Review

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Review

CYR61 as a Potential Biomarker and Target in Cancer Prognosis and Therapies

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Abstract: Cysteine-rich protein 61 (CYR61) is a matricellular protein in the CCN family that is involved in cellular adhesion, migration, proliferation, and angiogenesis. The ligand interacts with integrins $\alpha 6\beta 1$, $\alpha v\beta 3$, $\alpha v\beta 5$, and $\alpha IIb\beta 3$ to modulate tumor progression and metastasis while modifying the tumor microenvironment. CYR61 exhibits context-dependent roles in cancer, acting as both a tumor promoter and suppressor. Increased expression is linked to extracellular matrix remodeling, immune modulation, and integrin-mediated signaling, making it a potential prognostic biomarker and therapeutic target. Emerging research highlights the utility of CYR61 in liquid biopsies for cancer detection and monitoring. Integrin-targeted therapies, including CYR61-blocking antibodies and CAR-T approaches, offer novel treatment strategies. However, therapy-induced toxicity and resistance remain challenges. Further elucidation of the molecular mechanisms of CYR61 may enhance targeted therapeutic interventions and improve patient outcomes.

Keywords: CYR61; cancer; matricellular protein; CCN family

1. Introduction

Cysteine-rich protein 61 (CYR61) is a member of the CCN family of matricellular proteins and has been shown to play a critical role in cellular communication, adhesion, and migration [1]. The acronym CCN represents the original members of this family: Cysteine-rich protein 61, Connective Tissue Growth Factor (CTGF), and Nephroblastoma (NOV) [2]. Originally identified in 1990 as a growth factor-inducible immediate-early gene, CYR61 has since been recognized as a key regulator of angiogenesis, chondrogenesis, and fibrogenesis [3–5]. CYR61 interactions with integrins, heparan sulfate proteoglycans, and low-density lipoprotein receptor-related proteins enable it to modulate cell proliferation, differentiation, and immune responses [6].

CYR61 consists of conserved domains that mediate its diverse biological functions, including its ability to bind integrins such as $\alpha v\beta 3$, $\alpha v\beta 5$ $\alpha 6\beta 1$, and $\alpha IIb\beta 3$ [2]. These interactions influence DNA synthesis, cellular adhesion, and migration, particularly in vascularized tumors and cancerous environments [7]. Describing the roles of CYR61 in cancer is crucial, as its dual functions in promoting or suppressing tumorigenesis highlight the complexity of its biological impact [8–10]. Indeed, CYR61 has been implicated in various cancers, including breast, prostate, pancreatic, and lung cancers, where it affects tumor progression, metastasis, and treatment resistance [11–15].

Given its involvement in multiple pathological processes, CYR61 is being explored as a potential biomarker for cancer prognosis and a therapeutic target [16]. Understanding its molecular mechanisms could aid in the development of targeted therapies that disrupt CYR61-integrin signaling pathways. Furthermore, as research continues, CYR61's role in immune surveillance and tissue repair further underscores its significance in both normal physiology and disease states.

2. Discovery

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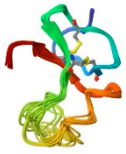
In 1990, O'Brien and colleagues in the Lau lab successfully cloned a growth factor-inducible immediate-early gene, CYR61, which encodes a 379 amino acid polypeptide with 38 conserved cysteines, a molecular mass of 42 kilodaltons, and an N-terminal secretory signal [3,4,17]. Once associated with the extracellular matrix, CYR61's half-life extends to greater than 24 hours, and with high heparin binding affinity, CYR61 was quickly theorized to be involved in cell-to-cell communication [6]. Bork recognized structural motifs in CYR61, CTGF and NOV. This established a designation of "CCN family proteins", which has expanded to encompass six members that regulate other bioactive peptides through direct binding interactions [2,17]. Kireeva and colleagues in the Lau Lab purified CYR61 and revealed its function as a chemotactic factor on fibroblasts, promoting cell proliferation, migration, and adhesion to endothelial cells [1,18]. As an angiogenesis-inducing ligand, CYR61 promotes cell adhesion through several binding interactions with integrins. Integrin $\alpha v\beta 3$ augments growth factor-induced DNA synthesis and mediates the adhesion of vascular endothelial cells; integrin $\alpha 6\beta 1$ binding influences fibroblast cell adhesion; and the $\alpha IIb\beta 3$ domain can promote platelet adhesion and aggregation [7,19]. Early *in vitro* studies demonstrated CYR61 involvement in tissue-specific stages of chondrogenesis and, therefore, theorized to aid in mammalian embryonic skeleton development [4,20]. By the early 2000s, CYR61 was established to be involved in fibrogenesis, angiogenesis, chondrogenesis, as well as cell proliferation and differentiation through direct binding of integrins, heparan sulfate proteoglycans, and low-density lipoprotein receptor-related proteins [1,17,21–23].

Recent findings uncovered the participation of the CCN family proteins in regulating the production of cytokines and chemokines through autocrine and paracrine feedback and directly modifying cellular migratory processes, suggesting a pivotal role in the human immune-surveillance process [24]. Since the discovery of CYR61 roles in inflammation and tissue repair, studies continue to explore it as a potential biomarker for therapeutic targeting and immune surveillance [16,25].

3. Structural Domain and Functions

As members of the CCN family proteins, CYR61, CTGF, and NOV share significant sequence homology with highly conserved intron-exon regions [2,26]. The CYR61 gene has been mapped to chromosome 1p22.31 and encodes a 381 amino acid polypeptide with 38 conserved cysteines, a molecular mass of 42 kilodaltons, and an N-terminal secretory signal [3,26,27]. The first of five exons (with four interspaced introns) encodes a secretory signal from the N-terminal, while the following four exons encode conserved mosaic CCN family domains [27–30]. Sequence analysis of these four conserved domains shares homology with insulin-like growth factor-binding proteins (IGFBP), von Willebrand Factor type C domain (vWC), thrombospondin type 1 repeat (TSR), and the C-terminal (CT) domains of some types of collagens and mucins [2,30]. The CCN family protein conserved secretory signal, insulin-like growth factor binding protein, vWC repeat, TSR, and CT domain regions are likely a result of exon shuffling [31]. Adhesion receptors for CYR61 include: $\alpha v\beta 3$ and $\alpha 6\beta 1$ with endothelial cells [32], $\alpha 6\beta 1$ with fibroblasts [33], $\alpha 6\beta 1$ with smooth muscle cells, $\alpha M\beta 2$ with monocytes, and $\alpha IIb\beta 3$ with platelets [1,5,19,32–35]. A summary of CYR61 domains, conserved sequences, binding sites, and ribbon diagrams is shown in **Table 1** [27,36–39].

Table 1. CYR61 domains and binding sites.

Domain	Conserved Sequence	Binding Sites	Ribbon Diagram
Insulin-like Growth Factor Binding Protein (IGFBP)	CPAACHCPLEAPKCA PGVGLVRDGCGCCKV CAKQLNEDCSKTQPC DHTKGLEC	Insulin-like growth factor binding proteins	
von Willebrand Factor type-C repeat (vWC)	CEYNSRIYQNGESFQP NCKHQCTCIDGAVGC IPLCPQESLPNLGCPN PRLVKVTGQCCE	$\alpha v\beta 3$ $\alpha v\beta 5$ $\alpha IIb\beta 3$	

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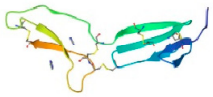
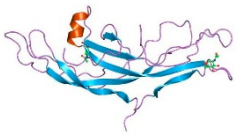
			
Thrombospondin type-1 repeat (TSR)	CIVQTTSWSQCSKTCG TGISTRVTNDNPECRL VKETRICEVRPC	α6β1	
C-terminal (CT)	PEPVRFTYAGCLSVKK YRPKYCGSCVDGRCC TPQLTRTVKMRFRCED GETFSKNVMMIQSCK CNYNCPHANEAAFPF YRLFND	αvβ3, α6β1-HSPG: H1, α6β1-HSPG:H2	

4. CYR61 Interactome

4.1. Integrin α6β1

The integrin α6β1 has binding sites in two domains of CYR61 (**Figure 1 and Table 1**) that allow for heparin binding and integrin α6β1/heparan sulfate proteoglycans (HSPGs)-mediated fibroblast cell adhesion. Within the third domain with homology to TSR; T1, with the sequence GQKCIVQTTSWSQCSKS (aa 223-239) as well as in the fourth domain (CT); H1, with the sequence KGKKCSKTKKSPEPVR (aa 280-295); and H2, with a sequence FTYAGCSSVKKYRPKY (aa 296-314) [40]. Both the α6β1 binding domain and the cell surface heparan sulfate proteoglycan binding sites work in tandem to support vascular smooth muscle cell adhesion and chemotaxis, but not chemokinesis [5]. Integrin α6β1 and HSPGs act as co-receptors in human skin fibroblasts, smooth muscle cells, and endothelial cells to mediate cell adhesion and support smooth muscle cell migration [40]. Successful binding of α6β1 and HSPGs leads to a substantial and sustained level of reactive oxygen species (ROS) and activates the cellular tumor antigen p53 and ERK/MAPK tumor suppression pathways [25,41]. Integrin α6β1 represents a promising target for antimetastatic therapies aiming to impair tumor metastasis through platelet-dependent mechanisms [42].

4.2. Integrin αvβ3

The binding sites for integrin αvβ3 reside within the third domain of CYR61 (**Figure 1 and Table 1**) and have been shown to promote pro-angiogenic activities in activated endothelial cells [31,43]. While there are several αvβ3 binding sites, Asp-125 in the 20-residue sequence of the vWC domain of V2 is particularly critical for integrin interactions [44]. Upon successful binding, downstream αvβ3-dependent pathways augment growth factor-induced DNA synthesis within the same cell type, which enables endothelial cell adhesion [7]. Binding to integrin αvβ3 allows CYR61 to promote cell proliferation, survival, and angiogenesis through the adhesion of vascular endothelial cells in a manner independent of heparin-binding activity elsewhere on the CYR61 protein [25]. The β3 class of arginylglycylaspartic acid (RGD)-integrins has α-N-(benzoxycarbonyl)-diaminopropanoic acid bundles, which contribute to the selectivity of αvβ3 over αvβ5. Although αvβ3 is typically expressed at low or undetectable levels in adults, it is involved in multiple signaling transduction pathways in cancer and tumor progression, including cell proliferation, adhesion, migration, stemness, immune escape, drug resistance, and bone metastasis. Therefore, high expression of αvβ3 in patients presents an opportunity for αvβ3-targeted therapeutics in biomarker-driven clinical trials [15]. The αvβ3 expression in carcinomas such as pancreatic cancer has been shown to increase lymph node metastases in vivo and enhance anchorage-independent tumor growth in vitro [13]. Current research addressing αvβ3 antagonist toxicity reduction and limited efficacy explores a new biometric-targeted drug delivery system utilizing exosomes derived from human umbilical cord mesenchymal stromal cells (hUCMSCs) to encapsulate triptolide and generate αvβ3-specific chimeric antigen receptor T cells, which have been proven to induce complete elimination of melanoma lesions [45].

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4.3. Integrin αvβ5

CYR61 has distinct expression profiles for three non-small lung cancer cell lines (H1155, H460 and H2122), five colorectal cancer cell lines (SW837, SW620, HT-29, HCA-7 and HCT116), one breast cancer cell line (MCF-7), and one esophageal squamous carcinoma cell line (TE-7) with enhanced expression of αvβ5 integrin [11]. Integrin αvβ5 binding on CYR61 (**Figure 1 and Table 1**) is within the vWC repeat region of the second domain. The adhesion and proliferation of human breast cancer cells and astrocyte adhesion to vitronectin, and fibroblast migration to CYR61 are mediated by integrin αvβ5 [31]. CYR61 tumor necrosis factor-a encounters require αvβ5, α6β1, and syndecan-4 interactions to inhibit the biphasic activation of JNK to induce apoptosis [11,46].

4.3. Integrin αIIbβ3

The αIIbβ3 binding site on CYR61 is within the second domain (**Figure 1 and Table 1**), homologous with the vWC repeat [11]. Antibodies from patients who develop thrombocytopenia post-treatment with an RGD-mimetic platelet inhibiting drug similarly recognize ligand-inducible binding sites at αIIbβ3 [47]. The availability of the pure orthosteric inhibitors of αIIbβ3 presents a tool to further research the mechanisms linking integrin conformation and deter thrombosis [48].

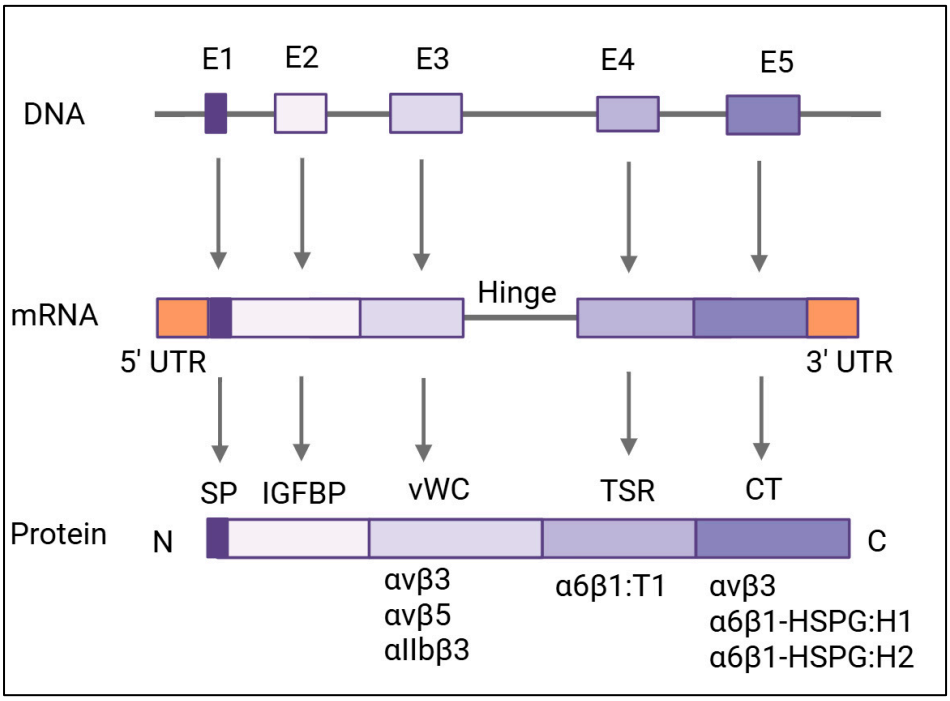

Figure 1. Gene and Domain Architecture of CYR61. The CYR61 gene undergoes transcription to produce RNA, which is subsequently translated into the CYR61 protein. Each exon, along with its corresponding RNA transcript and protein segment, is represented as a uniquely colored rectangle. Protein modules are labeled beneath each segment. Binding regions for integrins and heparan sulfate proteoglycans (HSPGs) on the CYR61 protein are indicated. Abbreviations: UTR – untranslated region; IGFBP – insulin-like growth factor binding protein domain; vWC – von Willebrand factor type C repeat; TSR – thrombospondin type 1 domain; HSPG – heparan sulfate proteoglycan; SP – signal peptide; CT – C-terminal.

5. CYR61 Roles in Cancer

Expression of CYR61 is multifaceted and is most often associated with tumorigenesis, but can also enable tumor suppression, such as in non-small cell lung cancer [14]. In certain cases, such as hepatocellular carcinogenesis, CYR61 induces pathways that generate ROS, which may both promote and inhibit tumorigenesis [49–52]. A study demonstrated that while CYR61 expression is decreased

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in endometrial cancer, endometrial adenocarcinoma cell lines (MDA-MB-231, AN3CA, HEC1A, HEC1B, KLE, and RL95–2) overexpressing CYR61 resulted in reduced tumor formation in nude mice [53]. This can be a result of the truncated isoform morphology of CYR61 more often having oncogenic properties, while full-length CYR61 often exhibits antiproliferative effects [29].

Somatic cells can secrete matricellular proteins into the extracellular space to join other matricellular proteins, soluble factors, and stromal cells to comprise a tumor microenvironment that is capable of mechanical modulation of cellular activities [54]. CYR61 is highly expressed in various tumor microenvironments and can influence tumor progression by modulating the extracellular matrix (ECM) to affect the adhesion, migration, and survival of cancer cells [55]. One study showed that CYR61 facilitates tumor progression in the pancreas by changing the morphology of pancreatic islets, altering the cellular microenvironment, and enabling tumor-promoting properties [56]. Expression of CYR61 in secreted endogenous phosphorylated form is associated with aggressive metastatic phenotypes and poor prognosis in breast cancer and correlates with more advanced clinical stages, larger tumor sizes, and lymph node positivity, indicating a role in promoting tumor aggressiveness [57]. CYR61 also promotes survival in endothelial cells through integrin $\alpha v\beta 3$ binding and induces p53-dependent apoptosis in fibroblasts through the engagement of $\alpha 6\beta 1$-HSPG binding domains [40,58,59]. An increased expression of CYR61 is associated with more frequent binding of integrin avβ3, which has been shown to play a major role in breast cancer progression through proangiogenic activity of tumor vascularization. Therefore, overexpression of $\alpha v\beta 3$ can be a biomarker for poor prognosis and a therapeutic target in breast cancer [57,60,61]. While CYR61 levels are low in healthy prostate tissue and increase during prostate cancer development within the epithelium, decreased serum CYR61 expression in patients after surgical treatment of prostate cancer is associated with a greater risk of relapse [62]. This increased expression has been shown to promote prostatic cell proliferation and, conversely, enhance the cytotoxicity of tumor necrosis factor-related induced apoptosis that selectively kills cancer cells [63–65]. The ambiguity of boundaries between tumor and surrounding tissue has resulted in mixed findings regarding the participation of CYR61 in different stages of various cancers [66]. Patients with ovarian epithelial carcinoma, however, had significantly higher CYR61 expression compared to patients with benign ovarian tumors, indicating a role in regional lymph node metastases and progression of clinical disease stage [67]. A summary of associated cancers to CYR61 domains and their respective ligands is shown in **Table 2**.

Table 2. Cancers associated with cyr61 binding domains and corresponding ligands.

Ligand	Binding domain	Associated cancers
$\alpha 6\beta 1$	TSR, CT	Breast, ovarian, lung, lung metastasis, prostate
$\alpha v\beta 3$	vWC	Bone metastasis, breast, cervical, colon, melanoma, non-small cell lung, ovarian, glioblastoma, prostate, and pancreatic.
$\alpha v\beta 5$	vWC	Breast, colorectal, gastric, liver metastasis, ovarian, glioblastoma, pancreatic, and prostate.
$\alpha IIb\beta 3$	vWC	Breast, ovarian, and prostate.

6. CYR61 in Liquid Biopsies

Liquid biopsies can facilitate the monitoring of treatment responses over time. Therefore, changes in CYR61 levels in serum may reflect the effectiveness of therapeutic interventions, allowing for real-time assessment of patient status and adjustment of treatment plans accordingly. Liquid biopsy of serum CYR61 has potential as a diagnostic and prognostic biomarker, aiding in the detection, monitoring, and management of cancer through non-invasive means. Measuring CYR61

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levels in serum presents a potentially minimally invasive and inexpensive clinical biomarker that is independent of the prostate-specific antigen and correlates with worse prognosis for colorectal cancer, breast cancer, and prostate cancer [12,41,57,68–71]. Enzyme-linked immunosorbent assays have revealed an increase in serum CYR61 levels in patients with colorectal cancer compared to patients with colorectal adenomas and healthy controls [70]. Detecting elevated serum CYR61 can improve diagnosis and decipher the clinicopathological status of breast cancer patients [72]. In prostate cancer, higher serum CYR61 levels have been observed in patients with non-organ-confined disease compared to those with organ-confined disease, suggesting its utility in differentiating between disease stages [12]. In a study, the breast cancer mesenchymal disseminated tumor cell (mDTC) line, BC-M1, had high CYR61 levels associated with a change in microenvironmental conditions by viable circulating tumor cells [73].

7. CYR61 as a Potential Target in Cancer

Due to its dual role in promoting apoptosis and influencing tumor cell behavior, CYR61 may serve as a potential biomarker and therapeutic target in cancer prognosis and treatment. Modulating its activity could aid in developing strategies to enhance the efficacy of cancer therapies that rely on inducing apoptosis in tumor cells [55]. CYR61 has been established as a critical factor in breast cancer progression, influencing tumor growth, invasiveness, and therapy resistance. CYR61 is also implicated in promoting neovascularization, as it enhances the expression of vascular endothelial growth factor (VEGF), which is crucial for tumor blood supply and growth. Cells expressing CYR61 acquire an antiestrogen-resistant phenotype, presenting a clinical challenge in breast cancer treatment [8]. One study found that the pro-angiogenic effects of CYR61 are dependent on the VEGF/VEGF-Receptor 2 (VEGF-R2) signaling pathway, and blocking this pathway with an anti-VEGF-R2 antibody abolishes the angiogenic effects of CYR61, decreasing the invasiveness of β tumors through enhanced integrin function [56]. One study found that the pro-angiogenic effects of CYR61 are dependent on the VEGF/VEGF-Receptor 2 (VEGF-R2) signaling pathway, and blocking this pathway with an anti-VEGF-R2 antibody abolishes the angiogenic effects of CYR61, decreasing the invasiveness of β tumors through enhanced integrin function [56]. Huang et al. identified CYR61-β1 integrin-AMPKα as a potential therapeutic target to mitigate participation in facilitating tumor cell extravasation and regulating anoikis migration of breast cancer metastasis to the lung [10]. Utilizing a blocking antibody against integrin αvβ3 is capable of inhibiting heregulin (HRG) induction of the aggressive phenotypes of the breast cancer cells *in vivo* [8]. Since heparin is often targeted in malignant diseases for antithrombotic prophylaxis, CYR61 is a potential target to interfere with the migration of PC-3 cells [65,74]. Even though integrins can be important therapeutic targets, current RGD-based anti-integrin drugs induce conformational changes that trigger incongruous cell adhesion and potentially fatal immune reactions [75].

8. Challenges

Current gaps in knowledge include addressing integrin antagonist toxicity reduction and precisely understanding the mechanisms by which CYR61 promotes aggressive cancer phenotypes [45,76]. The complexity of integrin functions and their sometimes-opposing characteristics pose challenges in developing effective integrin-targeting therapies [77]. Cancer cells have the ability to change their integrin repertoire and become resistant to drug treatments, which may be overcome through antagonist targeting of multiple binding integrins [78]. Recently, integrin αvβ3-chimeric antigen receptor (CAR)-T cells showed therapeutic potential to halt the survival and metastasis of solid tumors such as melanoma, glioblastoma, breast cancer, pancreatic cancer, and prostate cancer [79].

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9. Conclusions

As a key member of the CCN protein family, CYR61 plays a vital role in regulating cell adhesion, migration, proliferation, and angiogenesis through interactions with integrins and heparan sulfate proteoglycans [5]. Its ability to modulate the extracellular matrix and influence tumor microenvironments has positioned CYR61 as a critical factor in both normal cellular function and pathological conditions [54]. While its role in tissue repair and immune surveillance highlights its physiological importance, CYR61's involvement in tumor progression and metastasis underscores its dual nature in cancer biology [16,24,55]. The expression of CYR61 has been linked to both tumor-promoting and tumor-suppressive effects, depending on the cancer type and cellular context [49–52]. In cancers such as breast, prostate, and pancreatic cancer, CYR61 enhances tumor growth, invasion, and resistance to therapy, making it a promising biomarker for disease progression [8,12,13,15,78]. However, its apoptotic effects in fibroblasts and its association with tumor suppression in non-small cell lung cancer indicate a more complex regulatory function [14]. Targeting CYR61-integrin interactions presents an opportunity for novel therapeutic strategies, particularly in integrin-mediated tumor progression [43,46,74,80]. Current challenges in CYR61 research include mitigating integrin antagonist toxicity and understanding the molecular mechanisms driving its pro-tumorigenic versus tumor-suppressive effects [45]. Advancements in targeted therapies, including integrin $\alpha v\beta 3$-CAR T cells and CYR61-blocking antibodies, offer new possibilities for cancer treatment [8,56,79]. As research continues, further exploration of CYR61's role in cancer biology and immune modulation may lead to breakthroughs in precision medicine and targeted therapy development.

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Abbreviations

The following abbreviations are used in this manuscript:

CAR-T	Chimeric Antigen Receptor T cells
CCN	Cysteine-Rich Protein, Connective Tissue Growth Factor, Nephroblastoma
CT	C-Terminal
CTGF	Connective Tissue Growth Factor
CYR61	Cysteine-Rich 61
ECM	Extracellular Matrix
HRG	Heregulin
HSPG	Heparan Sulfate Proteoglycan
hUCMSC	Human Umbilical Mesenchymal Stromal Cells
IGFBP	Insulin-like Growth Factor Binding Protein

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mDTC	mesenchymal Disseminated Tumor Cell
NOV	Nephroblastoma
RGD	Arginine, Glycine, Aspartic Acid
ROS	Reactive Oxygen Species
TSR	Thrombospondin Type 1 Repeat
VEGF	Vascular Endothelial Growth Factor
vWC	von Willebrand Factor Type C Domain

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