

Current Research on the Role of Histidine-rich glycoprotein (HRG) in Neovascularization

Xiaohan Pan ¹, Wei Tan ^{2,*}

¹ Zunyi Medical University, Zunyi, Guizhou 563000, China

² Department of Ophthalmology, The Third Affiliated Hospital of Zunyi Medical University/ The First People's Hospital of Zunyi, Zunyi, Guizhou 563000, China

* Corresponding author: Wei Tan

Abstract: Angiogenesis is a critical mechanism for blood vessel formation in both physiological and pathological processes, regulated by multiple cytokines and signaling pathways. In recent years, histidine-rich glycoprotein (HRG), a multifunctional plasma protein, has garnered increasing attention for its role in angiogenesis. This review summarizes the structural characteristics of HRG, its mechanisms of action, and functional manifestations in angiogenesis, and explores its potential as a therapeutic target, thereby opening new avenues for overcoming anti-angiogenic therapy resistance and improving drug delivery.

Keywords: Histidine-Rich Glycoprotein (HRG); Angiogenesis; Anti-angiogenesis.

1. Introduction

Angiogenesis refers to the process of generating new blood vessels from existing vascular networks [1]. Under normal physiological conditions, mature blood vessels maintain a stable state—a balance between proangiogenic factors (e.g., VEGF) and antiangiogenic factors (e.g., TSP-1/TSP-2) [2]. However, this equilibrium is subject to change under both physiological and pathological conditions, which, in turn, influences vascular development. Thus, angiogenesis is essential in events such as embryonic development, tissue repair, and regeneration [3, 4]. During embryonic development, new blood vessels form complex vascular networks through angiogenesis and vascular remodeling, supplying oxygen and nutrients to tissues [3]. In adults, neovascularization is also involved in tissue repair and regeneration. For example, during wound healing, new blood vessels provide essential blood supply to damaged tissues, promoting tissue repair and regeneration. [5]

In contrast, under various pathological conditions, the neovascularization process becomes abnormal. For instance, during tumor growth, VEGF-A receptors—particularly VEGFR-1 and Nrp-1—are expressed on some tumor cells, indicating the presence of an autocrine loop that may stimulate tumor cell growth and migration [2]. Tumor cells can trigger the proliferation of vascular endothelial cells in surrounding normal tissues, leading to the formation of new vascular networks [4]. Additionally, angiogenesis plays a significant role in inflammatory responses. In acute inflammation, changes in microvascular integrity allow fluid and immune cells to accumulate at the injury site [6]. Subsequent inflammation induces NF- κ B/NLRP3-mediated release of factors such as VEGF, which activate the endothelium and recruit macrophages to secrete VEGF, thus creating a positive feedback loop that drives angiogenesis and worsens inflammation [5]; this process contributes to the onset and progression of various diseases.

In recent years, histidine-rich glycoprotein (HRG) has garnered increasing attention for its role in angiogenesis as a multifunctional plasma protein [7]. HRG possesses a multi-domain structure enabling binding to diverse ligands and

participation in various physiological processes, including cell adhesion, signal transduction, and immune regulation [8]. Research indicates that HRG exhibits complex effects in neovascularization, capable of both inhibiting angiogenesis and promoting it under certain conditions [9, 10]. This review summarizes the mechanisms of HRG in neovascularization, related research progress, and its potential clinical applications.

2. Structure and Function of HRG

(1) Structural Characteristics of HRG

Histidine-rich glycoprotein (HRG) is a plasma protein found in many vertebrates. Synthesized by hepatocytes, this glycoprotein comprises 507 amino acid residues and circulates at relatively high concentrations (100–200 μ g/ml) in plasma. As a multi-domain plasma protein, its molecular structure contains several functional domains, including an N-terminal cystatin-like domain (N1N2), a histidine-rich region (HRR) in the middle, and a conserved C-terminal domain [11]. The HRR region of HRG is rich in histidine and proline residues, enabling it to bind various ligands such as zinc ions (Zn^{2+}), heparin, and plasminogen [8]. This "multi-ligand bridging" capability enables HRG to function as an extracellular adaptor molecule, acting as a key regulator in multiple physiological systems, including cell adhesion, signal transduction, and immunoregulation [7].

(2) Biological Functions of HRG

HRG plays crucial roles in both physiological and pathological processes. Evidence shows HRG modulates angiogenesis, coagulation, and fibrinolysis [12]. For example, HRG inhibits endothelial cell adhesion to fibronectin by binding to protease-released His/Pro-rich domains, thus restricting cell migration and exerting anti-angiogenic effects [9]. In addition, HRG participates in immunoregulation by influencing macrophage polarization toward M1/M2 phenotypes [13] and acting as an extracellular adaptor that selectively binds IgG to reduce insoluble immune complex formation and promote their clearance by macrophages [7, 14]. During inflammation, HRG binds CD36 with high affinity, serving as a decoy receptor to block TSP-1/2 mediated signaling on CD36, which leads to sustained

recruitment of inflammatory cells and exacerbation of inflammation [10, 15]. This multiligand bridging capability places HRG as an essential molecule connecting vascular biology with immunology [7].

3. Mechanisms of HRG in Neovascularization

The role of HRG in neovascularization is complex and multifaceted. Rather than acting as a direct angiogenic factor, HRG influences angiogenesis through multiple pathways. Notably, current studies suggest that HRG exhibits both pro- and anti-angiogenic effects depending on the context. The specific function of HRG appears to be modulated by factors such as the cellular microenvironment and ligand interactions, highlighting the necessity to examine these contextual influences.

(1) HRG's Inhibitory Effect on Angiogenesis

1) HRG: Zn^{2+} -Concentration-Dependent Switch

The HRG core architecture follows a " Zn^{2+} -HRR-N1N2" ternary switch model: The N-terminal N1N2 domain directly binds to cell surface heparan sulfate (HS), while the central histidine-rich region (HRR) acts as a Zn^{2+} sensor. Upon Zn^{2+} chelation at physiological concentrations (0–10 μ M, compatible with platelet-activated release concentrations), the HRR induces an allosteric effect that significantly enhances the HS-binding capacity of full-length HRG. This effect does not directly influence the N1N2 domain itself, enabling dynamic regulation of HRG function by Zn^{2+} concentration [11]. Structural studies reveal that the 35-aa peptide segment HRGP330 exhibits absolute Zn^{2+} dependence for HS binding, with over 90% loss of binding capacity in the absence of Zn^{2+} . Furthermore, the Zn^{2+} -HRG complex recognizes HS with a minimum length of only an 8-mer oligosaccharide, ensuring efficient, low-threshold activation within the microenvironment [16].

This Zn^{2+} switch imparts spatial selectivity to HRG, restricting its function to Zn^{2+} -enriched pathological microenvironments. At vascular injury sites, Zn^{2+} released by activated platelets allows HRG to counteract heparin and reverse its suppression of vascular smooth muscle cell growth, supporting repair [17]. Within the tumor microenvironment, increased Zn^{2+} concentrations and lower pH levels enhance HRG ligand-binding via the HRR domain, intensifying HRG effects specifically in tumor areas [8]. Elevated Zn^{2+} in septic tissues strengthens HRG's inhibition of erythrocyte-endothelial adhesion, mitigating hemolytic injury [18]. HRG also participates in coagulation regulation: PDI-reduced HRG allows Zn^{2+} -HRG to rapidly initiate procoagulant effects by neutralizing endothelial HS, while simultaneously inhibiting FXIIa to control excessive propagation. Zn^{2+} gradients determine the biphasic modulation exerted by HRG at the injured site [19]. Zn^{2+} preferentially enhances HRG's neutralization of high molecular weight heparin (UFH/HMWH) but has limited influence on low molecular weight heparin (LMWH), ensuring HRG action is prominent in UFH-rich areas such as at surgical wounds [12]. Zn^{2+} also acts as a molecular glue, enabling HRG to bridge multiple ligands such as HS, plasminogen, and TSP simultaneously. Within Zn^{2+} -enriched regions, HRG favors high-affinity ligand binding, while its affinity for low-affinity ligands is preserved in Zn^{2+} -depleted zones [20]. As a Zn^{2+} -dependent molecular switch, HRG acquires spatially-selective regulatory effects through microenvironmental metal ion

gradients, thereby linking coagulation, angiogenesis, and immune responses.

2) HRG blocks the adhesion-migration cascade

Studies indicate that HRG's anti-angiogenic activity primarily resides in its histidine-proline-rich region (HRR). This domain binds with high affinity to tropomyosin on the surface of FGF-2-activated human umbilical vein endothelial cells (HUVECs) in a Zn^{2+} - or low pH-dependent manner, achieving this binding via at least two independent sites [21]. Functionally, HRG-myosin binding directly disrupts focal adhesion structures in endothelial cells, diminishing their ability to adhere to vitronectin, thereby significantly inhibiting cell migration and lumen formation [9]. Notably, this inhibition occurs not through inducing endothelial cell apoptosis or suppressing proliferation, but rather by specifically blocking the adhesion-migration cascade [22]. Mechanistic studies further revealed that only the free HRR released from intact HRG via proteolytic cleavage possesses anti-angiogenic activity [23]. At the same time, the synthetic tetrameric peptide (HHPHG)₄ (16-mer) sufficiently mimics the anti-angiogenic effects of intact HRG with an IC_{50} of approximately 600 nM, confirming myosin as a novel targetable anti-angiogenic site [24]. Within the tumor microenvironment, HRG significantly reduces tumor vascular density (>60%) via this mechanism [9]. It exhibits high expression in human brain cancer tissues and localizes to the tumor basement membrane, suggesting clinical relevance in vascular remodeling [25]. HRG blocks the adhesion-migration cascade by directly binding tropomyosin on endothelial cell surfaces, representing one of its core mechanisms for anti-angiogenic effects.

3) HRG interferes with adhesion signals

HRG directly anchors to heparan sulfate (HS) proteoglycans on the cell surface via its N-terminal N1N2 domain, while Zn^{2+} chelation with the central histidine-rich region (HRR) indirectly enhances this binding. This process is dynamically regulated by heparanase [11]. HS serves as the critical cell surface ligand for HRG, and its binding is a prerequisite for HRG function: heparin pretreatment completely blocks HRG-induced endothelial cell focal adhesion rearrangement [16]. Once proteolytically released and bound to the cell surface, the His/Pro domain of HRG specifically disrupts endothelial cell adhesion to fibronectin, thereby inhibiting migration and tumor angiogenesis (inhibition rate >60%) without affecting cell proliferation or apoptosis [9]. Notably, HRG-HS interactions (with minimal recognition units being 8-mer oligosaccharides) are significantly enhanced in injury/tumor microenvironments characterized by elevated Zn^{2+} and low pH [8, 16]. Clinical sample analysis revealed that HRG is highly expressed in human brain cancer tissues and localized to the tumor basement membrane [15], further suggesting that HS-mediated anchoring is a key mechanism by which HRG regulates vascular remodeling in the tumor microenvironment.

4) HRG-Mediated Tumor Vascular Normalization

Theek et al. first directly demonstrated that supplementing HRG or macrophage-mediated vascular normalization significantly improves tumor vascular structural integrity. This enhances the accumulation of 10–20 nm polymeric nanocarriers within tumors and increases their interstitial penetration depth, thereby overcoming the barriers posed by tumor vascular heterogeneity to drug delivery [26]. The cellular basis of this mechanism lies in the tissue-specific distribution regulation of HRG by the mononuclear

phagocyte system: Tugues et al. demonstrated rapid uptake of HRG from circulation by monocyte-macrophages and its transport to the tumor stroma, where it colocalized with CD45⁺ inflammatory cells. This process was blocked by anti-CSF-1 antibodies, confirming macrophages as key mediators of HRG enrichment in the tumor microenvironment [27]. Conversely, Foglia et al. found that HRG knockout in a MASLD-associated hepatocellular carcinoma model reduced tumor-associated macrophage infiltration and secretion of proangiogenic factors like VEGF, suggesting HRG may promote macrophage-mediated angiogenesis under specific pathological conditions [13]. Synthesizing these studies, HRG-mediated vascular normalization by macrophages may occur through circulating macrophages capturing HRG and delivering it to the tumor stroma. HRG then acts on endothelial cells or regulates macrophage polarization, inducing vascular structural reorganization and ultimately improving tumor perfusion and drug delivery efficiency [26, 27]. However, the lack of molecular mechanisms remains a significant limitation in this field—existing studies have not elucidated how macrophages sense HRG signals and translate them into reprogramming instructions for endothelial cells [26]. Furthermore, the functional differences of the HRG-macrophage axis in tumor versus non-tumor environments (promoting angiogenesis vs. vascular normalization) require further elucidation [13]. HRG-mediated tumor vascular normalization via macrophages represents an emerging immunovascular regulatory mechanism.

(2) HRG's Pro-Angiogenic Effects

1: HRG's Pro-Angiogenic Activity

1) HRG neutralizes TSP-1/TSP-2

HRG neutralizes the anti-angiogenic activity of TSP-1/TSP-2 by directly binding to their Type I repeat sequence (TSR) and masking their CD36 binding epitope. [10] Simantov et al. demonstrated that HRG binds to TSP-1 with high affinity, blocking its interaction with endothelial cell CD36 and reversing TSP-1's inhibition of migration, luminal formation, and corneal angiogenesis in mice [23]. Further studies confirmed this mechanism also applies to TSP-2: TSP-2 interacts with CD36 via TSR (binding site aa 93-120), while HRG binds TSP-2 with high affinity and blocks its anti-angiogenic activity [28]; in CD36 knockout mice, TSP-2 completely lost its ability to inhibit bFGF-induced angiogenesis [29, 30]. This action correlates with HRG's properties as a multiligand adaptor, whose function is regulated by Zn²⁺ [7, 8].

2) HRG neutralizes Vstat120 (BAI1 fragment)

Histidine-rich glycoprotein (HRG) attenuates the anti-angiogenic effects of the extracellular fragment Vasculostatin (Vstat120) of brain angiogenic inhibitor 1 (BAI1) by neutralizing it. [15] Klenotic et al. (2010) first elucidated this mechanism: Vstat120 requires binding to CD36 on microvascular endothelial cell surfaces to activate caspase-mediated proapoptotic pathways [25]. HRG acts as a "CD36 decoy receptor" by directly binding Vstat120, blocking its interaction with CD36 and thereby completely inhibiting Vstat120-induced endothelial apoptosis [15]. In vitro studies demonstrated that HRG restored endothelial cell migration and tubule formation capabilities suppressed by Vstat120. In vivo, subcutaneous and orthotopic brain tumor models showed that HRG overexpression significantly promoted tumor growth and increased vascular density. Further research revealed elevated HRG expression in human brain cancer tissues, primarily localized to the tumor basement membrane,

confirming the clinical relevance of this HRG-Vstat120-CD36 proangiogenic axis. Notably, HRG also neutralizes the anti-angiogenic effects of thrombospondin-1/2 (TSP-1/TSP-2) [23, 29], revealing a common mechanism where HRG modulates angiogenesis by "hijacking" multiple endogenous anti-angiogenic factors.

3) HRG Supports Pro-angiogenic Macrophages

Histidine-rich glycoprotein (HRG) promotes angiogenesis in the tumor microenvironment by supporting proangiogenic macrophages. [13] Foglia et al. demonstrated in a metabolic dysfunction-associated steatohepatitis (MASH)-associated hepatocellular carcinoma (HCC) model that HRG knockout mice exhibited significantly reduced tumor volume and number [31], accompanied by decreased infiltration of pro-inflammatory/pro-angiogenic macrophages producing IL-1 β , IL-6, IL-12, IL-10, and VEGF, along with suppressed angiogenesis [32]. This mechanism relies on HRG's function as a "CD36 decoy receptor": Simantov et al. demonstrated that HRG neutralizes the anti-angiogenic effects of thrombospondin-1/-2 (TSP-1/TSP-2) [10, 29], while Klenotic et al. further discovered that HRG similarly binds and inhibits the CD36-dependent anti-angiogenic effects of the BAI1 fragment Vstat120 [15], thereby releasing inhibition of the proangiogenic phenotype in macrophages. Tugues et al. elucidated that monocyte-macrophages are key cellular mediators of HRG tissue distribution and functional execution [27]. Some researchers have reviewed that HRG modulates macrophage polarization, promoting the survival and function of mixed tumor-associated macrophages (TAMs) with both proinflammatory and proangiogenic capabilities in the tumor microenvironment [33]. In summary, HRG shapes a pro-angiogenic immune microenvironment by neutralizing multiple CD36-mediated anti-angiogenic factors [34], thereby driving MASLD/MASH progression to HCC. This axis serves as a prognostic biomarker and therapeutic target.

4) HRG Structural Rearrangement Indirectly Enhances Vascular Function

Histidine-rich glycoprotein (HRG) induces tumor vascular normalization to enhance perfusion and drug delivery [26]. Theek et al. demonstrated in HRG knockout/overexpressing mice that HRG-mediated macrophage-dependent vascular remodeling significantly increased tumor accumulation and interstitial permeability of 10-20 nm nanocarriers [23, 35]. Cheng et al. further demonstrated through hypoxia-targeted HRG delivery that it not only reduces abnormal vascular density but also downregulates the HIF-1 α -VEGF/Ang-2 pathway to improve the hypoxic microenvironment. This concurrently achieves anti-angiogenesis and vascular normalization, inhibiting melanoma growth and metastasis [36]. Concurrently, Foglia et al. discovered that HRG supports proangiogenic macrophage infiltration [13], suggesting vascular normalization may be indirectly mediated by HRG-remodeled macrophage function.

4. Summary and Outlook

Histidine-rich glycoprotein (HRG) exhibits a dual role in neovascular regulation that is highly microenvironment-dependent, reflecting its core function as a multifunctional plasma adaptor molecule. Its ultimate effects depend on the dynamic equilibrium of multiple factors, including proteolytic status, ligand availability, and local ion concentrations.

On one hand, the Histidine-Proline Rich Region (HRR) of HRG, released upon proteolytic cleavage, binds to myosin on

endothelial cell surfaces via a Zn^{2+} -dependent mechanism. This disrupts focal adhesion assembly and blocks migration signals, thereby inhibiting tumor angiogenesis [9, 21]. This activity requires N-terminal domain-mediated anchoring to heparan sulfate proteoglycans, with Zn^{2+} significantly enhancing this binding [11, 16], playing a crucial role in HRG's anti-angiogenic effects.

Conversely, as a "broad-spectrum CD36 decoy receptor," HRG binds with high affinity to the type I repeat sequence of TSP-1/2 and the anti-vascular fragment Vstat120 of BA11, physically shielding their CD36 binding epitopes [37]. This neutralizes endogenous inhibitory factors, thereby promoting angiogenesis [15, 38]; In hepatocellular carcinoma associated with metabolic liver disease, HRG further accelerates tumor progression by supporting pro-inflammatory/pro-angiogenic macrophage infiltration [13].

The microenvironment finely regulates this dual pro- and anti-angiogenic activity: Zn^{2+} released upon platelet activation or tissue injury acts as a "molecular switch" selectively enhancing HRG's neutralization of high molecular weight heparin [12, 17]. At the same time, the mononuclear phagocyte system mediates HRG's circulatory clearance and tissue distribution [27]. This process both drives vascular normalization to enhance drug delivery and shapes the pro-cancer immune microenvironment [26]. In summary, the ultimate effect of HRG is not fixed but determined by the dynamic equilibrium of multiple factors, including proteolytic status, ligand availability, and local ion concentrations.

Therefore, HRG serves as both a potential resistance mechanism against anti-angiogenic therapy in tumors [39] and a regulatory node for vascular normalization strategies [35]. Its clinical translation requires precision-based definition according to disease type, disease stage, and microenvironment characteristics. Future research should focus on exploring novel therapeutic strategies targeting the HRG- Zn^{2+} axis or leveraging its vascular normalization capacity to fully unlock its potential as a diagnostic biomarker and therapeutic target, thereby opening new avenues for overcoming anti-angiogenic therapy resistance and improving drug delivery.

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