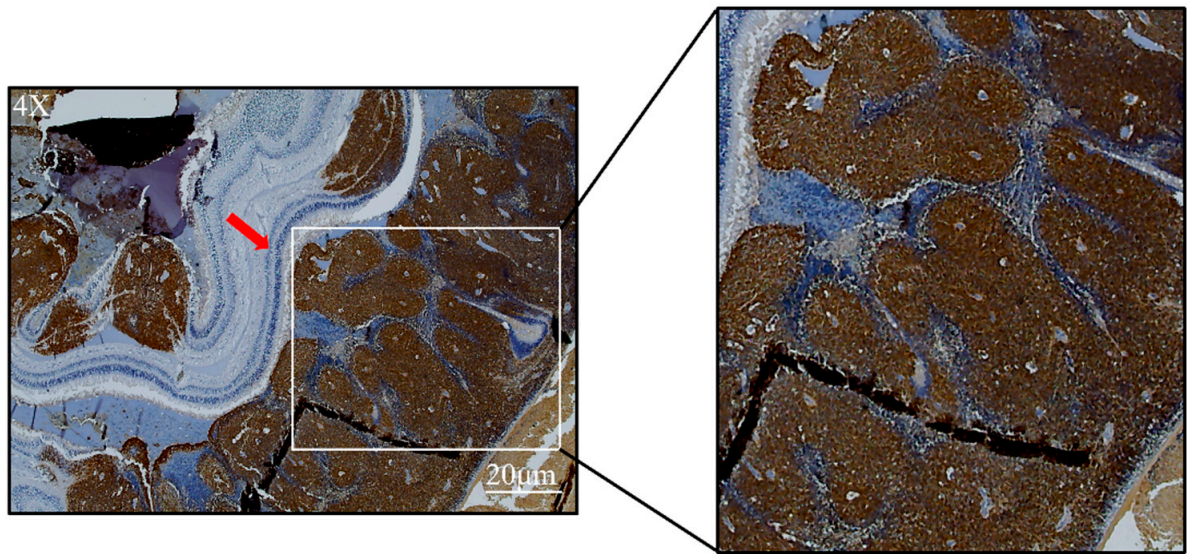
TFF1 is overexpressed in high-risk retinoblastoma but not in healthy retina, which has made it a potential biomarker (Figure 4) for high-risk retinoblastoma in recent years. A study by Weise and Dunker (2013) dissected the role and function of TFF1 in retinoblastoma cell lines in vitro and showed that TFF1 is a negative regulator of cell viability and proliferation by selectively downregulating CDK6, indicating that TFF1 is a tumour suppressor gene [24]. Philippeit et al. (2014) reported high endogenous TFF1 expression in retinoblastoma cell lines, driven by the epigenetic hypomethylation of the promoter CpG island [90]. Busch et al. (2017) demonstrated that exogenous TFF1 expression positively regulated apoptosis in retinoblastoma both in vitro and in vivo, and decreased cell growth, proliferation, and tumour development by downregulating p53 and miR-18a, suggesting a tumour suppressor role for TFF1 [91]. Also, higher levels of TFF1 were found in unilateral tumours with more advanced clinical tumour node metastasis and poorly differentiated tumours [22]. TFF1 is one of the highly expressed genes in subset 2, the patients associated with metastasis [23]. Aschero et al. (2024) have shown that TFF1 is an independent marker for poor prognosis in retinoblastoma via immunohistochemical expression [21]. The apparent paradox between the tumour-suppressive activity of TFF1 in experimental models and its enrichment in high-risk tumours likely reflects context-dependent signalling, compensatory expression, and selection in stressed or treatment-exposed tumour subpopulations. Consequently, TFF1 should be interpreted as a state-dependent biomarker rather than an intrinsic determinant of tumour aggressiveness.

Given the contraindications of eyeball tissue biopsy for tumour tissue due to the risk of tumour cell dissemination, studies have explored the use of liquid biopsy to identify tumour signatures. TFF1 has been studied in aqueous humour biopsy, and its expression was found in aqueous humour via ELISA and Western blot, validated by primary cell culture and supernatants. It was also explored in patients undergoing therapy, showing promising results as a non-invasive biomarker [20,92]. These studies have supported the emergence of TFF1 as a potential marker for high-risk retinoblastoma patient subtypes and its non-invasive detection for treatment monitoring. A summary of retinoblastoma-specific studies of TFF1 is presented in Table 3.

Ideally, a biomarker should be specific, sensitive, clinically relevant, stable and reproducible, easy to measure by non-invasive or minimally invasive means, and cost-effective. TFF1's strength to be considered as a biomarker in retinoblastoma lies in its aberrant overexpression in aggressive retinoblastoma compared to a healthy retina and its easy measurement at the protein and mRNA levels in a non-invasive way. However, it lacks retinoblastoma specificity as it is found in many other cancers, and its establishment as a liquid biomarker and clinical validation are still warranted. Thus, at present, TFF1 can be considered as a potential or exploratory biomarker that needs further clinical validation. TFF1 shows differential expression and limited clinical association in retinoblastoma, with aberrant expression reported across transcriptomic and protein studies and suggestive links

to tumour aggressiveness. But independent cohort validation and direct functional perturbation studies in retinoblastoma-specific models are still lacking, with mechanistic insights partly extrapolated from other epithelial cancers. Thus, the role of TFF1 as a mediator of retinoblastoma has yet to be established. With respect to therapeutic targeting, TFF1 shows functional relevance and practical targetability due to its extracellular/secretory nature; however, pathway redundancy and the lack of tumour exclusivity limit its suitability as a standalone target. Thus, at present, TFF1 is best viewed as a candidate biomarker and potential adjunct or experimental therapeutic target, rather than a validated primary therapeutic target in retinoblastoma.

(A)



(B)

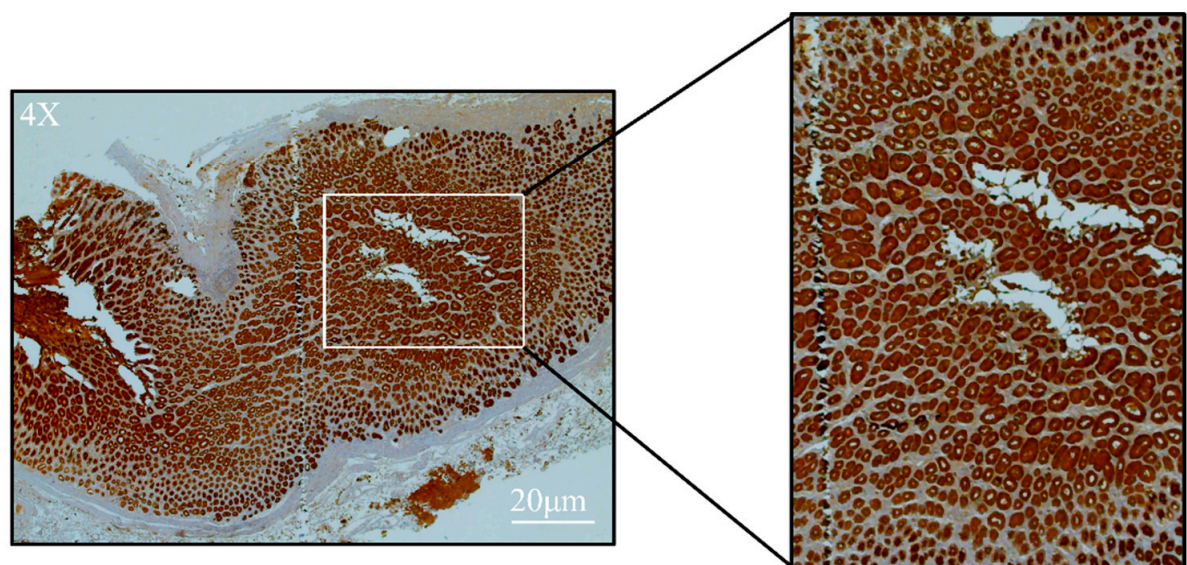


Figure 4. Expression of TFF1 in retinoblastoma (A) and gastric epithelium (positive control) (B): Human retinoblastoma with high expression of TFF1 is shown in (A), along with an unaffected retina showing no TFF1 (indicated with red arrow). The right-side image is the enlarged view of the inset shown in the left-side image. (B) TFF1 expression in the gastric epithelium as a positive control. The right side image is the enlarged view of the inset shown in the left side image. Magnification used is 4× objective, and the scale bar is 20 μm.

Table 3. Role(s) of trefoil factor family (TFF) in retinoblastoma.

Group/Model	Sample Type	Sample Size	Key Outcome	Interpretation	Reference
In vitro	Human retinoblastoma cell lines	N = 8 (RBL-13, RBL-15, RBL-30, RB 247C3, RB 355, RB 383, Y-79, and WERI-Rb1)	Rb cell lines with high TFF1 expression levels exhibited a selective downregulation of cyclin-dependent kinase (CDK) 6	Tumour suppressor role of TFF1	[24]
In vitro	Human retinoblastoma cell lines	N = 8 (RBL-13, RBL-15, RBL-30, RB 247 C3, RB 355, RB 383, WERI-Rb1, and Y-79	Regulation of TFF1 expression in Rb cell lines requires the involvement of additional mechanisms	TFF1 may be regulated by epigenetic regulation, but requires additional mechanisms	[90]
In vitro and in vivo	Human retinoblastoma cell lines	N = 3 (Y79, RB355, and RBL-30)	Overexpression of TFF1 induces apoptosis and decreases proliferation and tumour growth of human retinoblastoma cell lines in a p53- and caspase-dependent manner, with implicated miR-18a regulation	Tumour suppressive and pro-apoptotic role	[91]
Retinoblastoma Patients	Tumour tissue and post-mortem retinal tissues	N = 59 (29 males and 30 females), 41 unilateral and 18 bilateral tumour cases	Increased TFF1 expression significantly correlates with unilateral tumours diagnosed in older children and with poorly differentiated tumours and higher tumour-node-metastasis stages	Unilateral tumours at a higher clinical tumour-node-metastasis stage and poorly differentiated tumour cells express significantly higher levels of TFF1 than those of differentiated tumours at lower tumour-node-metastasis stages	[22]
Retinoblastoma Patients	Tumour tissue, HRPf-specific fetal retinal tissue	N = 102 (50 males and 52 females) N = 112 (51 males and 61 females) N = 3	TFF1 highly expressed in more aggressive subset 2, associated with cone dedifferentiation and expression of neuronal markers	Linked to aggressive patient having metastatic potential	[23]
Retinoblastoma Patients	Tumor tissue	N = 273 (sex not specified)	Non-mutually exclusive expression of ARR3 and TFF1 had an increased risk of relapse and death	Validated prognostic biomarker	[21]

Table 3.
 Cont.

Group/Model	Sample Type	Sample Size	Key Outcome	Interpretation	Reference
Retinoblas- toma Patients	Tumour tissue, aqueous humour, and human retinoblastoma cell lines	N = 15 (sex not specified) Cell lines = 2 (Rb113 and Rb130)	Nine out of fifteen aqueous humour patient samples exhibited TFF1 expressions, which correlated well with TFF1 levels of the original tumour. TFF1 expression in most of the corresponding primary cell cultures reflects the levels of the original tumour, although not all TFF1-expressing tumour cells seem to secrete into the aqueous humour	Potential biomarker	[20]
Retinoblas- toma patients	Tumour tissue and aqueous humour, blood and aqueous humour from retinoblastoma patients under therapy and healthy controls	N = 8 (sex not specified) N = 7 (sex not specified), and N = 6 (sex not specified)	TFF1 consistently detectable in aqueous humour, confirming its potential as a biomarker. TFF1-secreting cells within the tumour mass originate from retinoblastoma tumour cells, not from surrounding stromal cells. IVC therapy-responsive patients exhibited remarkably reduced TFF1 levels post-therapy	TFF1 in aqueous humour of retinoblastoma patients potentially provides a minimally invasive tool for monitoring retinoblastoma therapy efficacy	[92]

6.
 Conclusions

Retinoblastoma is a significant clinical and public health burden, especially in low- and middle-income countries where delays in diagnosis and limited resources often result in children presenting with advanced diseases. While the loss of *RB1* remains the central initiating event, growing evidence suggests that this single event does not fully present the complexity of how retinoblastoma progresses. A wide range of molecular alterations influences disease progression, invasion, and response to therapy. Among these, Trefoil Factor 1 (TFF1) has emerged as an unexpectedly important player.

TFF1 is a multifaceted molecule with cancer-type- and context-dependent functions. Across malignancies, TFF1 displays a dual role, acting either as a tumour suppressor or as an oncogenic driver. Its divergent behaviour is evident when comparing cancers such as gastric and lung cancer, where TFF1 predominantly exerts protective effects, to breast, ovarian, prostate, colorectal, and pancreatic cancers, where its role varies with molecular subtype, stage, and microenvironment. Importantly, TFF1 expression frequently correlates with tumour differentiation status, metastatic potential, therapeutic response, and patient prognosis. These attributes position TFF1 as a promising diagnostic and prognostic biomarker across multiple malignancies. However, its paradoxical functions necessitate its cancer and context-specific interpretation. TFF1 is normally absent in the healthy human retina, but its appearance in retinoblastoma, especially in tumours with aggressive clinical features, has drawn increasing interest in recent years. Multi-omics studies have revealed that an elevated level of TFF1 is associated with high-risk subtypes, where it aligns closely with poor differentiation, metastatic potential, and adverse outcomes.

This strong association of TFF1 with aggressive disease underscores that it is far more than a passive bystander.

In retinoblastoma, one of the most promising developments has been the ability to detect TFF1 in the aqueous humour. Since direct tumour biopsy is unsafe in retinoblastoma, the possibility of using liquid biopsy markers to follow tumour activity represents a major step forward. The presence of TFF1 in these samples and its apparent correlation with tumour behaviour and treatment response point toward a practical and minimally invasive tool for diagnosis and risk assessment. This is particularly valuable in settings where early detection and close follow-up remain difficult. However, the interpretation of aqueous humour TFF1 should account for pre-analytical factors, including treatment timing, ocular inflammation, and hemorrhage, which may introduce biological variability. Additionally, current assays demonstrate that feasibility, standardization, range validation, and sensitivity optimization are needed for longitudinal use. Thus, at present, TFF1 is best positioned as part of a multi-analyte aqueous humour biomarker panel rather than a standalone indicator. Beyond its diagnostic value, TFF1 may also hold therapeutic potential. Its involvement in pathways related to cell-cycle control, epigenetic regulation, and tumour microenvironment interactions suggests that disrupting TFF1-mediated signalling could benefit a subset of patients, including those whose tumours progress independently of *RB1* loss. However, more work is needed to unravel these mechanisms and determine whether TFF1 is a driver, a modifier, or part of a broader oncogenic programme.

Taken together, the evidence places TFF1 at an important intersection of tumour biology, clinical behaviour, and potential translational utility in retinoblastoma. Its selective expression in high-risk disease, detectability through non-invasive means, and possible functional significance highlight its promise as a biomarker, a mediator and a target worth exploring further. Continued research will be essential to validate its clinical usefulness, clarify its mechanistic role, and incorporate it into strategies that can improve outcomes, particularly for children in regions where retinoblastoma remains a life-threatening diagnosis.

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