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Biomedical Sciences

Original article

In silico identification and characterization of transcription factor binding sites upstream of the human PDGF gene

Identificación y caracterización *in silico* de los sitios de unión a factores de transcripción aguas arriba del gen PDGF humano

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Abstract

The platelet-derived growth factor (PDGF) and its receptors are vital for a wide range of physiological processes such as development, proliferation, and migration, as well as pathological processes like tumor growth and invasion. Our aim here was to characterize *in silico* novel cis-regulatory elements (CREs) in the promoter sequences of PDGF genes to identify the transcription factors (TFs) associated with these sites. To do so, we retrieved those promoter sequences close to the transcription start site (TSS) from the ExPASy eukaryotic promoter database (EPD) and performed an *in silico* search and prediction of novel CREs in the promoter sequences of PDGF genes; then, we evaluated possible enriched transcription factors for these CREs. Our work demonstrated the co-expression between PDGFB and the transcription factor predicted to bind to the PDGF and POU2F1 in glioblastoma with a moderate correlation between the two (R^2=0.24). Similar positive associations were observed for PDGFB with ZNF680 ($R^{2=}$ 0.21) and PDGFB with FOXF1 ($R^{2=}$ 0.32). These findings suggest putative relationships between PDGFB and specific transcription factors in glioblastoma, although functional regulatory interactions remain to be experimentally validated. Overall, the data highlighted selective co-expression patterns involving PDGFB and candidate transcription factors. These observations provide a basis for further investigation of potential transcriptional relationships in glioblastoma biology.

Keywords: Cis-regulatory elements; health; bioinformatics; transcription factors; PDGF gene.

Resumen

El factor de crecimiento derivado de plaquetas (PDGF) y sus receptores son vitales para una amplia gama de procesos fisiológicos como el desarrollo, la proliferación y la migración, así como para procesos patológicos como el crecimiento y la invasión de tumores. El objetivo de nuestro trabajo fue caracterizar *in silico* nuevos elementos reguladores *cis* (CRE) en las secuencias promotoras de genes PDGF para identificar los factores de transcripción (TF) asociados con estos sitios. Para caracterizar los CRE, recuperamos la secuencia promotora cercana al sitio de inicio de la transcripción (TSS) de la base de datos de promotores eucarióticos (EPD) *ExPASy y* realizamos una búsqueda y predicción *in silico* de nuevos CRE en las secuencias promotoras de los genes PDGF. Asimismo, evaluamos posibles factores de transcripción enriquecidos para estos CRE. Nuestro trabajo demostró la coexpresión en el glioblastoma del gen PDGFB y el factor de transcripción POU2F1, el cual se prevé que se una al gen PDGF, con una correlación moderada entre ambos (R^2 = 0,24). Se observaron asociaciones positivas similares entre el gen PDGFB y el factor de transcripción ZNF680 (R^2 = 0,21) y entre el gen PDGFB y el factor de transcripción FOXF1 (R^2 = 0,32). Estos hallazgos sugieren posibles relaciones entre el gen PDGFB y factores de transcripción específicos en el glioblastoma, aunque las interacciones reguladoras funcionales aún deben validarse experimentalmente. En general, los datos ponen de relieve patrones de coexpresión selectivos que involucran al gen PDGFB y a factores de transcripción candidatos. Estas observaciones proporcionan una base para investigar más a fondo las posibles relaciones transcripcionales en la biología del glioblastoma.

Palabras clave: elementos reguladores cis; salud; bioinformática; factores de transcripción; genes PDGF.

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Introduction

There is considerable evidence that strongly implicates platelet-derived growth factors (PDGFs) as an autocrine and/or paracrine agent in the development of numerous human tumor types (**Chen *et al.***, 2022). PDGFs are potent mitogenic factors (mitogens) that regulate cell growth and division in connective tissue and the developing nervous system. These factors are secreted from many cell types, including platelets, endothelial, epithelial, glial, and inflammatory cells (**Li *et al.***, 2022).

The platelet-derived growth factor (PDGF) family consists of five disulfide-linked dimeric isoforms, PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD, formed from four polypeptide chains encoded by the genes PDGFA, PDGFB, PDGFC, and PDGFD. These biologically active proteins can exist as homodimers (PDGF-AA, PDGF-BB, PDGF-CC, and PDGF-DD) or heterodimers (PDGF-AB) and share a conserved eight-cysteine residue homology domain known as the PDGF/VEGF homology domain (**Frederike Kramer *et al.***, 2020; **Kardas *et al.***, 2020).

PDGFs exert their biological functions through two class III receptor tyrosine kinases: the platelet-derived growth factor receptors alpha (PDGFRα) and beta (PDGFRβ), displaying distinct binding affinities for receptor combinations (αα, αβ, and ββ). PDGFRα interacts with PDGF-A, -B, and -C isoforms, whereas PDGFRβ preferentially binds PDGF-B and -D, contributing to differences in receptor activation and downstream cellular responses. When these ligands attach to the receptors, they cause their dimerization, and they undergo cross-phosphorylation at intracellular tyrosine residues (**Li *et al.***, 2021).

This phosphorylation event triggers downstream signaling pathways, including PLCγ, PI3K, and JAK-STAT. Through the formation of homo- or heterodimeric receptor complexes, PDGFs promote various cellular responses such as cell proliferation, chemotaxis, actin cytoskeleton reorganization, and the inhibition of apoptosis. In fact, the nuclear factors involved in the gene regulation of PDGFA, PDGFB, PDGFC, and PDGFD genes may vary depending on the cellular context and the type of regulation. However, in the genetic construction of these isoforms, we find some common nuclear factors known to participate in general gene regulation, including the dimeric transcription factor complex activator protein 1 (AP-1), the specific protein 1 (SP1), the nuclear factor kappa B (NF-κB), and other tissue-specific transcription factors (**Parra *et al.***, 2021).

Alternative splicing results in multiple transcript variants, and some miRNAs may regulate the expression of PDGF genes by binding to the 3'UTR regions of their mRNAs. Several reports indicate various anomalies in the PDGF pathway, such as gain-of-function point mutations, activating chromosomal translocations, and overexpression or amplification of PDGF receptors (PDGFRs) (**de Villenfagne *et al.***, 2024). Glioblastoma is a highly aggressive brain tumor where PDGF signaling plays a critical role in tumor progression. Identifying transcription factors that regulate PDGF expression may uncover novel mechanisms sustaining oncogenic pathways.

Our analysis highlights selective co-expression between PDGFB and putative TFs, supporting their consideration as candidate factors for further investigation. These findings provide a rationale for exploring PDGF–TFs networks as therapeutic targets. Thus, our study contributes to understanding transcriptional regulation in glioblastoma and its biomedical relevance.

Materials and methods

Search and promoter regions retrieval

We retrieved promoter sequences of PDGF-related genes in *Homo sapiens* from EPD, ExPASy eukaryotic promoter database (https://epd.expasy.org/epd) (**Dreos *et al.***, 2017). In the dialogue box on the web page, we selected the PDGFs and the species we searched for (*H. sapiens*). The promoter sequences of PDGF genes (PDGFA: Accession number NM_033023, PDGFB: Accession number NM_033016, PDGFC: Accession number NM_016205, PDGFD: Accession number NM_033135) were extracted using the hg38 version of the human genome as a reference.

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To extract the promoter sequence close to the transcription start site (TSS) in PDGF-related genes, we recovered the 1000 bp sequence site close to the TSS. The sequence of interest was located between -700 bp upstream and +300 bp downstream of the TSS site by setting the "Sequence Retrieval Tool" it to -700 bp to +300 pb relative to the TSS and then using the "Get sequence" function on the web page.

Analysis of regulatory sequences

To search for cis-regulatory elements (CREs) in the PDGF-related genes' promoter sequences, we used a MEME (Multiple Em for Motif Elicitation) web-based application (http//: memesuite.org/tools/meme) (**Bailey *et al.***, 2015). An expectation maximization algorithm was used to predict cis-regulatory elements, and a position weight matrix model (PWM) was used to determine the frequency of the nucleotides A, C, G, and T at each position in the motif. In the MEME web program, we selected MEME in the section "Motif Discovery", completing the data submission form where we selected the motif discovery mode (Classic mode, in our case); then, we selected the sequence alphabet: DNA, RNA, or Protein and input the primary sequence by copying and pasting the promoter sequence of the PDGFs to be interrogated. We then selected the site distribution using the "Any Number of Repetitions" option to analyze whether there were non-overlapping repeats of the motif sequence. This search yielded more accurate motifs than when using other options of the program. We selected the number of motifs that MEME should find (50 motifs) and pressed the "Start Search" button. We used no additional filters.

In the "Discovered Motifs" section, we submitted the motif to the GOMo program to identify possible roles of the motif using Gene Ontology terms. In the GOMo program, we input the submitted motifs, selected the species *Homo sapiens* (Human), and started the search. GOMo program looks for the enrichment of each motif in the promoters (in regions -1000, +200 bp relative to the TSS) of all the annotated genes in *Homo sapiens* in all promoter sequences in the database using the motif provided to determine whether it is significantly related to genes belonging to one or more Gene Ontology (GO) terms. The resulting significant GO terms can suggest the biological roles of the motif.

Additionally, the response elements obtained were compared with others and analyzed to determine their putative function using the JASPAR database (**Fornes *et al.***, 2020), an open-access database for eukaryotic transcription factor binding profiles (TFBS).

We also used the Tomtom motif comparison tool version 5.1.1 (http://meme-suite.org//tools/tomtom) (**Gupta *et al.***, 2007). This program compares one or more motifs against a database of known transcription factors (e.g., JASPAR). Tomtom ranks the motifs in the database and produces an alignment for each significant match. Finally, the program delivers a result with each motif found to be significantly enriched with some transcription factor.

Briefly, we followed these steps in the Tomtom tool: Step1. The data submission form searched for one or more motifs against a motif database. Step 2. We input query motifs to compare to known motifs and typed in DNA motifs. Step 3. We selected target motifs and a motif database, or provided motifs to compare (JASPAR Non-REDUNDANT DNA and JASPAR CORE 2024 Vertebrates). Step 4. We run the "Search" function for one motif without queuing. Step 5. We input the job details. Step 6 (optional): We chose the advanced search option with Pearson's correlation coefficient and a significance threshold of E-10. Step 7. We started the search.

Biological validation of the data found

To demonstrate the biological validity of the transcription factors related to the binding motifs discovered in PDGF genes using this methodology, we added gene expression data in human tissues for the different PDGF genes and predicted transcription factors. These data were retrieved from the public GTEx (The Genotype-Tissue Expression) PORTAL database (https://www.gtexportal.org/home/). In brief, in the 'Expression' tab of the GTEx PORTAL, the 'Search gene/transcript expression' section is displayed, and a 'search gene

ID' dialogue box appears. We typed PDGF and pressed Enter and the gene expression data in tissues for all PDGFs appeared. We also searched in the cBioPortal for Cancer Genomics database (https://www.cbioportal.org/) to demonstrate whether there were correlations between PDGF gene expression and transcription factors predicted to bind to the PDGF motifs found.

On the website, there is a drop-down box labelled 'Data type'. We selected "RNAseq", and there we chose the tissue to search for 'CNS/Brain'; we selected "Glioblastoma (TCGA, cell 2013)" and clicked the "Query By Gene" button. In the section "Select genomic profiles", we ticked the "mRNA expression---enable" first option, i.e., 'mRNA expression z-scores relative to diploid samples (RNA Seq V2 RSEM)' in the "Enter genes" section and wrote PDGFA in the blank space, and then clicked on the "Submit Query" button. On the next page, we selected the 'Co-expression' tab, then entered the name of the transcription factor to search for in the dialogue box (eg: POU2F1).

Statistical analysis

The Tomtom software uses the expected number of false positives in the matches up to this point and estimates the *E*-value by multiplying the *p*-value by the total number of target motifs in all the target databases.

Results

Promoter sequence extraction and analysis of regulatory sequences

We retrieved the promoter sequences of PDGF-related genes and then analyzed them for cis-regulatory elements (CREs) using a MEME web-based application and the GOMo program to investigate the potential molecular functions of the CREs identified through the enrichment of Gene Ontology (GO) terms. The analysis of these regulatory sequences with the GOMo program revealed 199 CREs in PDGF-related genes, which were identified by searching for the top 50 motifs of each PDGF gene in the MEME program.

The length of the CREs varied between 6 and 15 bp (**Figure 1**). Most of the CREs were 6 bp in length. The CREs found in PDGF-related genes were grouped into different categories according to their predicted term of Gene Ontology and their possible function in some biological process (**Figure 2**). In these categories, olfactory receptor activity was the major process observed, with 18 CREs found, corresponding to 31% of the total, while sensory perception of smell had 16 CREs (27.1%). Other CREs related to tumor processes were found (keratin filament, intermediate filament, positive regulation of protein secretion, calcium-dependent cell-cell adhesion, phosphoinositide 3-kinase activity, and eukaryotic cell surface binding) with an average specificity percentage of 82% (data not shown).

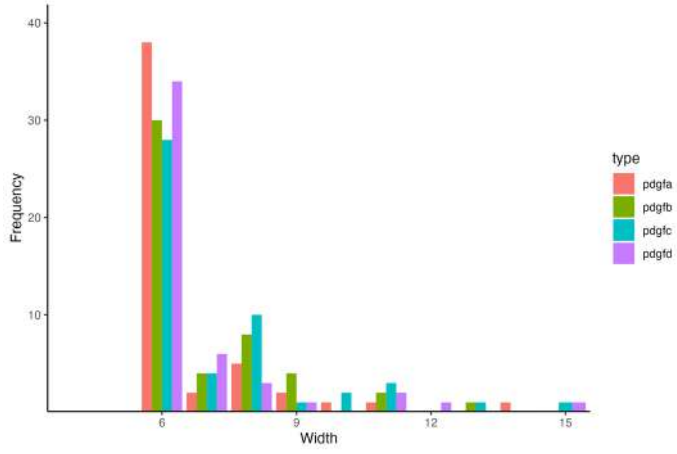

Figure 1. Analysis of regulatory sequences in PDGF gene promoters. A total of 199 CREs were found, with lengths varying between 6 and 15 bp.

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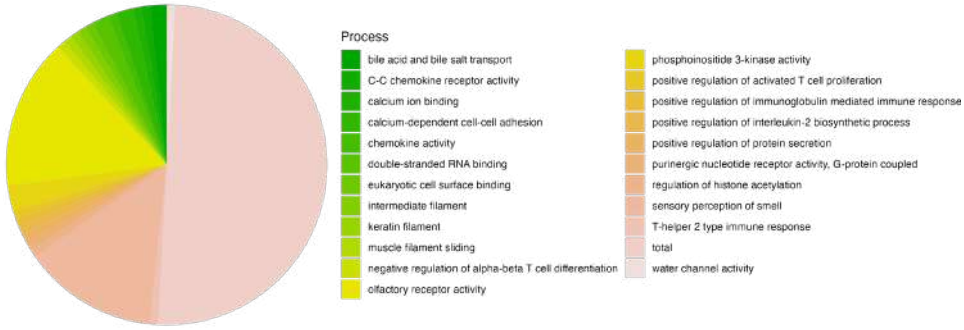

Figure 2. Biological processes related to novel CREs found in promoter sequences of human PDGF genes

Many motifs were found in the promoter region of PDGF-related genes, both in the forward (n=299) and reverse (n=106) regions (Figure S1). We also found a repeated pattern of CREs in more than one promoter region of PDGF-related genes. These sites were: GCGGCGGCGGC (position 472 from the forward strand), TCTCCA (position 1 from the forward strand), TCYAGCCT (position -12 from the reverse strand), AGASGGA (position 30 from the forward strand), and AGASSACG (position 207 from the reverse strand).

Binding sites for transcription factors

In the comparison of the discovered motifs performed by the Tomtom program, the top five motifs generated by MEME from the promoter sequences of each PDGF gene were selected to search for transcription factors associated with these motifs (**Table 1S,** https://www.raccefyn.co/index.php/raccefyn/article/view/3785/5379). Several transcription factors (TFs) were found to have enrichment in these CREs (**Table 1S,** https://www.raccefyn.co/index.php/raccefyn/article/view/3785/5379). One of these TFs was POU2F1, which has been classified as a homeodomain factor belonging to the *Homo sapiens* species (database: JASPAR2022_CORE_vertebrates_non-redundant_v2). The other transcription factors involved in the CREs discovered are listed below.

POU2F1

The UniProt database (https://www.uniprot.org/uniprotkb/P14859/entry) shows that POU2F1 acts as a transcription factor that binds to the octamer motif (5'-ATTTGCAT-3') and activates the promoters of the genes for some small nuclear RNAs (snRNAs) and of genes such as those for histone H2B and immunoglobulins. It modulates transcription transactivation by NR3C1, AR, and PGR (**Préfontaine *et al.***, 1999; **Strubin *et al.***,1995). In the case of human herpes simplex virus (HSV) infection, POU2F1 forms a multiprotein-DNA complex with the viral transactivator protein VP16 and HCFC1, thereby enabling the transcription of the viral immediate early genes (**Wysocka & Herr**, 2003).

ZNF680

ZNF680 is a transcription factor classified among the C2H2 zinc finger factors, and it belongs to the species *Homo sapiens* (JASPAR 2022 database). As for its function, it may be involved in DNA binding and transcriptional regulation (**Gaudet *et al.***, 2011).

HSF1

The human heat shock factor protein 1, HSF1, functions as a stress-inducible and DNA-binding transcription factor that plays a central role in the transcriptional activation of the heat shock response (HSR), leading to the expression of a large class of molecular chaperones, heat shock proteins (HSPs) that protect cells from cellular insult damage

(**Asano *et al.***, 2016; **Xu *et al.***, 2008). This transcription factor also plays a role in the regulation of mitotic progression (**Y.-J. Lee *et al.***, 2008) and as a negative regulator of non-homologous end joining (NHEJ) repair activity in a DNA damage-dependent manner (**Kang *et al.***, 2015). In relation to tumor biology, HSF1 is involved in stress-induced cancer cell proliferation in an IER5-dependent manner (**Asano *et al.***, 2016).

POU5F1

POU5F1 is a transcription factor that binds to the octamer motif (5'-ATTTGCAT-3'). It forms a trimeric complex with SOX2 or SOX15 on DNA and controls the expression of a number of genes involved in embryonic development, such as YES1, FGF4, UTF1, and ZFP206, and it is critical for early embryogenesis and for embryonic stem cell pluripotency (**Takahashi *et al.***, 2007).

DMRT3

DMRT3 is a probable transcription factor that plays a role in configuring the spinal circuits controlling stride in vertebrates. It is involved in neuronal specification within a specific subdivision of spinal cord neurons and in the development of a coordinated locomotor network controlling limb movements. It may regulate transcription during sexual development. Besides, DMRT3 is a marker for a subset of spinal cord neurons (**Aleksander *et al.***, 2023).

Foxf1

Foxf1 is a fork head/winged helix factor and a probable transcription activator for several lung-specific genes in *Mus musculus* (**Aleksander *et al.***, 2023).

Elf5

Elf5 is a tryptophan cluster factor in *Mus musculus*. It is a transcriptional activator that may play a role in regulating the later stages of keratinocytes' terminal differentiation. It binds to DNA sequences containing the consensus nucleotide core sequence GGA[AT]. It also transcriptionally activates the TK promoter (**Zhou *et al.***, 1998; **Choi & Sinha**, 2006).

Validation of predicted transcription factors and interaction with PDGFs

The GTEx PORTAL database was used for the biological validation of the relationships between the predicted transcription factors and PDGF genes. The graph in **Figure 3** shows the expression level of PDGF genes expressed in transcripts per million in different human tissues. There is high expression of PDGF genes in tissues of the circulatory system, but there is also significant expression of these genes in nervous tissue, especially when the expression of PDGFA is observed. **Figures 4** and **5** show the level of mRNA expression of transcription factors predicted to bind to PDGF genes in different human tissues. It can be seen that the transcription factors DMRT3, FOXF1, HSF1, POU2F1, POU5F1, and ZNF680 predicted to bind to PDGF genes are significantly expressed in both circulatory system and nervous system tissues, with transcription factors POU2F1 and ZNF680 showing the highest level of transcript expression in the nervous system compared to the other TFs.

We performed an analysis using the cBioPortal for Cancer Genomics to explore potential correlations between PDGF gene expression and transcription factors predicted to interact with the identified PDGF motifs. The search aimed to find correlations in human glioblastoma cells. The database was able to find mRNA expression of PDGFs and predicted TFs in 152 human glioblastoma samples. **Figure 6A** shows the co-expression of mRNA from the PDGFB gene and the transcription factor POU2F1, predicted to bind to PDGF genes, in human glioblastoma cells. A positive correlation was observed between the expression of PDGFB and POU2F1, with a coefficient of determination (R^2) of 0.24. This same trend was observed for the co-expression of PDGFB and ZNF680 ($R^{2=}$ 0.21) (**Figure 6B**) and PDGFB and FOXF1 ($R^{2=}$ 0.32) (**Figure 6C**). The remaining transcription factors and PDGFB genes did not show positive correlations in their expression at the mRNA level (data not shown).

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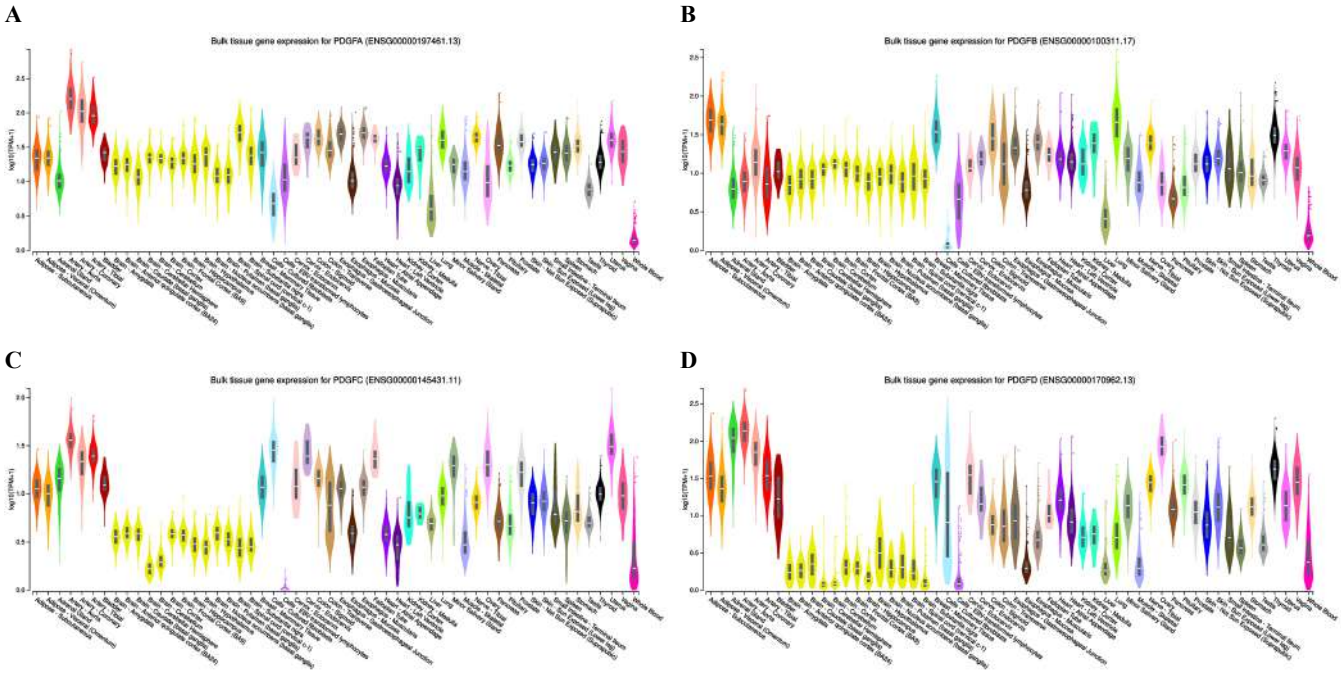

Figure 3. Level of mRNA expression of PDGF genes in human tissues. Gene expression RNA-sequence data comes from the public GTEx (The Genotype-Tissue Expression) PORTAL database and are expressed in transcripts per million in different human tissues. **A)** PDGFA, **B)** PDGFB, **C)** PDGFC, **D)** PDGFD

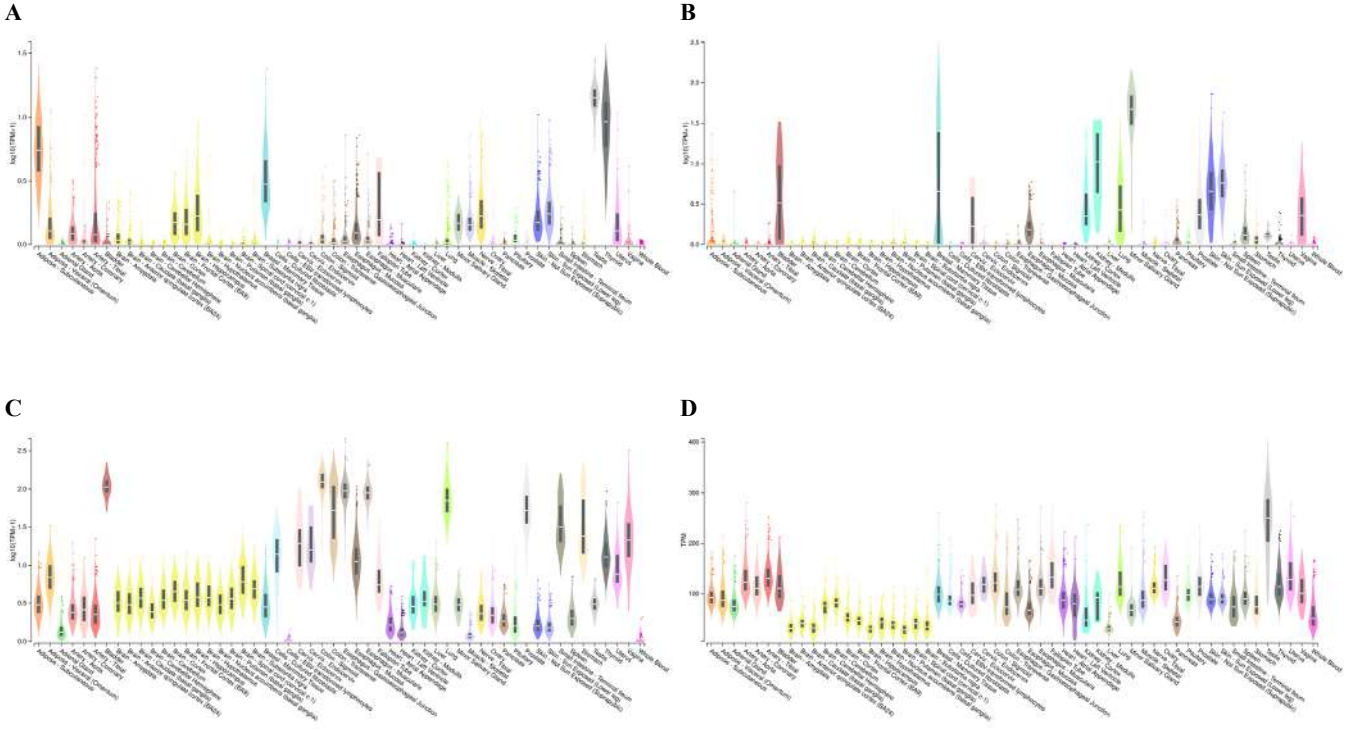

Figure 4. Level of mRNA expression of transcription factors predicted to bind to PDGF genes in different human tissues. Gene expression RNA-sequence data come from the public GTEx PORTAL database, and are expressed in transcripts per million. **A)** DMRT3 **B)** ELF5 **C)** FOXF1 **D)** HSF1

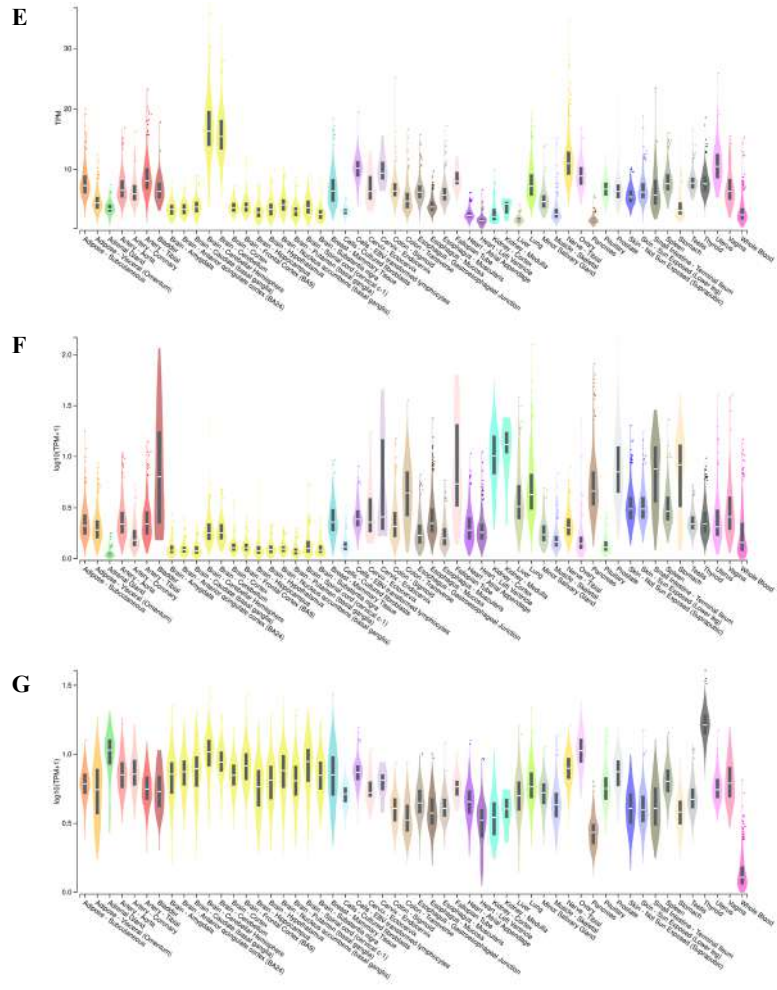

Figure 5. Level of mRNA expression of transcription factors predicted to bind to PDGF genes in different human tissues. Gene expression RNA-sequence data come from the public GTEx PORTAL database and are expressed in transcripts per million. **E)** POU2F1 **F)** POU5F1 **G)** ZNF680

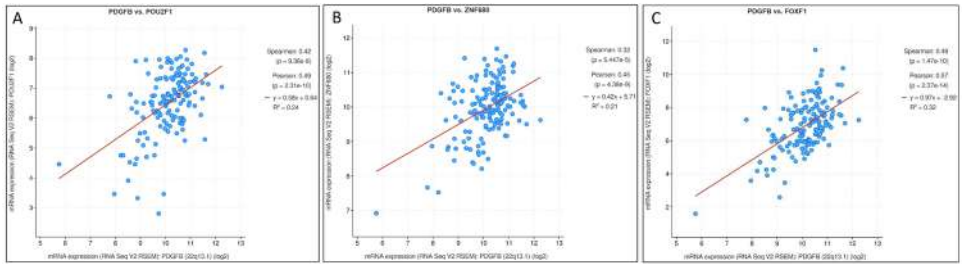

Figure 6. Co-expression at the mRNA level (RNA Seq) between PDGFB gene and the transcription factor predicted to join PDGF genes. A) PDGFB v/s POU2F1 B) PDGFB v/s ZNF680 C) PDGFB v/s FOXF1.

Although motif matches identified by Tomtom (**Table 1S,** https://www.raccefyn.co/index.php/raccefyn/article/view/3785/5379) did not meet conventional statistical significance thresholds (E-value < 0.05), these transcription factors were retained as exploratory candidates because independent transcriptomic evidence from GTEx

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demonstrated positive co-expression of POU2F1, ZNF680, and FOXF1 with PDGF (**Figure 6 A-C**). Therefore, motif similarity was not interpreted as confirmatory evidence of TF binding, but rather as a complementary hypothesis-generating approach. The motif enrichment alone was not statistically significant, but the biological plausibility of these TFs was supported by concordant expression patterns in GTEx, where TF expression positively correlated with PDGF expression across relevant tissues.

Discussion

Platelet-derived growth factors (PDGFs) and platelet-derived growth factor receptors (PDGFRs) play a crucial role in neuronal survival and the growth of the nervous system, and they are expressed in various cell types (**Li *et al.***, 2022). This may explain the presence of CREs with olfactory receptor activity and sensory perception of smell. Moreover, it has been found that PDGFC, a transcription factor expressed in the surface ectoderm and in the germinal layer of the skin, in the olfactory and otic placode and their derivatives, and in the lining of the oral cavity, plays an important role in development (**Ding *et al.***, 2000). On the other hand, the expression of the rat alpha-PDGF receptor in cells other than neuronal cells, such as the olfactory epithelium and the olfactory bulb, has also been reported, which suggests a role of PDGF in glial cell generation (**Lee *et al.***, 1990).

Some motifs found in the PDGF promoter region (**Figure 3**) are repeated in more than one promoter, which may indicate their functional importance. One of the most frequently observed motifs in PDGF promoter sequences is TCYAGCCT, associated with extracellular components that are secreted by the cell (**Aleksander *et al.***, 2023). Another repeated sequence in more than one PDGF promoter is AGASGGA, with the molecular function of DNA-binding transcription factor activity. GACTCA motif, also involved in up-regulation of STAT protein tyrosine phosphorylation, has the potential to activate gene transcription. STAT proteins are known to be involved in the development, progression, and metastasis of several types of cancer, including prostate cancer (**Ebersbach *et al.***, 2021). In this sense, the interaction between PDGF and STAT proteins has been reported: PDGF-BB and PDGF-DD activate the JAK/STAT1/3 cell signaling pathway via PDGFRβ, promoting tumoral growth and invasion through STAT3 protein activation (**Pandey *et al.***, 2023).

As for the CREs associated with cytoskeletal functions found, it has been described that PDGF can alter the flow of calcium into cells, such as human epidermoid carcinoma A431 cells, and produce activation of the cytoskeleton and changes in surface adhesion molecules; the binding of these tumor cells to fibrinogen induces the formation of mixed aggregates that could increase the potential for invasion (**Pulcinelli *et al.***, 1995). In this mechanism, PDGF is released by platelets, and there is an increase in intracytoplasmic Ca2+ content in human epidermoid carcinoma A431 cells that leads to the activation of microfilaments and the emission of membrane extensions, as well as the exposure of integrin molecules. It is believed that this process may unleash a mechanism of cooperation and interaction between A431 cells and platelets. The subsequent binding of fibrinogen or fibronectin to this complex would lead to mixed aggregates of tumor cells and platelets, allowing the transport of tumor cells into the bloodstream (**Pulcinelli *et al.***, 1995). During development, soluble growth factors such as PDGF have a strong effect on mesenchymal cells that causes them to produce extracellular matrix molecules, changing the composition of this tissue and affecting the epithelium in a palate development context (**Ferguson**, 1988).

Regarding the CREs found and their relationship with PI3K activity, we can mention that in rat models of myocardial infarction (MI), *in vitro* results demonstrated that the treatment of bone marrow mesenchymal stem cells (MSCs) with PDGF-BB enhanced the migration of these cells and protected them from hydrogen peroxide (H_2O_2)-induced apoptosis. On the other hand, in the *in vivo* rat model of acute myocardial infarction

(AMI), the treatment of MSCs with PDGF-BB and the subsequent transplantation of these cells reduced myocardial apoptosis, promoted neovascularization and tissue repair, and increased cardiac function 30 days after MI. From the molecular point of view, pretreatment with PDGF-BB promoted MSC migration and inhibited H_2O_2-induced apoptosis, an effect produced by the activation of the phosphatidylinositol 3-kinase/serine-threonine kinase (PI3K/Akt) pathway (**Sun *et al.***, 2023).

The analysis conducted using the GTEx PORTAL database showed that PDGF genes exhibit strong expression in circulatory tissues and notable expression in nervous tissues. Consistently, transcription factors predicted to bind PDGF motifs (DMRT3, FOXF1, HSF1, POU2F1, POU5F1, ZNF680) are expressed across both systems, with POU2F1 and ZNF680 showing the highest transcript levels in nervous tissue. This demonstrates that PDGF genes and TFs predicted to bind to PDGF are active in different human tissues.

Ultimately, in glioblastoma, PDGFB expression was positively correlated with POU2F1, ZNF680, and FOXF1, suggesting that these transcription factors may contribute to the regulation of PDGF signaling in tumor cells. The absence of significant correlations with other predicted TFs suggests a selective pattern of association, which may be relevant for further investigation of PDGF-related biological processes in glioblastoma.

The transcription factors POU2F1, ZNF680, and FOXF1 emerged as potential regulators of PDGFB, despite the absence of statistically significant motif matches in the Tomtom analysis (Table 1S). While the motif comparison results alone did not provide sufficient evidence to support direct DNA binding, their selection was reinforced by independent expression data obtained from GTEx, which showed positive associations between the expression levels of these transcription factors and PDGFB (**Figure 6A–C**).

Consequently, the motif similarities should be regarded as preliminary observations that may help identify candidate regulatory mechanisms rather than as definitive proof of transcriptional control. The convergence of motif-based predictions and co-expression patterns suggests a possible involvement of these transcription factors in PDGFB-associated regulatory processes in glioblastoma. However, establishing a causal regulatory relationship will require additional experimental studies, including chromatin-binding analyses and functional transcriptional assays, to verify whether these factors directly interact with regulatory regions of PDGFB and influence its expression.

Conclusions

Our findings indicate selective co-expression patterns between PDGFB and transcription factors such as POU2F1, ZNF680, and FOXF1 in glioblastoma, supporting their consideration as candidate factors for further investigation. However, these observations do not establish direct regulatory interactions, and functional validation through experimental approaches, such as chromatin immunoprecipitation sequencing (ChIP-seq) or promoter reporter assays, will be necessary to determine whether these transcription factors directly regulate PDGFB expression.

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Author contributions

Conception and contextualization of the study: VR, EP. Study design: VR, EP. Writing and editing: VR, EP. Data analysis and visualization: VR.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

The data used for the analyses described in this manuscript were obtained from the GTEx Portal on 01/11/2025 and/or CBioPortal on 101/11/2025.

Availability of data

Figshare repository:
https://doi.org/10.6084/m9.figshare.32519628
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Supplementary information

See the supplementary information in https://www.raccefyn.co/index.php/raccefyn/article/view/3785/5379

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