Mechanisms of infantile hemangioma involution (Review)

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Abstract. Infantile hemangioma (IH) is the most common benign vascular tumor of infancy, characterized by a distinctive life cycle of rapid postnatal proliferation followed by spontaneous involution. However, the mechanisms underlying this regression process remain incompletely understood. In this narrative review, current IH-specific evidence was synthesized and candidate pathways were organized according to their relative strength. A total of three core mechanistic modules with moderate-to-high supporting evidence were identified: Endothelial proliferation restraint, immune microenvironment remodeling and adipogenic differentiation of hemangioma-derived progenitor cells. Additional pathways, including extracellular matrix remodeling, regulated cell death and endocrine signaling, were discussed as potential contributors but remain less validated. Overall, IH involution appears to represent an active and coordinated process of immunovascular remodeling rather than passive regression. Future studies should prioritize longitudinal human samples, single-cell and spatial profiling and functional validation in immune-competent models to clarify the temporal hierarchy and causal interactions among these pathways.

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Abbreviations: IH, infantile hemangioma; HemECs, hemangioma endothelial cells; HemSCs, hemangioma stem cells; EndMT, endothelial-to-mesenchymal transition; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; PPARγ, peroxisome proliferator-activated receptor γ; HIF-1α, hypoxia-inducible factor 1α; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor 1; IGF-1R, IGF1 receptor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; IL-1β, interleukin-1β; IFN-γ, interferon γ; IDO, indoleamine 2,3-dioxygenase; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase

Key words: infantile hemangioma, spontaneous regression, involution, immune microenvironment, endothelial plasticity, adipogenic differentiation

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1. Introduction

Infantile hemangioma (IH) is the most prevalent benign vascular tumor of infancy, characterized by a unique life cycle of rapid postnatal proliferation, stabilization and spontaneous involution with fibro-fatty replacement (1,2). However, the mechanisms driving IH involution remain poorly understood (3,4). Existing studies, based on human tissues, *in vitro* models and animal systems, have implicated processes such as reduced endothelial proliferation, immune microenvironment remodeling and adipogenic differentiation. Nevertheless, the evidence remains fragmented and lacks a coherent synthesis (5). Recent work has further highlighted stage-dependent cell-fate transitions in hemangioma stem cells, including differentiation toward endothelial, perivascular and adipocytic lineages across IH development and involution (6). Single-cell profiling has also revealed marked cellular heterogeneity and intercellular communication between endothelial and mural-cell populations, supporting a multicellular model of IH progression (7). More recent evidence further emphasizes dynamic immune-vascular crosstalk during the transition from proliferation to involution, particularly changes in macrophage states and stromal remodeling (8). In this narrative review, the key mechanisms underlying IH involution were summarized and current evidence was organized according to its relative strength, with an emphasis on pathways most consistently supported across studies. For many pathways, however, available evidence remains largely associative and their causal roles in IH involution have yet to be fully established.

2. Methods

Evidence appraisal and grading. To evaluate the strength of evidence for candidate mechanisms of IH involution, a modified grading system based on the Oxford Centre for Evidence-based Medicine and the U.S. Preventive Services Task Force guidelines was adopted (9), focusing on the integrity and causal clarity of IH-specific evidence: Grade A requires a complete closed loop of clinical, *in vitro*, molecular mechanism and *in vivo* validation, confirming the direct causal relationship of the pathway in mediating IH involution; Grade B necessitates clinical or *in vitro* functional evidence plus validation of key pathway nodes, but lacks a full causal chain; Grade C only involves expression associations between molecules and IH involution without direct mechanistic validation; Grade I has no IH-specific experimental support and relies solely on indirect speculation or extrapolation from other disease models, with insufficient evidence to support mechanistic relevance (Table I). This grading framework is intended to provide a structured overview of relative evidence strength rather than a formal systematic evaluation.

Scope of the review. Studies using human tissue, *in vitro* experiments and animal models suggest that reduced endothelial proliferation, immune remodeling and adipogenic differentiation contribute to regression. Key candidate mechanisms are outlined in Table I and illustrated in Fig. 1, including endothelial proliferation restraint, immune remodeling and adipogenic replacement.

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Original research with experimental validation (clinical, *in vitro*, *in vivo* or bioinformatics analyses specific to IH); ii) studies focusing on infantile hemangioma (human tissues, IH-derived cells or IH-specific animal models); iii) research on molecular or cellular mechanisms underlying IH involution; iv) publications reporting outcomes related to IH involution (molecular changes, cellular phenotypes, histology or lesion regression); and v) full-text articles in English or Chinese with accessible methods and data. Priority was given to original research, while selected reviews were used for contextual support.

The following exclusion criteria were applied: i) Case reports, editorials, letters or abstracts without experimental validation; ii) studies on non-IH vascular anomalies or unrelated diseases without IH-specific mechanistic evidence; iii) descriptive studies without investigating involution mechanisms; iv) duplicates, inaccessible full texts or studies with critical design flaws; and v) research extrapolating from non-IH models without IH-specific verification.

3. Core mechanisms of IH Involution

Mechanisms that may restrain endothelial proliferation and initiate phenotypic change. Attenuation of endothelial proliferation is a consistent feature of involuting IH, indicating active suppression of aberrant endothelial growth accompanied by phenotypic remodeling. KIAA1429 is best considered part of a broader network of post-transcriptional and cell-cycle regulators rather than an independent driver of involution.

Post-transcriptional and cell-cycle mechanisms constraining endothelial proliferation. KIAA1429 is an RNA-binding protein associated with the N6-methyladenosine (m6A) methyltransferase complex, with potential additional roles in transcript-specific regulation (10). In IH, KIAA1429 expression is increased in involuting lesions and is enriched in hemangioma endothelial cells (11). Functional studies show that KIAA1429 overexpression suppresses endothelial proliferation, migration and tube formation, while promoting a fibroblast-like phenotype (12).

Mechanistically, KIAA1429 binds target RNAs in hemangioma endothelial cells (HemECs) and downregulates Cyclin D1 and Cyclin E, leading to cell-cycle arrest and reduced endothelial activity, thereby facilitating phenotypic transition and priming cells for adipogenic differentiation. However, the relative contribution of m6A-dependent vs. m6A-independent regulation remains elusive (13). Current evidence supports a role for KIAA1429 in endothelial reprogramming rather than as a primary initiator of involution.

p16 inhibitor of cyclin-dependent kinase 4 A (INK4a) and the broader growth-arrest program. The p16INK4a-retinoblastoma protein (Rb) pathway is a canonical regulator of the G1-S transition and provides a mechanistic basis for endothelial growth arrest during IH involution (14,15). In IH, p16 expression is low in proliferative lesions and increases during involution, consistent with reduced endothelial cycling and angiogenic activity (16). Mechanistically, p16INK4a upregulation activates the Rb pathway, inducing G1/S arrest and limiting endothelial proliferation. This growth-arrest program contributes to suppression of vascular expansion but does not account for downstream tissue remodeling.

Accordingly, p16INK4a should be interpreted as part of a broader endothelial de-escalation program. Together with regulators such as KIAA1429, it constrains endothelial proliferation, while additional processes are required to drive immune remodeling, vascular regression and fibro-fatty replacement.

Immune remodeling and regulated cell-death programs. Immune remodeling is a consistent feature of IH involution and links vascular regression with tissue clearance. Compared with proliferative lesions, involuting IH exhibits altered immune composition and increased inflammatory signaling. Available evidence suggests a shift from immune tolerance toward inflammatory activation, involving reduced immune suppression, macrophage polarization, cytokine-mediated endothelial disruption and activation of regulated cell-death pathways. These processes collectively contribute to endothelial destabilization and tissue remodeling, rather than representing a single dominant trigger.

Indoleamine 2,3-dioxygenase (IDO) and the waning of an immune-tolerant niche. IDO regulates local immune tolerance by metabolizing tryptophan and activating the kynurenine pathway. In proliferative IH, elevated IDO expression is associated with suppressed T-cell activity and the maintenance of an immune-permissive microenvironment (17). During involution, reduced IDO expression likely restores T-cell surveillance, particularly $CD8^+$ T-cell activity, facilitating clearance of abnormal vascular cells. This shift suggests a transition from an immune-tolerant to an immune-reactive state.

Table I. Relative evidentiary weight of representative mechanisms proposed in IH involution based on modified Oxford Centre for Evidence-based Medicine and the U.S. Preventive Services Task Force criteria.

Mechanism	IH-specific evidence	Grade	Interpretation for a mechanistic review
Adipogenic differentiation of hemangioma-derived progenitors	HemSCs/Hem-MSCs adipogenic *in vitro*; IGF-1/PI3K/AKT/PPARγ axis validated; clinical fibro-fatty replacement; animal model correlation	A	Strong recommendation; core histological endpoint with complete causal chain, high translational potential.
KIAA1429-associated endothelial reprogramming	Involution lesions/HemECs high expression; suppresses endothelial function, enhances stemness/adipogenesis; animal model microvessel reduction; Non-m6A dependent	A	Strong recommendation; definitive endothelial de-escalation node, consistent *in vitro*/*in vivo*/clinical evidence.
Propranolol-mediated PI3K/Akt/eNOS/VEGF attenuation	Clinical VEGF/eNOS downregulation; inhibits HemEC function via p-Akt/p-eNOS suppression; rescue with LY294002; animal model vascular density reduction.	A	Strong recommendation; clinically validated pathway that explains propranolol's therapeutic effect.
p16INK4a/cell-cycle restraint	Low in proliferation, high in involution; correlates with reduced endothelial cycling; consistent across cohorts	B	Strong recommendation; critical for growth restraint, lacks tissue replacement causal validation.
Macrophage-associated inflammation and EndMT	Involution M1 infiltration; TNF-α/IL-1β induces EndMT in HemECs; functional phenotypic switch correlation	B	Moderate recommendation; immune remodeling supported, EndMT causality needs lineage tracing.
HIF-1α/Notch/bFGF attenuation	High in proliferation, reduced in involution; inhibits HemEC proliferation/angiogenesis; xenograft anti-angiogenic effect.	B	Moderate recommendation; supports growth suppression, insufficient for full fibro-fatty replacement.
IDO/immune tolerance axis	High in proliferation, declined in involution; T-cell surveillance dampening; immune cell infiltration correlation	C	Weak recommendation; plausible, lacks IH-specific knockout/overexpression validation.
ECM remodeling and exosomal signaling	Altered matrix turnover/integrin signaling; exosomal miRNAs/lncRNAs regulate communication; correlates with vascular collapse/adipogenesis.	C	Weak-moderate recommendation; contributory, instructive vs. reactive role unclear.
Pyroptosis/necroptosis/ferroptosis	Signature-level gene upregulation; indirect oxidative stress/immune activation; no direct *in vivo*/lineage validation	I	Insufficient evidence; hypothesis-generating, associative/extrapolated from non-IH models.
Endocrine signaling (estrogen/FSH)	FSHR expression; estrogen supports HemSC self-renewal; FSH promotes proliferation/inhibits apoptosis; phase correlation	I	Insufficient evidence; plausible phase modulator, no involution-triggering validation.

IH, infantile hemangioma; HemECs, hemangioma endothelial cells; HemSCs, hemangioma stem cells; EndMT, endothelial-to-mesenchymal transition; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; PPARγ, peroxisome proliferator-activated receptor γ; HIF-1α, hypoxia-inducible factor 1α; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor 1; IGF-1R, IGF1 receptor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; IL-1β, interleukin-1β; IDO, indoleamine 2,3-dioxygenase; m6A, N6-methyladenosine; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; FSHR, follicle-stimulatory hormone receptor; miRNA, microRNA; lncRNA, long non-coding RNA; bFGF, basic fibroblast growth factor.

However, current evidence is primarily associative. IDO is therefore best interpreted as a modulator of immune context rather than a primary initiator of involution.

Macrophage-associated inflammation and endothelial fate transition. Macrophages are a major immune component in IH and exhibit functional plasticity between pro-angiogenic and pro-inflammatory states. During involution, available evidence supports a shift from an M2-like, pro-angiogenic phenotype toward an M1-like, inflammatory phenotype (18-20). Mechanistically, M1-associated cytokines, including TNF-α, IL-1β and IFN-γ, disrupt endothelial stability and activate TGF-β/Smad2/3 signaling in HemECs, upregulating transcription factors such as Snail and Twist. This is associated with reduced expression of endothelial markers (e.g., vascular endothelial cadherin, CD31), morphological changes and features consistent with endothelial-to-mesenchymal transition (EndMT) (21).

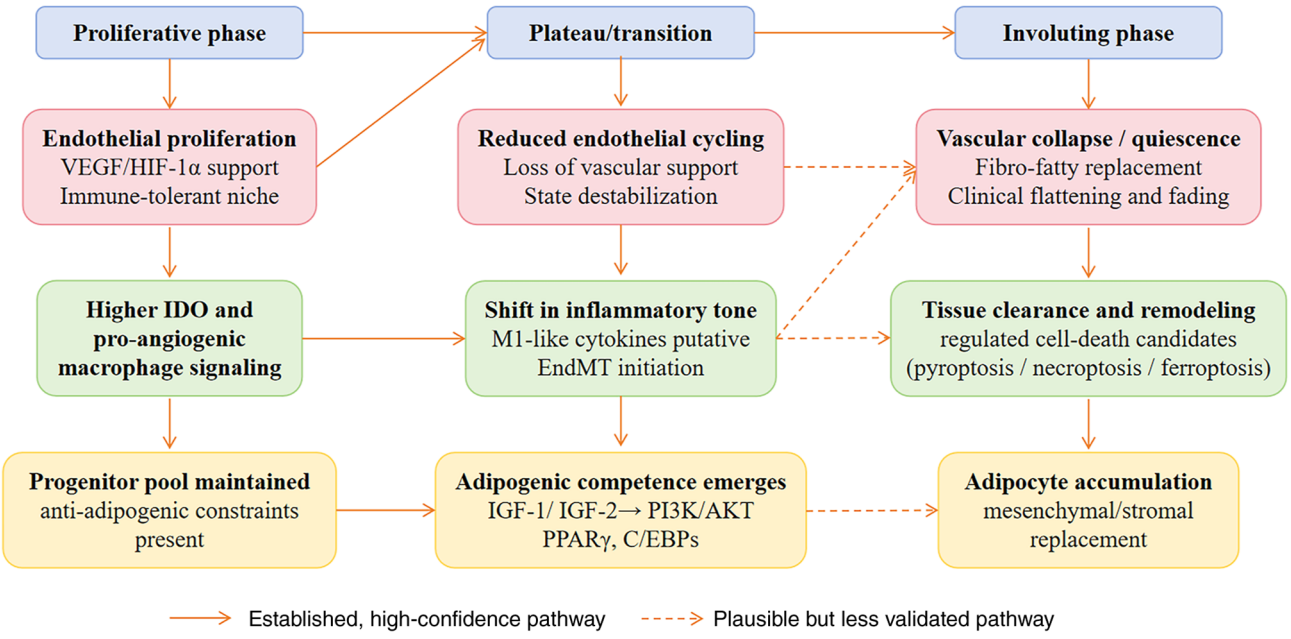


Figure 1. Schematic overview of coordinated immunovascular changes during infantile hemangioma involution. EndMT, endothelial-to-mesenchymal transition; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; C/EBPs, CCAAT-enhancer-binding proteins; PPARγ, peroxisome proliferator-activated receptor γ; HIF-1α, hypoxia-inducible factor 1α; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor 1; IGF-1R, IGF1 receptor.

These findings support a role for macrophage-driven inflammation in endothelial destabilization and phenotypic transition. However, whether EndMT represents a required mechanism in IH involution remains to be established (22,23).

Pyroptosis as a candidate contributor to inflammatory tissue clearance. Pyroptosis is an inflammasome-mediated form of inflammatory cell death characterized by caspase-1 activation and release of pro-inflammatory cytokines. In IH, its involvement has been suggested primarily by gene-expression signatures associated with immune infiltration (23,24). Mechanistically, pyroptosis may promote inflammatory amplification and immune cell recruitment, contributing to the clearance of vascular cells and tissue remodeling. However, direct functional evidence in IH remains lacking.

Accordingly, pyroptosis is best regarded as a candidate mechanism of inflammatory clearance rather than an established driver of involution.

Necroptosis-related signatures: Signal or by-product? Necroptosis-related gene signatures have been identified in IH and are associated with immune-related features and lesion heterogeneity. Mechanistically, necroptosis may contribute to inflammatory signaling by activating the receptor interacting serine/threonine kinase (RIPK1)/RIPK3/ mixed lineage kinase domain like pseudokinase pathway, potentially enhancing immune-mediated tissue remodeling.

However, current evidence is limited to associative analyses without functional validation. Necroptosis should therefore be regarded as a hypothesis-generating pathway rather than a confirmed contributor to IH involution.

Ferroptosis, oxidative stress and macrophage function. Ferroptosis has been proposed as a mechanism linking oxidative stress and lipid peroxidation to endothelial vulnerability during IH involution. Observations involving glutathione peroxidase 4-related pathways, redox imbalance and macrophage-associated changes suggest that involution occurs within an oxidatively altered microenvironment (25). Mechanistically, ferroptosis may promote selective endothelial cell loss through lipid peroxidation and reactive oxygen species accumulation, potentially interacting with inflammatory signaling pathways.

However, supporting evidence in IH remains indirect. Ferroptosis is therefore best interpreted as a potential contributor to oxidative stress-mediated vascular regression rather than a primary driver of involution.

Extracellular matrix (ECM) remodeling and intercellular communication. Regression of IH requires not only changes in endothelial cell fate but also structural reorganization of the tumor microenvironment. During involution, ECM remodeling contributes to vascular destabilization and tissue replacement (26). Mechanistically, altered integrin signaling and ECM turnover disrupt focal adhesion kinase and Rho GTPase pathways, weakening endothelial adhesion and destabilizing the vascular scaffold. In parallel, extracellular vesicles carrying microRNAs and long non-coding RNAs mediate intercellular communication among HemECs, hemangioma stem cells (HemSCs) and stromal cells, coordinating endothelial regression and stromal remodeling (27-29).

These processes likely facilitate structural reorganization required for involution. However, whether ECM remodeling functions as an active driver of phase transition or primarily reflects downstream adaptation remains elusive.

Endocrine and hormonal influences. Endocrine signaling may modulate the cellular context in which IH develops and regresses. Compared with involution-specific mechanisms, current evidence supports a role in regulating proliferative capacity rather than initiating regression. Mechanistically,

estradiol activates estrogen receptor (ER)α/ERβ signaling in HemSCs, leading to PI3K/Akt activation and upregulation of VEGFA, basic fibroblast growth factor (bFGF) and Cyclin D1, thereby promoting cell proliferation and survival (30-32). Similarly, follicle-stimulatory hormone (FSH) signaling through FSH receptor activates the cyclic AMP/protein kinase A pathway, increasing Cyclin D1 and Bcl-2 expression, which enhances cell-cycle progression and resistance to apoptosis (33,34).

These pathways contribute to the maintenance of a proliferative niche and may indirectly influence the timing of involution. However, direct evidence supporting a role in initiating regression remains lacking.

Adipogenic differentiation and fibro-fatty replacement. Fibro-fatty replacement represents the defining histological endpoint of IH involution, placing adipogenic differentiation at the center of regression models. Compared with other proposed mechanisms, this process is supported by relatively strong experimental evidence (35).

Insulin-like growth factor (IGF)-related signaling and adipogenic competence. The IGF axis regulates progenitor-cell fate in IH through IGF-1R-mediated PI3K/Akt signaling. Mechanistically, IGF-1 and IGF-2 activate PI3K/Akt signaling, upregulating adipogenic transcription factors including peroxisome proliferator-activated receptor (PPAR)γ, CCAAT-enhancer-binding protein (C/EBP)α and C/EBPβ, thereby driving differentiation of HemSCs into adipocytes (36-38). IGF-2 may also contribute to propranolol-associated adipogenesis through the same pathway (39,40).

These findings support a role for IGF signaling in establishing adipogenic competence. However, given its broad physiological functions, IGF signaling is more likely to enable lineage transition after vascular regression rather than act as a primary initiating trigger.

Platelet-derived growth factor (PDGF) signaling as a counterweight to adipogenesis. PDGF signaling has been proposed as a counter-regulatory pathway opposing adipogenic differentiation. Mechanistically, PDGF activates PI3K/Akt, ERK1/2 and STAT3 signaling via PDGFR-β, which suppresses adipogenic transcription factors such as PPARγ and C/EBPα/β, thereby inhibiting HemSC differentiation into adipocytes.

Reduced PDGF signaling may therefore shift the balance toward adipogenic differentiation during involution. However, current evidence remains limited and its position within the causal hierarchy of IH regression remains elusive.

Hemangioma-derived mesenchymal populations and terminal tissue replacement. Hemangioma-derived mesenchymal and stem-like populations exhibit adipogenic differentiation potential, providing a cellular basis for fibro-fatty replacement (41). This supports a model in which involution involves active lineage transition rather than passive vascular loss. These progenitor populations likely serve as the primary cellular source of adipocytes during tissue remodeling.

T-box transcription factor 2 (TBX2) and additional regulators of adipogenic transition. Transcriptional regulators, including TBX2 and related factors, have been implicated in modulating adipogenic differentiation in IH-derived progenitors (42,43). Mechanistically, these factors regulate the promoter activity of adipogenic genes, such as PPARγ and C/EBP family members, and may interact with regulators, including Kruppel-like factor 4 and sterol regulatory element binding transcription factor 1, to fine-tune lineage commitment.

However, current evidence is limited and these regulators should be interpreted as modulators of adipogenic transition rather than as central drivers of involution.

Anti-angiogenic and hypoxia-related pathways. Attenuation of pro-angiogenic signaling is a consistent feature of IH involution but does not alone define a regression-specific program. Mechanistically, reduced activity of hypoxia-inducible factor (HIF)-1α, Notch and bFGF/FGFR1 signaling is associated with decreased expression of VEGFA and angiopoietin 2, suppression of the MAPK/ERK and PI3K/Akt pathways, and reduced endothelial proliferation and survival (44-48). These changes contribute to diminished angiogenic support and facilitate vascular regression. However, growth suppression alone does not account for coordinated tissue remodeling and fibro-fatty replacement (49).

Accordingly, anti-angiogenic and hypoxia-related pathways are best interpreted as creating a permissive environment for involution rather than acting as primary drivers.

4. Summary of key mechanisms, current limitations and future directions

Core findings and limitations of existing research. Through a systematic review of 150 original studies (clinical specimens, primary cell experiments and animal models), the present study summarized three core mechanisms underlying the spontaneous regression of IH. Several key pathways within these mechanisms carry Grade A evidence and represent key components of the current mechanistic understanding.

The PI3K/Akt/PPARγ axis-mediated adipogenic differentiation of HemSCs represents the terminal phase of involution and the only tissue-replacement mechanism with Grade A evidence. IGF-1 and IGF-2 activate AKT phosphorylation, thereby upregulating adipogenic transcription factors, including PPARγ, C/EBPα and C/EBPβ. Histological observations and animal data support this pathway. Notably, IGF-2 also mediates propranolol-induced adipogenesis, directly linking clinical therapy to endogenous involution programs.

Endothelial proliferation restraint and phenotypic reprogramming are mediated by KIAA1429-associated endothelial reprogramming and propranolol-mediated attenuation of PI3K/Akt/endothelial nitric oxide synthase/VEGF signaling (both Grade A) (50). These pathways inhibit endothelial function and reduce vascular density, consistent with propranolol's therapeutic effects (20,51,52). In addition, HIF-1α/Notch/bFGF signaling decay and p16INK4a-mediated cell cycle arrest (Grade B) further contribute to growth suppression. Macrophage-mediated immune remodeling (Grade B) shifts the microenvironment from pro-angiogenic M2-like toward pro-inflammatory M1-like macrophages, which promote EndMT and vascular breakdown. Additional mechanisms, such as IDO-related immune tolerance and regulated cell death pathways, remain largely unsupported by causal evidence (Grades C/I).

While these findings provide a useful overview, key gaps remain that hinder the full understanding of the molecular underpinnings of IH regression (53). Specifically, the upstream triggers of core pathways, the molecular crosstalk between complementary mechanisms and the integration of mechanistic findings with clinical needs-such as predicting individual regression trajectories and optimizing propranolol efficacy-remain unresolved (54,55).

Future mechanistic research directions. Future studies should prioritize mechanisms supported by high-evidence data to establish causal relationships rather than mere descriptive associations. First, upstream regulators of the PI3K/Akt/PPARγ axis and KIAA1429 remain to be identified. Phosphoproteomic and transcriptomic profiling of paired proliferative and regressing IH specimens can help pinpoint candidate kinases (e.g., pyruvate dehydrogenase kinase 1, mTOR complex 2) or phosphatases (e.g., phosphatase and tensin homolog) for subsequent functional validation (56).

Second, key downstream effectors should be defined, including fate-determining transcription factors governing HemSC adipogenesis and direct molecular targets of KIAA1429 in angiogenesis and adipogenic transition, using integrated sequencing strategies (57).

Third, the molecular basis of macrophage-mediated recognition and clearance of abnormal vascular structures remains to be investigated. Patient-derived organoids and immune-competent mouse models will be valuable to dissect these cellular interactions (58).

Translational value and technical pathway recommendations. These research directions carry clear translational potential. By advancing these pathways, clinical applications could be significantly improved, with potential for more precise, personalized therapies. Identifying upstream regulators of the PI3K/Akt/PPARγ axis may enable the development of small-molecule inhibitors that accelerate IH regression, thereby reducing treatment duration and systemic side effects (59). Targeting regulators of HemSC differentiation may offer alternative strategies for patients with propranolol resistance (60,61). KIAA1429 expression may serve as a predictive biomarker, with high levels likely associated with favorable responses to propranolol.

A three-step validation strategy (clinical specimens → primary cell experiments → animal models) is recommended. This three-step validation strategy ensures that mechanistic findings are biologically relevant and can be effectively translated into clinical applications. Incorporating patient-derived models will further improve preclinical predictive value and strengthen translational outcomes (62).

5. Conclusion

Spontaneous involution of IH is best understood as an active process of coordinated immunovascular remodeling rather than passive vascular regression. This review summarizes current evidence into three interconnected mechanistic modules, endothelial proliferation restraint, immune remodeling and adipogenic replacement, while distinguishing pathways by their level of support. Key challenges remain in defining upstream triggers, resolving interactions between pathways and linking mechanistic insights to clinical variability. Addressing these gaps through longitudinal human studies and functional models will be essential for improving mechanistic understanding and informing more targeted therapeutic strategies.

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Availability of data and materials

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection, analysis and administrative support were performed by XZ, YZ, JL, YW, XW, WP, WF, HL, QL and FC. The first draft of the manuscript was written by XZ, and all authors commented on and revised previous versions of the manuscript for important intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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