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Review

The G protein-coupled receptor GPRC5A—a phorbol ester and retinoic acid-induced orphan receptor with roles in cancer, inflammation, and immunity

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Abstract

GPRC5A is the first member of a new class of orphan receptors coupled to G proteins, which also includes GPRC5B, GPRC5C, and GPRC5D. Since its cloning and identification in the 1990s, substantial progress has been made in understanding the possible functions of this receptor. *GPRC5A* has been implicated in a variety of cellular events, such as cytoskeleton reorganization, cell proliferation, cell cycle regulation, migration, and survival. It appears to be a central player in different pathological processes, including tumorigenesis, inflammation, immune response, and tissue damage. The levels of *GPRC5A* expression differ depending on the type of cancer, with increased expression in colon, pancreas, and prostate cancers; decreased expression in lung cancer; and varied results in breast cancer. In this review, we discuss the early discovery of *GPRC5A* as a phorbol ester-induced gene and later as a retinoic acid-induced gene, its regulation, and its participation in important canonical pathways related to numerous types of tumors and inflammatory processes. *GPRC5A* represents a potential new target for cancer, inflammation, and immunity therapies.

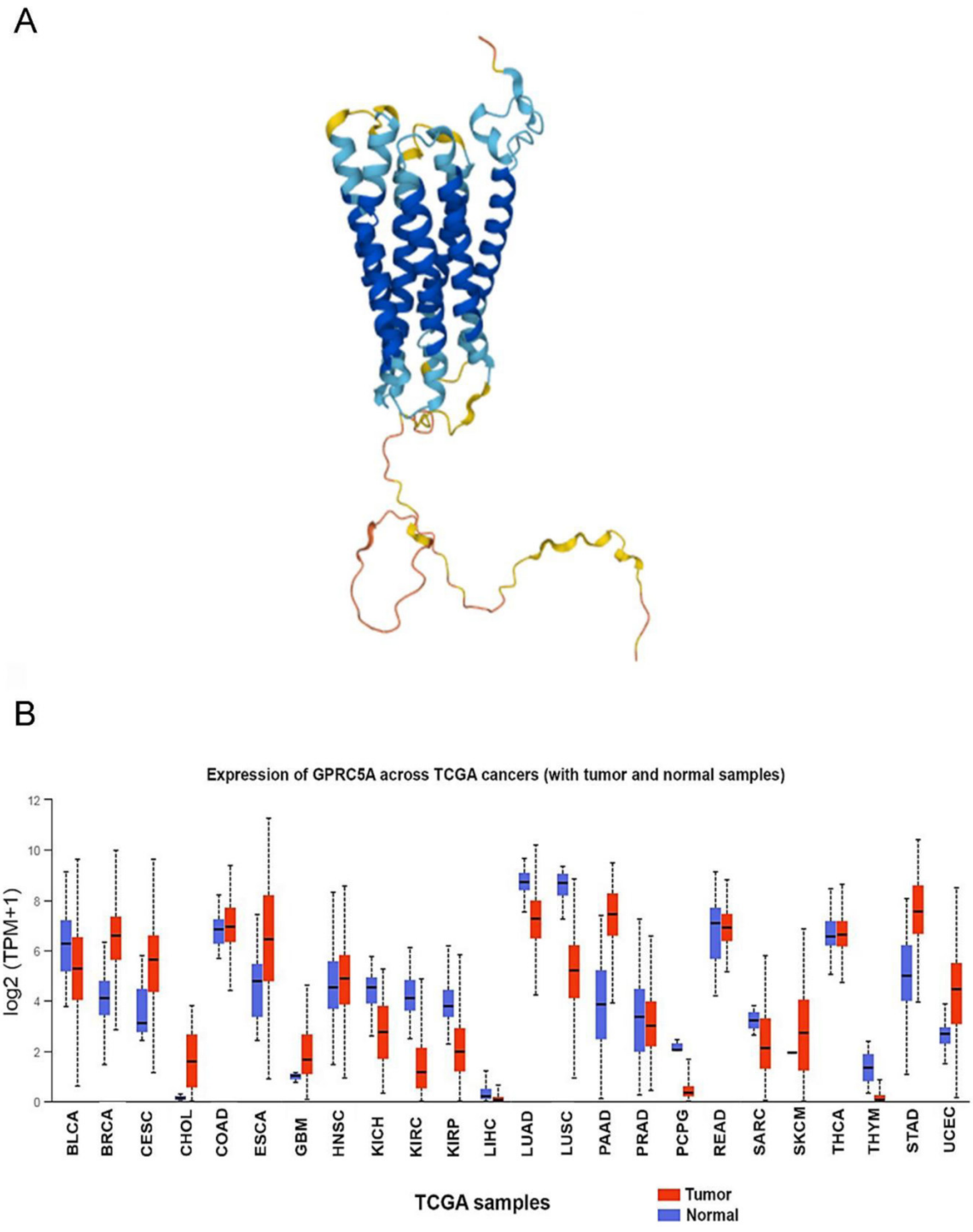
Key words: GPRC5A, cancer, immunity, inflammation, signaling

1. Introduction

The GPRC5A receptor is a member of the *G-protein-coupled receptors* (GPCRs) family (Zhou and Rigoutsos 2014). The mRNA for this receptor was initially discovered, cloned, partially sequenced, and characterized in our laboratory using differential display while searching for genes that responded to the presence of the tumor promoter *12-O-tetradecanoylphorbol-13-acetate* (TPA, PMA) in T84 colon carcinoma cells (Cafferata et al. 1995, 1996; Cafferata 2002). Initially, we named this gene "TPA-induced gene 1" with the symbol *TIG1* (later deposited as BE519991) due to its regulation by TPA. However, as another gene had the same symbol, "retinoic acid receptor responder (tazarotene-induced) 1", we renamed it "phorbol ester-induced gene 1" with the symbol *PEIG-1* (AF506289.1, AAM77594.1) (Cafferata 2002). Later, Cheng and Lotan also discovered this mRNA, now expressed in the squamous carcinoma cell line UMSCC-22B stimulated with retinoic acid (RA) and named the gene "retinoic acid-induced gene 1" with the symbol RAIG1 (NM_003979). The HUGO Genome Nomenclature Committee (HGNC) then approved the name "retinoic acid-induced 3" with the symbol RAI3 (Cheng and Lotan 1998). The official HGNC name is now "G protein-coupled receptor class C group 5 member A", with the symbol *GPRC5A* (genenames.org). Based on the published *GPRC5A* sequence, the other three members of this family were found by Robbins et al. (2000), Bräuner-Osborne and Krogsgaard-Larsen (2000), and Bräuner-Osborne et al. 2001), and include *GPRC5B*, *GPRC5C*, and *GPRC5D*. We later extended the original sequence (Cafferata et al. 1995, 1996; Cafferata 2002) and recently further characterized its TPA response (Mori 2020; Mori et al. 2020).

GPRC5A, like the other members of this family, is composed of seven transmembrane alpha-helix domains, an extracellular N-terminal domain, and an intracellular C-terminal domain. The predicted 3D structure of GPRC5A, generated by AlphaFold 2 (alphafold.ebi.ac.uk/entry/Q8NFJ5), is presented in Fig. 1A. A distinctive feature of the four GPRC5 receptors is the short N-terminal domain, which ranges from 20 to 53 amino acids in length (Zhou and Rigoutsos 2014; Mori et al. 2020). This suggests that the ligand might be a small molecule, or even an ion, which could also interact with other loops of the transmembrane regions. Notably, the N terminus of GPRC5 receptors lacks the *Venus fly trap* (VFT) ligand-binding domain, which is characteristic of class C receptors, and is the proposed binding domain for L-amino acids and other ligands of GPCR receptors (Mun et al. 2004; Cao et al. 2009). However, it has been shown that GPRC5C might function as a pH sensor, as it is internalized at alkaline pH

Fig. 1. Structure and expression of GPRC5A. (A) 3D structure of GPRC5A predicted by AlphaFold v2 (alphafold.ebi.ac.uk), available as Uniprot entry Q8NFJ5. The ligand for this G protein-coupled receptor with seven transmembrane domains is still unknown. The GPRC5 family has a noticeably short N-terminal region and a long C-terminal region. (B) Expression of *GPRC5A* in various types of primary tumors. Real-time PCR mRNA analysis was performed on samples from healthy individuals and tumor patients. Marked differences in *GPRC5A* expression levels were observed among different tumor types. BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head, and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PAAD, pancreatic adenocarcinoma; PRAD, prostate adenocarcinoma; PCPG, pheochromocytoma, and paraganglioma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; THCA, thyroid carcinoma; THYM, thymoma; STAD, stomach adenocarcinoma; UCEC, uterine corpus endometrial carcinoma. The graph was generated using UALCAN (ualcan.path.uab.edu). The values correspond to The Cancer Genome Atlas (TCGA).



(Rajkumar et al. 2018), suggesting that H^+ or OH^- could be ligands for this family of receptors. Nevertheless, other specific ligands cannot be disregarded. The GPRC5A-D family of receptors are orphan receptors since the ligands for these receptors have not yet been identified. Therefore, the nomenclature used is GPRC5A-D instead of GPCR5A-D. Recently, it has been suggested that hyaluronic acid and one of its precursors, *N*-acetyl-D-glucosamine (NAG), bind to GPRC5C and activate its signaling, maintaining a deep state of quiescence in mice and human bone marrow hematopoietic stem cells (Zhang et al. 2022). However, the pathway involved in this signaling is yet unknown.

The participation of GPRC5 receptors in various pathological processes, including inflammation, immunity, atherosclerosis, diabetes, neuropsychiatric disorders, kidney dysfunction, and several cancer types, has been increasingly evidenced (Sano et al. 2011; Zhou and Rigoutsos 2014; Amisten et al. 2017; Ma et al. 2018; Carvalho et al. 2020). However, the mechanisms of activation and signaling for these receptors, as well as their role in diseases, are not yet fully understood.

Each receptor exhibits a characteristic distribution pattern. The highest expression of *GPRC5A* mRNA has been found in the lungs and, to a lesser extent, in the thyroid gland, small intestine, urinary bladder, colon, and ovary (Cheng and Lotan 1998; Zhou and Rigoutsos 2014) (Fig. 1B). GPRC5B is predominantly expressed in tissues from the central nervous system and has been implicated in behavioral changes and motor learning, affecting the synapsis of Purkinje cells during cerebellar development (Sano et al. 2011, 2018). Additionally, this receptor controls smooth muscle contractibility and differentiation by inhibiting prostacyclin receptor signaling (Carvalho et al. 2020). On the other hand, GPRC5C, which appears to behave as a pH sensor, plays a role in blood and urine pH homeostasis as well as glucose-stimulated insulin secretion (Amisten et al. 2017; Rajkumar et al. 2018). Meanwhile, GPRC5D has been identified as a key marker in multiple myeloma, and its expression has been observed in a wide variety of tissues (Bräuner-Osborne et al. 2001).

GPRC5A is primarily located in the plasma membrane, although it has also been observed in cytoplasmic organelles such as the endoplasmic reticulum, the Golgi system, and perinuclear vesicles (Cheng and Lotan 1998; Zougman et al. 2013; Mori 2020; Mori et al. 2020) (see "The Human Protein Atlas", proteinatlas.org). Recently, GPRC5A has been found to be present extracellularly in exosomes from urine, along with GPRC5B, and GPRC5C, and this combination is being considered a possible biomarker of bladder cancer (Gonzales et al. 2009; Murakami et al. 2018). Although the *GPRC5A* gene has been primarily studied in humans, mice, and rat models, it has also been detected in other species, including chimpanzees, rhesus monkeys, dogs, cows, chickens, and frogs. There are approximately 203 organisms with orthologs of the human *GPRC5A* gene (GenBank nucleotide data; ncbi.nlm.nih.gov/nuccore/GPRC5A). In this review, we focus on the main findings regarding the regulation of GPRC5A and its role in cancer, inflammation, and immunity.

2. Regulation of GPRC5A expression

In the following sections, we will examine the regulation of GPRC5A and its involvement in various biological processes.

2.1. Transcriptional regulation

As mentioned earlier, the transcriptional activity of *GPRC5A* in T84 carcinoma cells can be stimulated by incubation with the phorbol ester TPA or by using OAG (1-oleoyl-2-acetyl-sn-glycerol), a permeable analog of diacyl-glycerol (DAG), through a DAG/Ca^{2+}-dependent classical PKC pathway (Cafferata et al. 1995, 1996; Cafferata 2002; Mori 2020; Mori et al. 2020) (Fig. 2). However, the specific PKC involved in this process has not been identified yet. Lotan's laboratory later rediscovered this gene while searching for RA-inducible genes (Cheng and Lotan 1998; Ye et al. 2009). The upregulation of *GPRC5A* induced by TPA and RA will be further discussed in the following paragraphs.

2.1.1. Phorbol ester TPA

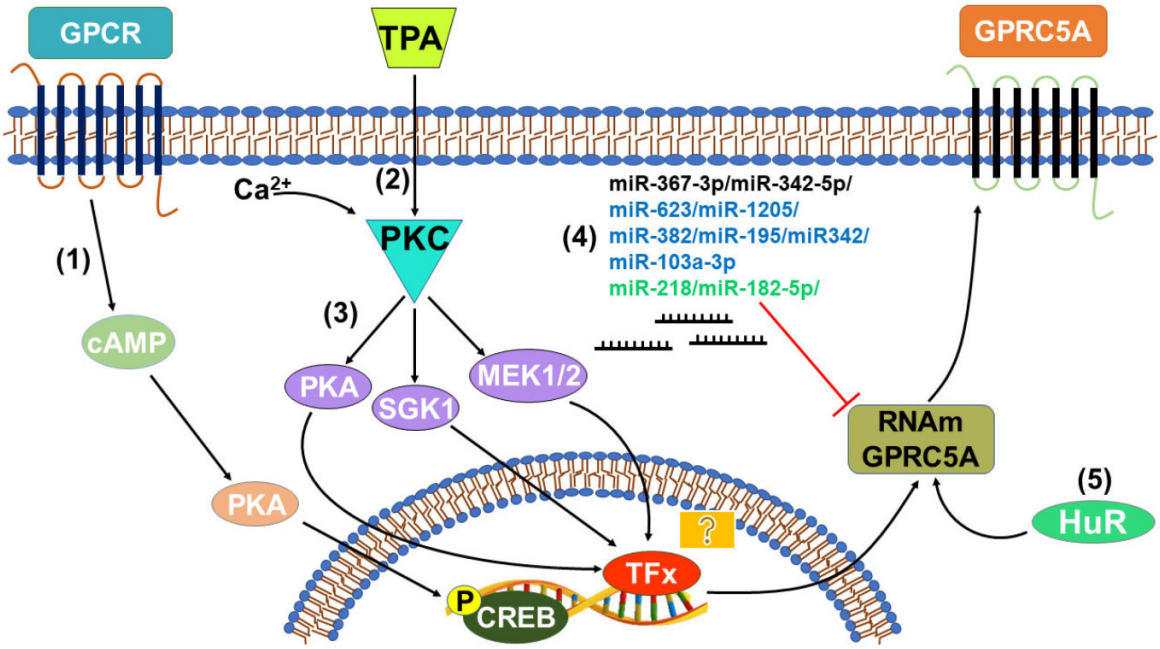
We demonstrated a strong upregulation of GPRC5A expression (20- to 40-fold stimulation) in T84 colon carcinoma cells upon stimulation with the phorbol ester TPA. The highest levels of GPRC5A mRNA were observed after 4 h of TPA treatment, leading to the appearance of distinct Western blot bands (Mori 2020; Mori et al. 2020), which can be attributed to different degrees of GPRC5A glycosylation (Cheng and Lotan 1998). The positive regulation of GPRC5A is primarily attributed to the activation of PKC (Fig. 2). Inhibition of this kinase using Gö6983 effectively blocked the upregulation of GPRC5A induced by TPA. Additionally, approximately 50% inhibition was observed when Ca^{2+} was chelated with BAPTA-AM, suggesting the involvement of a Ca^{2+}-dependent classical PKC (cPKC) pathway in the response to TPA. Other nonclassical PKCs, such as PKCη (PKC eta), might account for the stimulation by TPA independent of Ca^{2+}, as occurs with mTORC1 activation by cPKC and PKCη (Liu et al. 2017*b*). Thus, it would be of interest to identify the specific PKC isoforms involved in *GPRC5A* regulation.

The inhibition of the MEK1/2 pathway with U0126 also led to a reduced *GPRC5A* response to TPA (Mori 2020; Mori et al. 2020). This result suggests that TPA may regulate *GPRC5A* expression in these cells through the PKC/Ca^{2+} → MEK1/2 pathway (Fig. 2). In contrast, the inhibition of the c-Jun N-terminal kinase (JNK) with SP600125 enhanced the TPA-induced upregulation of GPRC5A (Mori 2020; Mori et al. 2020). Although response elements for AP-1 (FOS and JUN) have been identified in the GPRC5A promoter sequence (Zhou and Rigoutsos 2014), it remains unknown whether AP-1 can bind to these response elements and modulate GPRC5A expression.

2.1.2. Retinoic acid

In their investigation of regulatory elements in the GPRC5A promoter, Ye et al. identified three potential retinoic acid response elements (RAREs), consisting of two RAR/retinoid X receptor (RXR) binding sites and one VDR/RXR binding site (Ye et al. 2009). These binding sites were located within three di-

Fig. 2. Regulation of the *GPRC5A* gene by cAMP, TPA, miRs, and HuR. The cAMP → PKA → CREB signaling pathway stimulates *GPRC5A* expression (1). TPA, an analog of diacylglycerol (DAG), positively modulates the messenger and protein levels of *GPRC5A* (2), an effect that was inhibited by the PKC inhibitor Gö6983. The inhibition of TPA-stimulated *GPRC5A* expression by BAPTA in T84 cells suggests the involvement of a Ca^{2+}-dependent PKC. In turn, PKC activates PKA, SGK1, and MEK1/2 (3), as suggested using the PKA inhibitor H-89, the MEK inhibitor U0126, and the SGK1 inhibitor GSK650394. The protein levels of GPRC5A can be reduced by the degradation of its mRNA by miRs (4). The RNA-binding protein HuR (5) increases GPRC5A levels by stabilizing its mRNA through binding to the 3'UTR region.



rect repeat 5 (DR5) motifs in the proximal 5′ upstream region, specifically referred to as DR5I (−489 to −473), DR5II (−136 to −120), and DR5III (−81 to −65). However, only DR5III (VDR/RXR) was found to be a functional RARE, mediating GPRC5A induction (Fig. 3A). The binding of retinoic acid receptors (RAR) α and γ, as well as RXRs α and β, to DR5III in intact cells was confirmed through a chromatin immunoprecipitation assay. The canonical pathway of RA signaling for GPRC5A has not been thoroughly explored, and the repressors and activators associated with these RAREs in this promoter have yet to be identified.

2.2.3. Additional transcription factors involved in GPRC5A regulation.

In addition to the previously mentioned RA and AP-1 (FOS/JUN) response elements, the *GPRC5A* promoter sequence includes binding sites for CREB, P53, BRCA1 (Zhou and Rigoutsos 2014), and HIF (Greenhough et al. 2018).

2.2.4. CREB

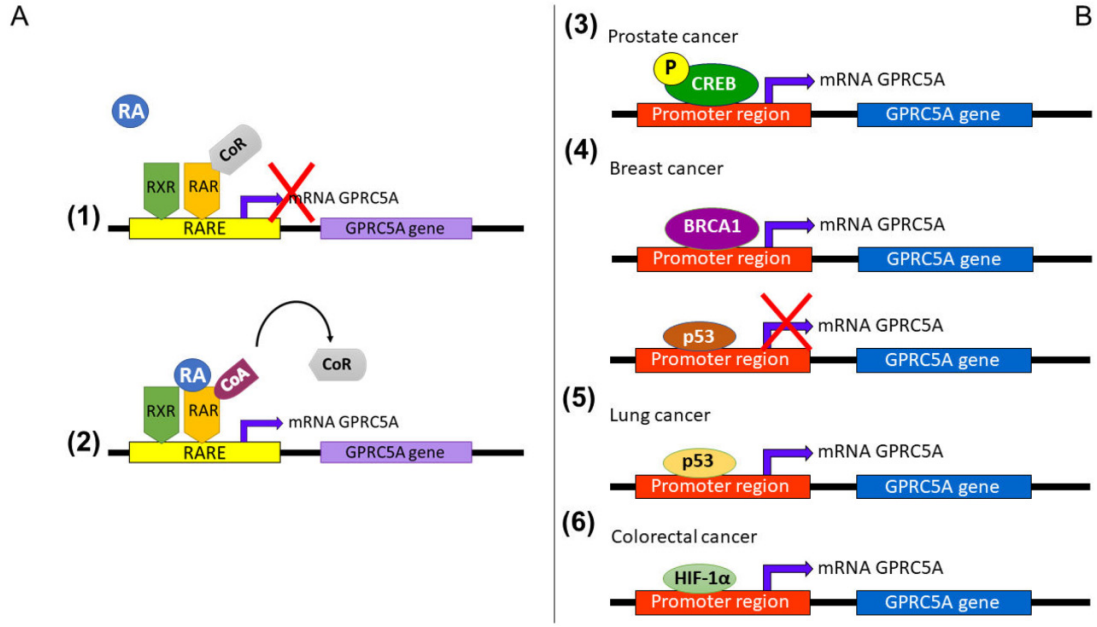
The transcription factor *cAMP response element-binding protein* (CREB) belongs to the canonical GPCR → *adenylate cyclase* (AC) → cAMP → PKA → CREB signaling pathway (Fig. 2) (Mayr and Montminy 2001; Wang et al. 2018). Interestingly, the promoter region of *GPRC5A* contains binding sites for CREB, located at the proximal 5′ end (Zhang et al. 2005; Zhou and Rigoutsos 2014). When Hirano et al. investigated the promoter region of GPRC5A, they found that only the CRE motif located −50 to −43 bp upstream from the transcription initiation site was responsible for the GPRC5A response to cAMP. Furthermore, cAMP and RA synergistically regulate GPRC5A expression (Hirano et al. 2006). Recently, we also showed that PKA inhibition using the pharmacological inhibitor H-89 decreased TPA-induced expression of *GPRC5A*, suggesting that PKA is partially involved in the GPRC5A response to TPA (Mori 2020; Mori et al. 2020). In addition, as will be discussed when considering its downstream signaling, GPRC5A inhibits cAMP production and CREB phosphorylation (Sawada et al. 2020). Thus, GPRC5A and CREB reciprocally modulate each other in opposing ways.

2.2.5. TP53

The *tumor protein p53* (TP53) is a transcription factor that plays a critical role in regulating a diverse set of genes essential for normal cellular functions, including DNA repair, apoptosis, cell cycle arrest, cell metabolism, and antioxidant defense (Levine and Oren 2009). Mutations in the exonic regions of the *TP53* gene, particularly in the DNA-binding domain, significantly alter these cellular processes, contributing to the development of various types of cancer (Zhang et al. 2020*a*).

As illustrated in Fig. 3B, it has been demonstrated that in breast cancer, the binding of TP53 to the promoter region of

Fig. 3. Regulation of the *GPRC5A* gene by the VDR/RXR, BRCA1, P53, and HIF transcription factors. (A) In the absence of retinoic acid (RA), *GPRC5A* expression is repressed (1). Upon binding of RA, the repressor is released, and transcription begins (2). The GPRC5A promoter contains three potential retinoic acid response elements (RAREs), two of which correspond to RAR/RXR binding sites and one to a VDR/RXR binding site. However, only the VDR/RXR site was found to be a functional RARE in mediating *GPRC5A* induction. (B) In prostate cancer, CREB upregulates *GPRC5A* expression (3). In breast cancer, the tumor suppressor BRCA1 positively regulates *GPRC5A* expression, while p53 represses *GPRC5A* expression (4). Conversely, in lung cancer, p53 has been found to positively affect *GPRC5A* expression (5), although the reasons for these apparently contradictory results are unknown. On the other hand, in colorectal cancer cells, HIF-1α induces *GPRC5A* gene expression (6).



the *GPRC5A* gene can reduce its expression in cells at the onset of apoptosis (Wu et al. 2005). In breast tumor cell lines lacking estrogen receptors and with mutated TP53, elevated levels of *GPRC5A* mRNA expression were observed. In contrast, breast tumor cell lines with estrogen receptors and normal TP53 function exhibited lower levels of *GPRC5A* mRNA expression (Wu et al. 2005). Conversely, in non-small cell lung cancer (NSCLC) cells, studies have shown that GPRC5A may be involved in the antitumor effect of TP53. In this case, the overexpression of *TP53* induces an increased expression of *GPRC5A*, which correlates with greater apoptosis and antitumor effects (Jin et al. 2017). This dual behavior is typical of the complex regulation of TP53, which depends on multiple posttranslational modifications, including phosphorylation, myristylation, and acetylation (Arief Ichwan et al. 2012). However, the possible role of TP53's posttranslational modifications in the dual response of GPRC5A has not been studied yet.

2.2.6. BRCA1

Notably, the GPRC5A proximal promoter contains multiple BRCA1 binding sites (seven). This protein can function as either an activator or a repressor, depending on its associated proteins. However, there is currently no direct evidence regarding the activity of these response elements (Zhou and Rigoutsos 2014). In the MDA-MB-231 human breast cancer cell line, a siRNA-mediated knockdown of BRCA1 led to decreased levels of GPRC5A, suggesting that BRCA1 upregulates the expression of GPRC5A (Sokolenko et al. 2014) (Fig. 3B). This study also demonstrated that silencing the GPRC5A gene reduces the expression of BRCA1 and the formation of DNA repair foci by BRCA1, which are mediated through the RAD51 recombinase protein. The results suggest that reduced expression of GPRC5A has a detrimental effect on BRCA1-mediated DNA repair. However, direct evidence elucidating the mechanisms involved is currently lacking.

2.2.7. HIF

Recently, a new signaling pathway involving HIF-1α and GPRC5A was discovered, where hypoxia increased the expression of *GPRC5A* through HIF (Fig. 3B), and, in turn, GPRC5A activated the Hippo pathway effector YAP ("Yes-associated protein") (Greenhough et al. 2018; Zhao et al. 2020). This mechanism protected colorectal tumor cells from apoptosis during oxygen deprivation. Using the ChIP-qPCR technique, it was found that HIF-1α was able to bind to the hypoxia response element (HRE) present in the promoter region of *GPRC5A*, upregulating its expression (Greenhough et al. 2018).

2.2.8. Post-transcriptional regulation

One post-transcriptional regulatory mechanism involves *microRNAs* (miRNA or miR). Several miRs have been found to modulate *GPRC5A* expression, as detailed in Fig. 2 and Table S1 (Supplementary file). In addition to microRNAs, *GPRC5A* is regulated by *long non-coding RNAs* (LncRNAs) and *circular RNAs* (circRNAs). Several LncRNAs have been found to indirectly regulate *GPRC5A* expression, with the LncRNA DSCAM-AS1 aggravating the progression of osteosarcoma by sequestering miR-186-5p and therefore positively regulating *GPRC5A* (Ning and Bai 2021). Circular RNAs also contribute to the post-translational regulation of GPRC5A. For example, the overexpression of circular RNA circ_0000144 in gastric cancer (GC) modulates cancer progression by increasing *GPRC5A* expression through the sequestration of miR-623 (Mi et al. 2020). Additionally, the circular RNA circ-UBAP2 modulates glioma progression by sequestering miR-1205 and miR-382, leading to an increase in *GPRC5A* expression (Wang et al. 2021*a*).

On the other hand, *RNA-binding proteins* (RBPs) such as HuR, an RBP of the Elav family, may also participate in the post-transcriptional regulation of *GPRC5A* by increasing its expression through mRNA stabilization via binding to its 3′ UTR region (Zhou et al. 2016).

2.2.9. Other pathways or kinases involved in GPRC5A regulation.

Serum- and glucocorticoid-regulated kinase-1 (SGK1) is another kinase associated with *GPRC5A* regulation (Fig. 2). SGK1 shares similarity with PKC and PKA in the catalytic domain (Webster et al. 1993). Noteworthy, inhibiting SGK1 can result in an ambivalent response in *GPRC5A* expression. Specifically, under basal conditions in T84 cells without TPA, inhibiting SGK1 using GSK650394 leads to increased *GPRC5A* expression. However, in TPA-stimulated T84 cells, inhibition of SGK1 decreases *GPRC5A* expression, albeit at higher doses (Mori 2020; Mori et al. 2020). Further studies are needed to fully understand this biphasic response to SGK1. On the other hand, the pharmacological inhibition of AKT, p38, and IKK-2 (NF-κB pathway) did not influence the TPA-induced upregulation of *GPRC5A*. Under basal conditions, AKT, p38, and IKK-2 inhibitors produced a minor increase in *GPRC5A* expression, with only the AKT inhibitor demonstrating significant upregulation. However, TPA-induced *GPRC5A* expression was significantly higher when JNK was inhibited using SP600125 (Mori 2020; Mori et al. 2020). This result suggests that AP-1 does not upregulate, but rather inhibits, *GPRC5A* expression. Further studies are needed to elucidate the role of AP-1 in *GPRC5A* expression.

3. GPRC5A signaling pathways

Since the discovery of the *GPRC5A* gene, it has become increasingly clear its role in important canonical pathways that regulate processes such as cell proliferation, tumorigenesis, and inflammation. However, the underlying mechanisms remain largely unclear. Below, we describe the most well-known signaling pathways in which GPRC5A participates.

3.1. GPRC5A negatively modulates cAMP/CREB signaling

In human thyroid follicular epithelial cells *Nthy-ori 3-1* (Nthy), *GPRC5A* overexpression resulted in negative modulation of cAMP levels, which could not be inhibited by pertussis toxin, indicating that Giα was not involved in this inhibition. Rather, *GPRC5A* overexpression caused decreased Gsα mRNA expression, resulting in reduced levels of cAMP, which caused more cell death by apoptosis (Hirano et al. 2006). The reduction in cAMP levels, in turn, led to less activation of cAMP-dependent protein kinase (PKA). Additionally, *GPRC5A* overexpression caused decreased phosphorylation of CREB, leading to enhanced cell proliferation in prostate cancer cells and cancer bone metastasis (Sawada et al. 2020). Furthermore, *GPRC5A* overexpression negatively regulated the transcriptional activity of CREB (Hirano et al. 2006).

On the other hand, CREB phosphorylation was significantly increased in GPRC5A-KO PC3 prostate cancer cells, resulting in reduced expression of cell cycle genes such as CCNA2, CCNB1, CCNB2, CCND1, and CDK1, and this was associated with a cell cycle arrest in G2/M phase (Sawada et al. 2020). Thus, GPRC5A could have potential activity as a proto-oncogene in prostate cancer, favoring bone metastasis. Conversely, cAMP, through PKA → CREB signaling, increases GPRC5A expression. Consequently, the levels of GPRC5A and cAMP are mutually regulated in opposing manners (Hirano et al. 2006). In summary, a negative feedback loop seems to exist between GPRC5A and CREB, where CREB stimulates GPRC5A expression and, in turn, GPRC5A inhibits cAMP levels and CREB phosphorylation.

It should be noted that all data regarding GPRC5A have been obtained without knowing the level of GPRC5A activation since it is an orphan receptor, and no specific ligands are known yet. The identification of its natural ligand and the development of agonists and antagonists for this receptor and the rest of its family members, GPRC5B, C, and D, are therefore issues of great interest.

3.2. GPRC5A inhibits gp130-JAK-STAT3 and EGFR-cSrc-STAT3 signaling

The *signal transducer and activator of transcription 3* (STAT3) is a transcription factor that gets activated in response to stimulation with growth factors, cytokines, and peptide ligands. STAT3 regulates numerous cellular functions, including cell cycle progression, proliferation, apoptosis, angiogenesis, and immune evasion (Butturini et al. 2020). STAT3 plays a critical role in promoting tumor proliferation and survival by inhibiting the recruitment of immune cells to the tumor microenvironment (Alexandrow et al. 2012). Mechanistically, IL-6 (or another member of this family such as LIF) binds to its receptor, inducing gp130 homodimerization, activation of the *Janus kinase* (JAK), gp130 phosphorylation, and STAT3 recruitment. On the other hand, *suppressor of cytokine signaling 3* (SOCS3) binds to both the cytokine receptor subunit gp130 and *Janus kinase* (JAK), resulting in the inhibition of JAK activa-

tion, gp130 phosphorylation, and STAT3 recruitment (Carow and Rottenberg 2014).

Regarding GPRC5A, it has been observed that the activation of the Stat3 signaling pathway is more pronounced in normal and malignant epithelial cells derived from mouse trachea when *Gprc5a* is knocked out. This effect is attributed to autocrine Lif signaling through gp130 (Chen et al. 2010). Furthermore, depletion of Il-6, the key regulator of the Jak-Stat3 signaling pathway, can reverse the process of lung metastasis in *Gprc5a*-knockout mice (Jing et al. 2020). Gprc5a can suppress Stat3 activation by stabilizing Socs3. The loss of its expression leads to persistent Stat3 activation induced by autocrine Lif in normal Gprc5a$^{-/-}$ cells and in human MDA959 cells. (Chen et al. 2010). Figure 4B summarizes the GPRC5A → STAT3 pathway.

Additionally, it has been reported that *Gprc5a* deficiency in mice caused Egfr/Stat3 activation in bronchiole epithelial cells (Zhong et al. 2015). The levels of activated Egfr (p-Egfr) were higher in Gprc5a-KO mice than in Gprc5a-WT mice after incubation with the Egfr ligand. These results were further supported by the overexpression of GPRC5A in the HEK293T human cell line, where it was observed that GPRC5A inhibited EGFR autophosphorylation, thus reducing the downstream activation of STAT3. Interestingly, the authors demonstrated that GPRC5A physically interacts with EGFR, disrupting its dimerization and activation when cells are exposed to EGF. Also, silencing of GPRC5A expression promotes EGFR activation and TGF-β signaling by inhibiting EGFR phosphorylation when cells are incubated with EGF (Ma et al. 2018). Collectively, these results suggest that GPRC5A not only inhibits STAT3 through SOCS3 but also inhibits the EGFR → STAT3 signaling pathway (Fig. 4B).

Conversely, it was reported that GPRC5A stimulates cell growth, proliferation, and migration in pancreatic carcinoma cell lines (Jahny et al. 2017). In this study, the suppression of *GPRC5A* was accompanied by a decrease in STAT3 phosphorylation at Tyr705. These results contrast with most lung cancer studies and suggest that GPRC5A expression or signaling is necessary to activate STAT3. Furthermore, other studies have indicated that STAT3 activation was independent of EGFR and dependent on the levels of other STAT3-activating autocrine factors (Bcl-XL, Cryab, Hspa1a, and Mcl1), which were upregulated in Gprc5a-KO lung epithelial cells (Chen et al. 2010). Therefore, these positive effects of GPRC5A on cell growth, proliferation, and migration appear to be independent of EGFR, considering that this receptor stimulates STAT3, while GPRC5A inhibits EGFR.

3.3. The HIF–GPRC5A–YAP1 axis

Hypoxia plays a critical role in the progression and survival of tumor cells. In colorectal cancer cells exposed to hypoxia, HIF-1α upregulates *GPRC5A*, which in turn activates the *Yes1 associated transcriptional* regulator (YAP1) (Greenhough et al. 2018). In this hypoxic context, YAP1 stimulates the expression of BCL2L1 (Fig. 4B), promoting cell survival and inhibiting apoptosis in hypoxic tumor cells. This anti-apoptotic effect enables tumor cells to evade cell death and continue proliferating in the hypoxic environment (Greenhough et al. 2018).

Recent studies have also demonstrated that GPRC5A interacts with the Hippo pathway, contributing to the proliferation of pancreatic cancer cells. This mechanism involves the activation of YAP1 transcription through the cAMP → CREB pathway. Inhibition of YAP1 rescues the proliferation and migration induced by GPRC5A (Fang et al. 2023). Understanding the intricate molecular mechanisms underlying hypoxia-mediated tumor cell survival can provide valuable insights for the development of targeted therapies aimed at disrupting this pathway and improving cancer treatment outcomes. Figures 3B and 4A summarize GPRC5A and CREB relationships.

3.4. GPRC5A inhibits NF-κB activity

Gprc5a-KO mice exhibit spontaneous lung cancer development (Tao et al. 2007). Lung epithelial cells in these mice show activated *Nuclear factor-kappa b* (NF-κB) signaling, which enhances macrophage migration and increases the secretion of cytokines, chemokines, and growth factors. This increased NF-κB signaling promotes lung inflammation and tumorigenesis (Deng et al. 2010).

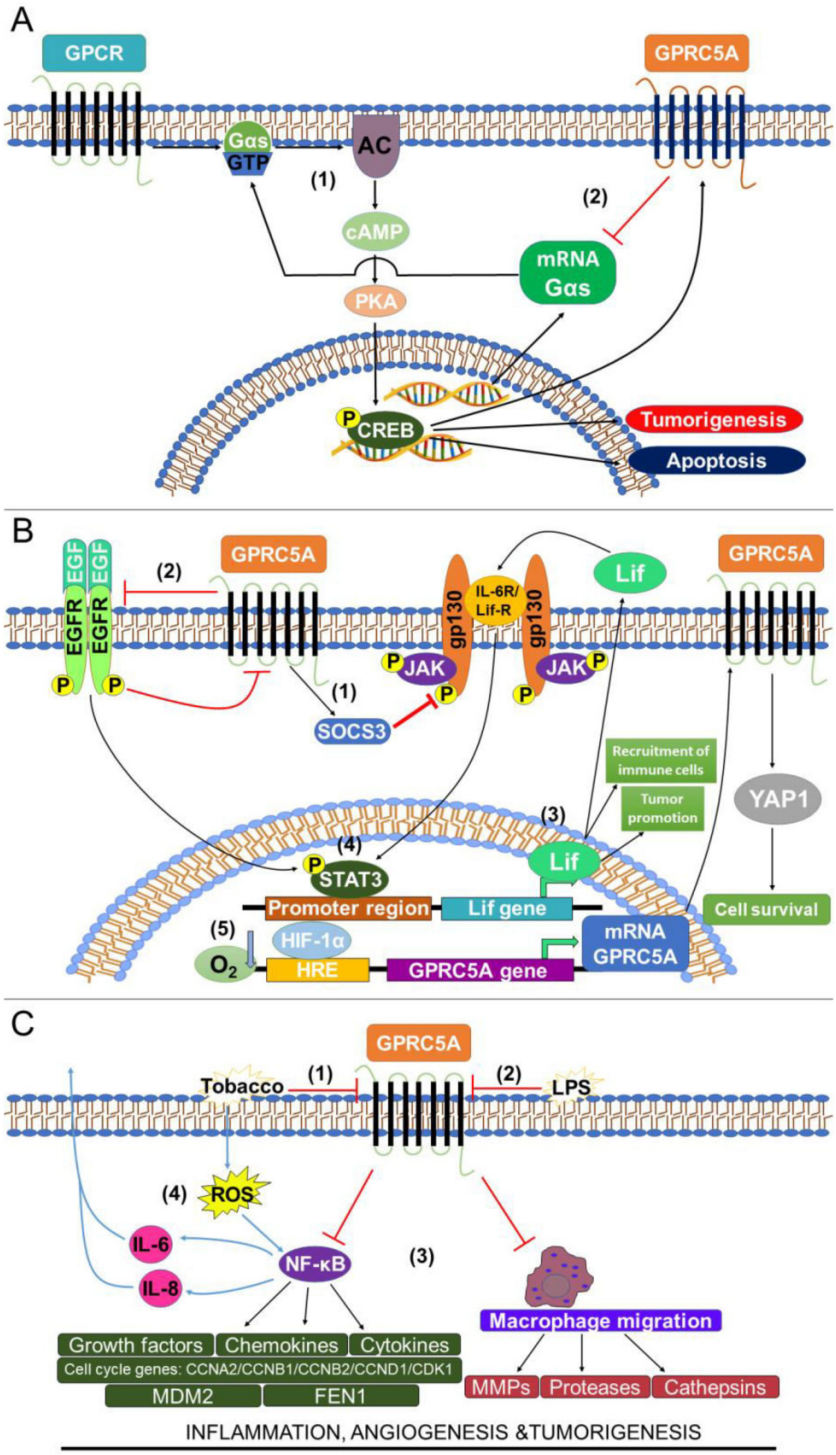
A recent study found that NF-κB is activated in epithelial stem cells (Lgr5 + cells) from the lungs of Gprc5a-KO mice, accompanied by increased expression and secretion of the ECM protein Ecm1. Further, Ecm1 interacts with the $\alpha6\beta4$ receptor on the surface of *alveolar type II cells* (AT2), leading to increased phosphorylation and acetylation of NF-κB, and expression of the Abcg1 oncogene (Yin et al. 2020). Additionally, in the human renal tubular epithelial cell line HK-2, exposed to high glucose, downregulation of MIAT (*lncRNA-myocardial infarction-associated transcript*) and upregulation of miR-182-5p caused increased activation of NF-κB and downregulation of *GPRC5A* expression (Dong et al. 2021). These findings suggest the existence of an inhibitory GPRC5A → NF-κB pathway (Fig. 4C). On the other hand, NF-κB represses RAR-mediated *GPRC5A* transactivation in lung epithelial cells via a complex of p65 with RARα/β, resulting in disrupted RNA polymerase II complexing and suppressed transcription (Song et al. 2023). Thus, a reciprocal negative regulation exists between GPRC5A and NF-κB in these cells.

4. GPRC5A in cancer

As mentioned above, the absence of *GPRC5A* expression has been linked to spontaneous lung cancer in mice (Tao et al. 2007). Data suggest that *GPRC5A* could have a role in diverse tumorigenic processes (Supplementary Table S2); however, its effect appears to vary depending on the type of tissue and the progression of the tumor (Supplementary Table S3). For instance, in lung tissue, it has been reported that basal expression of *GPRC5A* is necessary to prevent excessive cell proliferation (Tao et al. 2007). Conversely, increased expression of *GPRC5A* has been observed in colon cancer, and it has been associated with tumor progression (Zhang et al. 2017).

The challenge lies in the uncertainty regarding whether the increased expression of *GPRC5A* in tumors is a cause or a secondary effect of tumor progression, an adaptative re-

Fig. 4. GPRC5A signaling. (A) Activation of adenylate cyclase by Gαs produces an increase in cAMP and downstream CREB activation, leading to diverse cellular responses, including *GPRC5A* upregulation (1). GPRC5A overexpression leads to a decrease in cAMP levels and subsequently inhibition of CREB transcriptional activity, via Gsα expression inhibition instead of Gαi signaling (2). This inhibition produces a negative feedback loop between GPRC5A and cAMP signaling. (B) GPRC5A binds to SOC3 and inhibits the activation of the gp130/JAK receptor (1). GPRC5A also inhibits EGFR through a direct interaction of GPRC5A with EGFR (Richter et al. 2020). EGFR inhibition prevents STAT3 phosphorylation and its pro-oncogenic activity (3). The autocrine leukemia inhibitor factor (Lif) activates its receptor and STAT3 signaling. Upon activation, STAT3 binds to the promoter region of Lif, stimulating its expression and a positive feedback loop (4). Thus, GPRC5A signaling leads to inhibition of STAT3 activation and inhibition of Lif release. In models of colorectal carcinoma, GPRC5A expression is induced by the transcription factor HIF-1α under hypoxic conditions (5). GPRC5A subsequently promotes the expression of YAP, preventing its entry into apoptosis. C) Exposure to harmful stimuli, such as the carcinogen tobacco (1) or LPS (2), reduces GPRC5A expression, leading to NF-κB activation (3), thereby promoting a proinflammatory state. Tobacco's deleterious effects in pulmonary adenocarcinoma cells include ROS overproduction (4), which leads to increased levels and release of IL-6 and IL-8, through NF-κB.



sponse. Additionally, the potential ligand, its concentration, and the activation status of *GPRC5A* and signaling pathways in different tumors are presently unknown. Furthermore, different mutations in *GPRC5A*, resulting in gain or loss of function, could be present in diverse types of tumors (Sokolenko et al. 2014), making it more challenging to interpret the precise role of *GPRC5A* signaling in each type of tumor. The inability to measure its ligand and activity levels so far, as well as the unmeasured effects of the different mutations or isoforms, may contribute to the contradictory results regarding the activity of *GPRC5A* as a tumor promotor or suppressor. Moreover, parallel GPRC5A signaling pathways may elicit opposing cellular responses, which could simultaneously promote or reduce cancer progression, depending on their balance. For example, GPRC5A inhibits CREB, STAT3, and NF-κB signals but increases Integrin-FAK-cSrc and YAP signaling, both of which promote cancer progression. Additionally, the cell origin (i.e., the organ of origin, the cell origin, epithelial vs. mesenchymal, basal vs. luminal, etc.) might partially explain some of the differential results. A better understanding of the underlying mechanisms is required to comprehend this dual behavior of GPRC5A.

4.1. GPRC5A as an anti-oncogene

4.1.1. Lung cancer

Various factors, such as air pollution, dust, and smoking, can predispose individuals to lung tumorigeneses (Guo et al. 2019; Wu et al. 2020*b*). Recently, there has been a growing recognition of the role of *GPRC5A* in the fate of lung cells. *GPRC5A* exhibits higher expression levels in lung tissue compared with other tissues and contributes to the maintenance of lung tissue homeostasis (Cheng and Lotan 1998; Xu et al. 2005). In *Gprc5a*-KO mice (1–2 years old), it has been reported that there is a higher incidence of lung tumor development compared with heterozygous and wild-type mice. This was accompanied by the development of adenomas, with adenocarcinomas appearing to a lesser extent (Tao et al. 2007). In the case of NSCLC cells, it has been observed that *GPRC5A* expression is reduced, leading to a gradual decrease in the extent of cancerous areas. This is in contrast to the elevated expression of *GPRC5A* observed in the bronchial epithelium of healthy individuals (Fujimoto et al. 2012).

A crucial aspect in the development of adenocarcinoma is the excessive production of reactive oxygen species (ROS) (Liu et al. 2017*b*). Studies have revealed that *Gprc5a* deficiency in lung tumors leads to enhanced expression of the glutamate transporter SLC1A1 (Guo et al. 2021). Cancer cells use this transporter to facilitate increased cystine intake through the Xc-antiporter, resulting in heightened synthesis of GSH. In the presence of elevated levels of GSH, tumor cells can effectively manage the heightened ROS levels caused by their altered metabolism, allowing them to continue proliferating without undergoing apoptosis or senescence (Guo et al. 2021).

Head and neck squamous cell carcinoma (HNSCC) is recognized as one of the most aggressive forms of cancer, with a relative low average survival rate of approximately 5 years compared with other major oral cavity cancers (Jemal et al. 2009; Warnakulasuriya 2009). Similar to lung cancer, GPRC5A exhibits high expression levels in normal oral tissue, but its expression is decreased in HNSCC (Liu et al. 2013). The diminished expression of GPRC5A in HNSCC correlates with the activation of STAT3, as observed in lung cancer. This reduction in *GPRC5A* expression occurs during the initial stages of tumorigenesis and is associated with subsequent tumor development and progression. Notably, the significance of *GPRC5A* lies in its ability to inhibit IL-6 induced STAT3 activation and prevent anchorage-independent tumor growth when overexpressed in these cells (Liu et al. 2017*c*). In other words, the overexpression of the GPRC5A receptor can reverse the malignant phenotype in HNSCC cells (Fig. 4B).

4.2. GPRC5A acting as a proto-oncogene

4.2.1. Colon cancer

Unlike what occurs in lung cancer, where *GPRC5A* is downregulated compared with normal tissues, colon cancer is characterized by the overexpression of *GPRC5A* (Zougman et al. 2013). These different expression patterns suggest that GPRC5A may differentially regulate specific pathways depending on the type of tumor. In the case of lung cancer, GPRC5A had been found to inhibit NF-κB activation (Deng et al. 2010; Liao et al. 2015), while in colorectal cancer, its activation is promoted (Zhang et al. 2017). Accordingly, a certain correlation has also been found between the degree of malignancy and the expression of *GPRC5A* in colorectal tumors (Kume et al. 2014).

Colon cancer is associated with chronic inflammation, which induces elevated levels of ROS. This can direct cells toward a malignant phenotype by increasing oxidative DNA damage, leading to gene mutations and altered gene expression that can initiate and promote tumors (Reuter et al. 2010; Shawki et al. 2018). Therefore, tissues and cells from mice deficient in *Gprc5a* have low levels of oxidative stress associated with ROS (Zhang et al. 2017). This is also due to low levels of VNN1 (*Vanin-1*, *pantetheinase*), a ubiquitous enzyme that hydrolyses D-pantetheine into cysteamine, which inhibits the enzyme involved in the rate-limiting step of GSH synthesis (Zhang et al. 2017).

4.2.2. Gastric cancer

Liu et al. (2016) reported an increase in *GPRC5A* mRNA and protein levels in GC, which is associated with the malignant progression of the tumor. Several pathways have been associated with high expression of *GPRC5A* in GC, including WNT, RTK-Ras-PI3K-Akt, NF-kB, and JAK-STAT, all of which have a pivotal role in proliferation, apoptosis avoidance, and stimulation of angiogenesis (Cheng et al. 2012; Mi et al. 2020). Recently, it has been found that circular RNA circ_0000144 participates in tumorigenesis and the development of GC by regulating the expression of *GPRC5A*, acting as a sponge that inhibits miR-623, thus allowing high *GPRC5A* expression (Mi et al. 2020). Other miRs, such as miR-204 and miR-195, negatively regulate GPRC5A in GC (Table I, Supplementary material) (Liang et al. 2019).

The increased expression of GPRC5A in pancreatic cancer is associated with its role in the proliferation and migration of various types of cell lines (Liu et al. 2018). High expression of *GPRC5A* is linked to four characteristics in patients with pancreatic cancer: larger tumor size, more advanced stages of tumor nodule metastasis, higher tumor grade (higher growth and spread), and a more positive resection margin. In the group with mutant KRAS, TP53, CDKN2A, and SMAD4, the expression of *GPRC5A* was higher than in the non-mutant group. The mechanism by which *GPRC5A* promotes the metastasis of pancreatic cancer may include the regulation of the *epithelial-mesenchymal transition* (Qian et al. 2021).

Finally, it was reported that the downregulation of *GPRC5A* in pancreatic cancer cells led to less proliferation and migration, supporting the notion of a tumorigenic role for GPRC5A (Zhou et al. 2016). Using two GPRC5A constructs—one containing the 5'UTR region and the other the coding region—the authors observed that the first construct responded to overexpression of miR-103a-3p, indicating that the binding site for miR-103a-3p is located in the 5'UTR region of *GPRC5A* mRNA (Zhou and Rigoutsos 2014).

4.2.3. Prostate cancer

GPRC5A might play a role in the progression of prostate cancer and the initiation of bone metastasis. In GPRC5A-KO PC3 cells (from a prostatic small cell carcinoma), there is an increased phosphorylation of CREB, which is inhibited by the presence of GPRC5A (Sawada et al. 2020). The presence of a binding site for CREB in the promoter of *GPRC5A* suggests that GPRC5A might limit CREB phosphorylation through a negative feedback mechanism. Moreover, the expression of cyclin D1, encoded by the *CCND1* gene, was decreased in GPRC5A-KO PC3 cells, leading to cell cycle arrest in the G2/M phase and a decrease in the proliferation of prostate cancer cells (Sawada et al. 2020). However, in prostate carcinoma, the levels of *GPRC5A* mRNA in tumor and normal tissue are similar (Fig. 1B); therefore, other mechanisms should be preponderant in vivo that determine cancer progression in prostate cancer.

4.2.4. Glioma

This is the most common type of brain tumor. In gliomas, GPRC5A behaves as a proto-oncogene (Wang et al. 2019). The circular RNA circ-UBAP2 is expressed mainly in the cytosol of glioma cell lines and has been found to be responsible for increased cell viability and colony formation, while inhibiting apoptosis. These effects are achieved through the sponge function of circ-UBA, which sequesters miR-1205 and miR-382, thereby upregulating *GPRC5A* expression and contributing to its pro-tumor function. Elevated levels of circ-UBAP2 in gliomas result in reduced levels of miR-1205 and miR-382, leading to increased GPRC5 expression and facilitating its pro-tumorigenic activities. Silencing circ-UBAP2 leads to decreased expression of cyclin D1 and *matrix metallopeptidase 9* (MMP9), while blockade of miR-1205 and miR-382 enhances the expression of these genes, along with GPRC5A overexpression, highlighting the importance of GPRC5A in cell cycle regulation (Wang et al. 2021*a*). Similar observations have been made regarding miR-342, which functions as an anti-oncogene in both in vivo and in vitro settings. In primary brain tumors, decreased levels of miR-342 are correlated with several indicators of tumor progression, along with the loss of the precise regulation that normally maintains *GPRC5A* mRNA levels under control (Wang et al. 2019). However, the exact signaling mechanisms through which GPRC5A functions as an oncogene remain elusive and require further investigation.

4.3. Conflicting results regarding GPRC5A as proto- or anti-oncogene

4.3.1. Breast cancer

Contradictory findings regarding the function of GPRC5A in breast cancer have made it difficult to determine its precise role in disease. As a result, the classification of GPRC5A as either a pro-tumorigenic or anti-tumorigenic gene requires further research. Initially, elevated expression of *GPRC5A* mRNA was observed in both breast cancer cell lines and tissues. Notably, the inhibition of *GPRC5A* expression using siRNA demonstrated a notable suppression of cell growth (Nagahata et al. 2005). Furthermore, supporting these findings, it was found that the expression of p53 downregulated *GPRC5A* expression (Wu et al. 2005). Immunohistochemical analysis revealed that breast cancer tissues, similar to other types of cancer, displayed abundant expression of GPRC5A in comparison to normal breast tissue. However, no significant association was found between the expression of *GPRC5A* and clinicopathological characteristics (Jörißen et al. 2009).

As mentioned earlier, the silencing of *GPRC5A* in the breast cancer cell lines MDA-MB-231 and MCF7 led to reduced cell adhesion and enhanced proliferation of these epithelial cells. These effects were associated with a decrease in the FAK/Src complex, which regulates intracellular adhesion and the activity of Rho GTPases. In addition, the downregulation of GPRC5A resulted in a reduction in the expression of RhoA and Rac1 GTPases in MDA-MB-231 cells (Bulanova et al. 2017).

In breast cancer cells, a complex interrelationship between GPRC5A and EGFR has been identified. Specifically, in the MDA-MB-231 cell line with high EGFR expression, silencing GPRC5A resulted in increased colony formation, cell migration, and metastasis (Yang et al. 2016). However, this effect was not observed in other breast cancer cell lines lacking EGFR expression, such as MCF7 (Yang et al. 2016). Mutations in Ras, a protein involved in EGFR activation, have been shown to diminish the inhibitory effect of GPRC5A on proliferation (Richter et al. 2020). These results align with the inhibitory effect of GPRC5A on EGFR (Zhong et al. 2015). Simultaneously, EGFR can inhibit GPRC5A through phosphorylation (Lin et al. 2014), indicating a reciprocal inhibition between the two proteins depending on the physiological context of cells. Inactivation of GPRC5A in MCF10A cells led to the inhibition of EGF-mediated proliferation by downregulating EGFR (Richter et al. 2020). This may be attributed to GPRC5A's role in stabilizing EGFR monomers against degra-

dation while interfering with their dimerization and signaling. Overall, these results suggest an anti-oncogenic function of GPRC5A, contradicting initial reports of its protumorigenic role.

Consistent with the notion that GPRC5A may play an anti-oncogenic role, a recent study (Yang et al. 2021) found reduced expression levels of GPRC5A in triple-negative breast cancer cell lines compared with the MCF10A normal breast epithelial cell line. Overexpression of *GPRC5A* led to increased apoptosis and upregulation of caspase-3, caspase-9, and cytochrome c, key components of the intrinsic apoptotic pathway. Conversely, silencing of *GPRC5A* inhibited these processes. These findings suggest that *GPRC5A* may regulate apoptosis through the intrinsic pathway, which is activated by PI3K → Akt signaling (Yang et al. 2021).

4.3.2. Liver cancer

Regarding hepatocellular carcinoma, elevated levels of GPRC5A protein and mRNA were observed in liver tissue from patients with the disease in comparison to para-tumors and healthy tissues (Zheng et al. 2014). The expression of GPRC5A was also associated with a more advanced stage according to the TNM classification, increased levels of serum alpha-fetoprotein (a biomarker for diagnosing this type of cancer), and tumor invasion and recurrence (Zheng et al. 2014). Furthermore, patients with hepatocellular carcinoma and elevated GPRC5A levels exhibited a shorter life span (Zheng et al. 2014). However, contrary to these findings, other authors demonstrated reduced levels of *GPRC5A* mRNA in seven hepatocellular carcinoma cell lines (Xin et al. 2014). Consequently, the role of GPRC5A in hepatocellular carcinoma remains unclear, and further studies are necessary, using other model systems, to understand these conflicting results.

It is worth noting that some of the contradictory results regarding the role of *GPRC5A* in different tumors could potentially be explained by mutations occurring directly in the *GPRC5A* gene itself (Sokolenko et al. 2014) or in pathways related to *GPRC5A*. For example, the disparities observed between MDA-MB-231 and MCF7 cells in terms of the effects of GPRC5A on growth (Yang et al. 2021) could be partly attributed to the presence of KRAS mutations in MDA-MB-231 cells, while MCF7 cells have wild-type KRAS, as KRAS mutations can impact GPRC5A expression (Daouk et al. 2019). Additionally, mice with knockout Gprc5A develop lung tumors with Kras mutations (Fujimoto et al. 2017). However, a deeper understanding of the various factors involved in GPRC5A expression and activity is necessary to fully comprehend the dual behavior of GPRC5A in cancer.

4.4. GPRC5A in cancer therapy

The levels of *GPRC5A* in response to treatment with various chemotherapeutic agents may vary depending on whether the cells are normal or tumoral. In A549 lung cancer cells, treatment with the anti-tumorigenic drug phenanthriplatin results in a decrease in *GPRC5A* levels, whereas normal lung tissue IMR-90 cells do not show such a decrease. Conversely, treatment with cisplatin causes a decrease in *GPRC5A* levels in A549 cells, while inducing an increase in its expression in IMR-90 cells (Monroe et al. 2020). These findings suggest that *GPRC5A* can be stimulated through different pathways and may even exhibit diverse functions depending on the cellular origin.

It has been determined that the chemotherapeutic drug gemcitabine increases cell death in two GPRC5A-KO pancreatic cell lines (MIA PaCa-2 and TB32047) (Liu et al. 2018). Treatment with gemcitabine leads to increased expression of GPRC5A in non-KO MIA PaCa-2 cells, facilitated by the RNA-binding protein *Human antigen R* (HuR), which stabilizes *GPRC5A* mRNA in the 3′ UTR region (Zhou et al. 2016). The differential induction or suppression of *GPRC5A* in response to chemotherapy in cancer cells compared with normal cells can be partly attributed to the altered cellular responses to increased ROS concentrations induced by chemotherapy treatments. Tumor cells demonstrate modified abilities to respond to ROS when compared with normal cells (Nakamura and Takada 2021). Moreover, high levels of ROS stimulate NF-κB, leading to the repression of *GPRC5A* expression (Song et al. 2023).

5. GPRC5A and inflammation

The role of GPRC5A in protecting against exogenous agents in cancer development has also been investigated. Wang and colleagues conducted a study in which they exposed Gprc5a-KO mice to crystalline silica particles, revealing their heightened susceptibility to tumorigenesis induction. These mice exhibited pulmonary edema and elevated inflammation levels compared with wild-type mice (Wang et al. 2015). Consistent with these findings, the injection of LPS in Gprc5a-KO mice resulted in an increased incidence of acute lung injury, characterized by edema and the production of pro-inflammatory cytokines IL-1β and TNF-α, as well as the keratinocyte-derived chemokine Kc/Il-8 (Liao et al. 2015). Furthermore, mice exposed intranasally to crystalline silica showed Nlrp3 inflammasome activation in lung tissue, accompanied by an upregulation of Gprc5a protein expression (Wu et al. 2020*c*). However, this study did not demonstrate a causal relationship between Nlrp3 activation and Gprc5a expression.

The inflammatory microenvironment is a hallmark of tumors and plays a crucial role in promoting metastasis. Recent work conducted by Wang and colleagues highlighted the heightened activity of the prostaglandin E2 (PGE2) signaling pathway in Gprc5a-KO mice, suggesting its potential involvement in tumorigenesis and metastasis (Wang et al. 2020*b*). Interestingly, inhibiting PTGES, an enzyme involved in PGE2 synthesis, has shown potential for suppressing the recruitment of myeloid-derived suppressor cells, which provide protection to tumor cells against immune surveillance (Wang et al. 2020*b*). Furthermore, the inflammatory microenvironment observed in Gprc5a-KO mice was capable of inducing distinct populations of lung cancer initiator cells, especially Sca-1+ (*Stem cells antigen-1*) and ABCG1+ (*ATP-binding cassette sub-family G member 1*) cells, within the small and terminal bronchiole regions (Yin et al. 2020).

As mentioned earlier, GPRC5A overexpression may induce the repression of NF-κB, which is dysregulated in various diseases, including cancer, inflammatory disorders, and immune disorders (Didonato et al. 2012). Macrophage-secreted products, such as *matrix metalloproteinases*, serine proteases, and cathepsins, can promote angiogenesis and tumor metastasis, ultimately leading to the formation of adenomas and adenocarcinomas (Pan et al. 2020). The loss of *GPRC5A* expression increases susceptibility to edema and lung injury upon exposure to endotoxins like LPS, primarily through the activation of NF-κB in the bronchioalveolar epithelium (Liao et al. 2015).

6. GPRC5A in immunity and other diseases

GPRC5A has been implicated in various pathologies, including diabetic nephropathy, exposure to contaminants, ischemic/reperfusion injury, and asthma. In individuals with asthma, there is a downregulation of the GPRC5A protein in the bronchial epithelium (Hachim et al. 2021). Furthermore, lower levels of GPRC5A were detected in CD4+ lymphocytes from asthmatic patients, whereas higher levels of GPRC5A were observed in smokers with severe asthma (Hachim et al. 2021).

Diabetic nephropathy is a condition characterized by glomerular lesions, thickening of the glomerular basement membrane, and the loss of renal tubule epithelial cells. These changes are believed to be induced by elevated blood glucose levels (Ma et al. 2018). In patients with diabetic nephropathy, there is a significant decrease in *GPRC5A* expression in the glomeruli, despite its high expression in the podocytes of healthy individuals (Ma et al. 2018). In cellular models exposed to high glucose levels, the downregulation of *GPRC5A* by miR-218 has been identified as a crucial mechanism contributing to renal proximal tubule cell damage. Inhibiting miR-218 has been shown to reduce apoptosis and inflammation associated with this disease (Su et al. 2020). Moreover, Dong et al. (2021) reported elevated levels of the inflammasome NLRP3, the cytokine IL-1β, and the activation of NF-κB, all associated with the repression of *GPRC5A* in the same cellular model.

Mice exposed to ischemic/reperfusion conditions, as well as cardiomyocyte cell lines subjected to hypoxia/reoxygenation, exhibited elevated levels of *GPRC5A* mRNA and protein, closely correlated with cellular damage in these contexts. Concurrently with tissue damage, an increase in the enzymes lactate dehydrogenase and creatine kinase was observed in serum, indicating loss of selective membrane permeability. Interestingly, it has been demonstrated that downregulating *GPRC5A* levels through transfection of these cells with miR-342-5p resulted in a reduction of damage induced by the ischemic/reperfusion condition (Chen et al. 2020).

On the other hand, exposure to contaminants such as benzopyrene leads to a reduction in the expression of *GPRC5A*. This decrease in expression has been associated with high pulmonary fibrosis in Gprc5a-KO mice and a poorer prognosis for patients with idiopathic interstitial pneumonia (Huang et al. 2020). A similar trend was observed in a murine model of acute lung injury induced by sulfur mustard. In this model, the restoration of the alveolar epithelial barrier was linked to the increased expression of Gprc5a, which occurred following the administration of exosomes derived from BMSCs (Mao et al. 2021).

7. Concluding remarks

The available evidence suggests a strong regulation of *GPRC5A* expression by TPA and RA. GPRC5A could play a significant role in tumor development or inhibition, depending on the type of cancer, through mechanisms that are still poorly understood. The interaction between GPRC5A and the EGFR receptor induces a lower activation and proliferative response in lung cells. However, in other types of tumors, GPRC5A appears to stimulate cell proliferation by activating parallel pathways, which may be predominant or not depending on the specific tumor type and signaling (i.e., EGFR vs. YAP). In some cases, the level of *GPRC5A* expression correlates with the degree of tumor development and malignancy, suggesting its potential as a biomarker for cancer diagnosis and prevention. However, the regulation and expression details of *GPRC5A* in each type of cancer remain poorly understood. A reduction in *GPRC5A* expression may partially contribute to inflammatory responses by activating NF-κB and influencing cytokine secretion and macrophage migration. GPRC5A also plays a negative regulatory role in cAMP $\rightarrow$ PKA $\rightarrow$ CREB and EGFR $\rightarrow$ STAT3 signaling, while stimulating FAK/Src and YAP1 signaling. It is important to note that GPRC5A is still an orphan receptor, and the stage of activation or ligand concentration in each case is unknown. At present, agonists or antagonists for GPRC5A have not been developed. However, their future development could significantly aid in understanding the function of GPRC5A.

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Supplementary material

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