Angiotensin II-hnRNP K-VEGF Pathway: A Proposed Mechanism for Plasma Leakage in Dengue Virus Infection - A Narrative Review

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Abstract

Dengue virus infection (DVI) remains a global burden with increasing cases, deaths, and expansion of endemic areas. Plasma leakage (PL) as a major complication triggered by an immune response to DENV, but the molecular mechanism of increased vascular permeability has not been fully revealed. The hypothesis of the Angiotensin II (Ang II) – Heterogenous Nuclear Ribonucleoprotein K (hnRNP K) – Vascular Endothelial Growth Factor (VEGF) pathway is proposed as a key to the pathogenesis of PL. The aim of the paper is to review the scientific literature concerning the elements of the Ang II–hnRNP K–VEGF pathway, evaluate its association with PL in DVI, and develop a molecular hypothesis for future experimental research. Narrative review was conducted following Scale for Assessment of Narrative Review Articles (SANRA) guidelines. Literature search on PubMed, Scopus, ScienceDirect, and Google Scholar with keywords used alone or in

combination as follows “dengue”, "dengue infection", "dengue Virus", "Angiotensin II", "Ang II", “hnRNPK”, "Heterogenous Nuclear Ribonucleoprotein K", "hnRNP K", "plasma leakage", "Vascular Leakage", "Vascular Permeability", "Capillary Leak Syndrome". The inclusion criteria are English-language articles published between 2000-2025, while grey literature was left out from the source literature. Based on the results of the review search, it was found that Ang II increased in severe dengue that activated PKCδ. PKCδ phosphorylates hnRNP K on Ser302 residues so that hnRNP K translocate to the cytoplasm and binds to VEGF mRNA. It stabilizes the mRNA & enhances VEGF translation. VEGF interacts with VEGFR2 in endothelial cells, thus activating FAK, TSAd/Src, and PI3K/Akt signaling pathways that cause phosphorylation of VE-cadherin and decreased VE-cadherin expression through nitric oxide production, triggering disruption of intercellular connections. This triggers an increase in vascular hyperpermeability leading to PL. Based on this, the Ang II–hnRNP K–VEGF pathway is a strong hypothesis of the cause of PL in DVI. In vivo experimental validation is required to confirm this mechanism. Pathway modulation (e.g., Ang II inhibitors such as losartan) has the potential to be a novel targeted therapy to prevent severe DVI progressivity and reduce mortality.

Keywords: Dengue virus, Plasma leakage, Angiotensin II, hnRNP K, VEGF.

1. Context

Dengue virus infection (DVI) remains a challenge in Indonesia and other countries around the equator due to the increasing number of DVI cases, infections that occur and spread throughout the year, often give rise to outbreak, increase in mortality rates, and now extend to previously unaffected areas. The incidence rate of DVI is expected to increase with global warming, tourism, ease of population mobilization, and poor vector control. This situation not only increases the burden on the state but also the economic burden on the community (1).

DVI patients can experience mild symptoms (*flu-like symptoms*) to severe (bleeding and vascular leakage). DVI symptoms are affected by the immunological response. The immune response to dengue virus (DENV) is played by various cells, including hepatocyte, monocytes, and macrophages (2,3). DENV non-structural 1 (NS-1) stimulates hepatocytes to upregulate zonulin expression, resulting in enhanced vascular permeability (4). Meanwhile, recognition DENV by monocytes and macrophages triggers the formation of proinflammatory cytokine such as VEGF that contribute to the occurrence of cytokine storms (5). VEGF plays a role in increasing vascular

permeability which leads to plasma extravasation (6). However, the upstream pathways that trigger increased VEGF are still not clearly understood.

Angiotensin II (Ang II) is the main octapeptide in the renin-angiotensin (RAS) system. It is known that Ang II levels increase at DVI and cause plasma leakage (PL). Moreover Ang II activates the intracellular molecular cascade through attachment to the Angiotensin II Type 1 Receptor (AT1R) (7). Thus stimulating the activation of Protein kinase C δ (PKCδ) leading to hnRNP K phosphorylation (8). hnRNP K in the cytoplasm is known to bind to the DENV core, thereby facilitating DENV replication (9). In addition, hnRNP K also binds to VEGF mRNA so that VEGF mRNA becomes stable. This increases the synthesis of VEGF (8,10). Increased VEGF triggers PL (11).

Given that Ang II, hnRNP K, and VEGF are each separately related to the DVI pathway and the evidence that Ang II can affect hnRNP K leading to an increase in VEGF, we hypothesize that the Ang II–hnRNP K–VEGF pathway triggers plasma leakage in dengue infection. Therefore, this article aims to review the available scientific literature related to each component of the pathway, evaluate its possible association in the context of dengue, and lay the groundwork for molecular hypotheses as a direction for future experimental research. Understanding the involvement of these pathways more deeply is not only important for uncovering the pathogenesis of severe dengue but also has the potential to open up new directions in the development of therapies that target vascular regulation in the critical phase of dengue infection.

2. **Data Acquisition**

This article is compiled as a narrative review that aims to summarize and critically review the existing literature on Angiotensin II–hnRNP K–VEGF Pathway in Plasma Leakage in Dengue Virus Infection. The narrative review method was chosen because it is broad, conceptual, and requires an integrative approach that cannot be optimally covered by systematic review or meta-analysis methods.

To improve transparency and methodological quality, this article was compiled with reference to the Scale for the Assessment of Narrative Review Articles (SANRA), a validation tool used to assess the quality of narrative review articles. Six main criteria of SANRA are used as guidelines in the process of compiling articles, namely: 1) Justification of the importance of the article: The article provides by outlining the topic's importance and significance in the current scientific and/or clinical context. 2) Formulation of clear objectives or questions: The purpose of this review is explicitly outlined to guide the narrative synthesis. 3) Sufficiency of literature search: Literature searches were conducted using PubMed, Scopus, ScienceDirect, and Google Scholar

databases, with keywords used alone or in combination as follows “dengue”, "dengue infection", "dengue Virus", "Angiotensin II", "Ang II", “hnRNPK”, "Heterogenous Nuclear Ribonucleoprotein K", "hnRNP K", "plasma leakage", "Vascular Leakage", "Vascular Permeability", "Capillary Leak Syndrome". The inclusion criteria are English-language articles published between 2000-2025, while grey literature was left out from the source literature. 4) Critical engagement and evaluation of sources: Included references are selected based on methodological quality, scholarly relevance, and contribution to the topic's discussion. Evaluation is carried out critically on the content and quality of the source. 5) Logical argumentation structure: The article is thematically structured with a logical and integrated discussion flow. 6) Proper presentation and interpretation: Information from various sources is presented and interpreted objectively.

As part of the internal quality assurance process, authors have conducted an independent evaluation of this article using the SANRA checklist, to ensure that each quality criterion has been adequately met before the final manuscript is prepared. Overall, this approach is expected to produce review articles that are informative, systematic, and in accordance with internationally applicable academic standards.

3. Results

3.1 Angiotensin II

The renin-angiotensin-aldosterone system's primary octapeptide is Ang II. Prior to Ang II can be generated, the liver has to produce angiotensinogen and release it into the blood. Renin cleaves angiotensinogen, resulting in the formation of angiotensin I. Ang I is then transformed as Ang II by angiotensin-converting enzyme I. The formation of Ang II does not always occur through RAAS, it is known that Ang II can also be generated from the breakdown of Ang I by the enzymes cathepsin and chymase (5).

Ang II affects target cells through binding to Angiotensin II receptor I (AT1) and AT2 (12). Interaction between Ang II and the AT1 receptor triggers a signal path through Gq and G12/13. The Gq pathway activates phospholipase C (PLC) converting Phosphatidylinositol 4,5-bisphosphate (PIP2) to Inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 increases the release of Ca^{2+} from the endoplasmic reticulum, while DAG activates PKC-θ. In parallel, the G12/13 pathway activates Ras homolog family member A (RhoA) which activates Rho-associated coiled-coil containing protein kinase (ROCK) to further regulate Myosin Light Chain (MLC) phosphorylation. In addition, ANG II stimulates Nicotinamide Adenine Dinucleotide Phosphate Oxidase (NADPH oxidase) to produce Reactive Oxygen Species (ROS) which triggers Shedding of Heparin-binding epidermal growth factor like growth factor (HB-

EGF) by A Disintegrin and Metalloproteinase (ADAM) resulting in Epidermal Growth Factor Receptor (EGFR) activation. This EGFR transactivation activates the Extracellular Signal-Regulated Kinase 1 and 2 (ERK1/2) and Akt pathways. ANG II also causes stress of the endoplasmic reticulum that activates inflammatory pathways via Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and fibrosis via Transforming Growth Factor β (TGF-β) signaling (13). The activation effect of AT1 is different from that of AT2. It is believed that the role of AT1 activation is in contrast to AT2 and in general the effects of AT1 activation are more pathological (12)

3.1.1 Angiotensin II Induce Plasma Leakage

Ang II increases vascular permeability albeit with a slightly lower ability compared to VEGF. Ang II's binding with AT1R causes a signaling pathway into HUVEC (human umbilical vein endothelial cell) resulting in p38 phosphorylation. This process occurs within 30 minutes of exposure to Ang II which triggers the transfer of plasma to the extravascular tissue through a transcellular process mediated by caveolin. Increased vascular permeability by angiotensin by transcellular means occurs a few hours after exposure and peaks within 48 hours. The effect of transcellular vascular permeability enhancement is not dose-dependent and inhibited by the administration of angiotensin inhibitors (14).

Ang II's exposure to HUVEC for more than 48 hours decreased the expression of long noncoding RNA Maternally expressed gene 3 (Meg3). Decreased Meg3 expression increases p53 activity, so p53 stimulates the formation of pro-apoptosis proteins such as Bcl-2 Interacting Mediator of Cell Death (BIM), p53 Upregulated Modulator of Apoptosis (PUMA), and NOXA. These proteins then inhibit B-cell lymphoma 2 (Bcl-2) which is an anti-apoptotic protein. The end result of this process is cell apoptosis (15,16). Apoptosis and endothelial cell damage reminiscent of vascular permeability that causes PL (17).

Ang II enhances prostaglandin E2 (PGE2) synthesis (18). PGE2 binds to prostaglandin receptors (EP1-4). EP activation increases vascular permeability leading to PL (19). In addition, the bond between PDE2 and EP3 located in the mast cell membrane causes mast cell degranulation so that it releases a lot of histamine. Histamine is a substance known to increase vascular permeability when interacting with histamine receptors (20).

Ang II stimulates NF-κB activation by triggering the degradation of Inhibitor of kappa B α (IkBα) and IkBβ inhibitors. This process is mediated by ROS produced from mitochondria. Activation of NF-κB then enhances Vascular Cell Adhesion Molecule-1 (VCAM-1) transcription (21). VCAM stimulation activates Proline-rich tyrosine kinase 2 (Pyk2) subsequently phosphorylates VE-cadherin. This causes disruption of adhesion junction

formation which results in increased vascular permeability (22).

3.1.2 Angiotensin II Stimulate VEGF Synthesis

Ang II triggers the synthesis of VEGF through a process mediated by AT_1 R in the cell membrane. Activation of AT_1 R triggers NADPH oxidase (Nox) resulting in ROS production. ROS activates Akt which activates mammalian targets of rapamycin (mTOR). mTOR phosphorylates Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) leads to the eIF4E/4E-BP1 complex to break apart. Eukaryotic Initiation Factor 4E (eIF4E) then Together with eIF4E, eIF4A, and eIF4G form the eIF4F complex. eIF4F complex enhances VEGF mRNA translation (23). Ang II also triggers VEGF synthesis by activating p38 and phosphorylating cAMP Response Element-Binding protein (CREB). p38 enhances the transcription and translation of VEGF which is partially inhibited by p38 inhibitors. CREB phosphorylation increases its binding affinity to Cyclic Adenosine Monophosphate (cAMP) Response elements (CRE) in VEGF promoters (24). In addition to activating p38, Ang II also activates the ERK1/2 pathway, thereby enhancing the transcription and translation of VEGF (25).

3.1.3 Angiotensin II Activate hnRNP K

Heterogenous Ribonucleoprotein K is a ribonucleoprotein that can be found in the nucleus and cytoplasm. Stimulation of AT1R by Ang II activates Src kinase which then activates PKCδ. PKCδ phosphorylates hnRNP K in Serine 302 (Ser302) residues, causing hnRNP K to be located in the cytoplasm thereby increasing hnRNP K affinity to VEGF mRNA in the Cytosine–Uracil rich sequence within the 3′ Untranslated Region of mRNA (CU-rich 3′UTR region) (8,10).

Box 1. Role of Angiotensin II in Plasma Leakage

- Ang II triggers apoptosis and endothelial damage.
- Ang II triggers disruption of adhesion junction formation.
- Ang II increase synthesis of PGE2 and VEGF
- Ang II enhances VEGF expression through stabilization of VEGF mRNA

3.1.4 Angiotensin II in Dengue Virus Infection

In dengue virus infection, there is an increase in angiotensinogen (AGT) dan Ang II in the blood. AGT dan Ang II on severe dengue is higher than on non-severe. It was further found that AGT and Ang II can be used as markers of severe dengue with PL. Ang II was better at predicting severe dengue with PL than AGT although the combination of the two improved its ability as a predictor of severe dengue with PL (26). In addition, angiotensin receptor inhibitors such as Losartan on DVI decrease the formation of proinflammatory cytokines (27). This

indicate that Ang II is related to the severity of DVI.

3.1.5 Angiotensin II Facilitate Cellular Entry of DENV

Ang II affects the expression of various structures in the target cell membrane, such as increasing the expression of Cluster of Differentiation 206 (CD206), CD14, Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN), Glucose-Regulated Protein 78 (GRP78), AXL, Phosphatidylserine (PDS), Heparan sulfate, and Fc receptors. More specifically, Ang II elevates the expression of CD206 and CD14 in monocytes and macrophages, AXL in monocytes, DC-SIGN in dendritic cells, heparan sulfate and Fc receptors in macrophages, and PDS in endothelial cells. These cells are known to be the target of DENV infection, while these molecules are receptors for DENV, so the increase in structure makes it easier for DENV to attach to the target cell before it enters the cell (28).

The binding of DENV to its receptors will be succeeded by the entry of DENV into the cell via endocytosis. The process of endocytosis of DENV into cells occurs through the clathrin-mediated endocytosis mechanism (29). It is known that Ang II affects clathrin-mediated endocytosis, thus facilitating the entry of DENV into cells through endocytosis. The effect of Ang II on the entry of DENV into cells is supported by reports that losartan decreases the uptake of DENV into cells (27).

The process of DENV cellular entry is an important stage in the pathogenesis of DVI. The ease with which DENV enters the target cell makes it easier for DENV to immediately replicate to form new viruses (30). Viral replication not only causes viremia, but also increases NS-1 which is known to be associated with PL (31). Theoretically, it underlies the potential use of the next generation vaccine such as NS-1 DNA plasmid vaccine to inhibit PL in DVI (32,33).

Box 2. Angiotensin II in Dengue Pathogenesis

- Ang II increases viral replication by facilitating DENV's entrance into target cells.
- Viral replication coupled with elevated NS-1 expression
- NS-1 induces PL

3.2 Heterogenous Ribonucleoprotein K

Heterogeneous nuclear ribonucleoprotein K (hnRNP K) is one of the RNA-binding proteins that has a strategic position in the genetic regulation and dynamics of intracellular signals. hnRNP K exhibits a dual distribution in the nucleus and cytoplasm that reflects its diversity of functions in important biological processes such as gene expression (chromatin structure regulation, transcription, alternative splicing of RNA, to protein translation), interacting directly with various signaling molecules such as kinases, and as intermediates that

bridge signal transduction with the cell's genetic response (34).

3.2.1 Heterogenous Ribonucleoprotein K Increase VEGF Synthesis

The promoter of the human VEGF gene comprises a DNA sequence known as the polypurine/polypyrimidine (pPu/pPy) tract. In this area, DNA strands were found that are rich in guanine (G-rich strand) and cytosine-rich (C-rich strand). The cytosine-rich strand of the pPu/pPy promoter VEGF is attached by hnRNP K. Inhibition of hnRNP K expression using siRNA decreases the basal expression of the VEGF gene. This indiciates that hnRNP K functions as a VEGF transcription activator (35).

The rise in VEGF synthesis occurs not only due to elevated transcription, but also due to the influence of hnRNP K on increased VEGF translation. hnRNP K that has been activated is able to bind to VEGF mRNA so that VEGF mRNA becomes stable. hnRNP K also aids in the translocation of VEGF mRNA to polysome complexes and accelerates the translation process. Inhibition of any of the hnRNP K has been shown to decrease VEGF synthesis (8,10).

3.2.2 Heterogenous Ribonucleoprotein K in Dengue Virus Infection

Invitro studies on vero and A549 cells showed that dengue virus infection triggers the translocation of hnRNP K from the nucleus to the cytoplasm (36). Then, hnRNP K binds to the DENV core protein through protein-protein interactions. This interaction removes the negative regulation of hnRNP K against C/EBPβ (9). C/EBPβ activated by NS5 DENV is known to increase IL-8 expression. IL-8 increases viral replication (37).

Box 3. Key Roles of hnRNP K in VEGF Regulation and Dengue Infection

- hnRNP K increases transcription via binding to the VEGF promoter's C-rich strand.
- hnRNP K stabilizes VEGF mRNA and facilitates its recruitment to polysomes.
- Dengue virus infection causes hnRNP K to translocate to the cytoplasm and bind to the DENV core protein.

3.3 Vascular Endothelial Growth Factor (VEGF)

VEGF is a name for a protein family consisting of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF). Of all these types of VEGF, VEGF-A is the most widely expressed VEGF. VEGF-A has several isoforms, namely VEGF-A145, VEGF-A121, VEGF-A165, VEGF-A165b, VEGF-A183, VEGF-A189, VEGF-A206 and VEGF-Ax. The isoform VEGF-A165 is the isoform that plays the most role in physiological function (38)

VEGF-A affects target cells primarily through binding to VEGFR-1 and 2. VEGF1 is a decoy receptor that binds to VEGF thereby lowering the amount of VEGF that binds to VEGFR2. VEGFR2 has an intracellular domain capable of transmitting signals into cells. The

bond between VEGF and VEGFR2 triggers the dimerization of VEGFR2 followed by autophosphorylation of the intracellular domain tyrosine residue of VEGFR2 (39). Once this occurs, several adaptor proteins are recruited, including Grb2-associated binder-1 (Gab1) and Gab2, which subsequently activate the PI3K/AKT pathway (40), T cell–specific adaptor (TSAd), which activates Src via TSAd (41), Src homology 2 domain-containing protein B (SHB), which activates PI3K and phosphorylates focal adhesion kinase (FAK) (42), phospholipase C γ1 (PLCγ1) which breaks down PIP2 into IP3 and DAG so that IP3 stimulates the release of Ca^{2+} from the endoplasmic reticulum and the DAG activates PKC (43), and Cell Division Cycle 42 (CDC42), which activates Nck and Fyn to regulate p38 signaling (44,45).

The effects of target cell activation by VEGF on the bone marrow are to regulate hematopoiesis, on the nervous system regulates neuron migration and axon growth, on blood vessels regulates mitosis, cell migration, increases pro-survival activity, and vascular permeability. This function of VEGF can occur paracrine, autocrine, or intracrine (46). In pathological cases, VEGF triggers an increase in vascular permeability that triggers PL (47).

3.3.1 Vascular Endothelial Growth Factor Increase Vascular Permeabilities

VEGF increases vascular permeability through several mechanisms. VEGF affects VE-cadherin located at the adherent junction. VEGF activates FAK. The activation of FAK by VEGF causes FAK to head to the adherent junction. FAK then interacts with VE-cadherin to further phosphorylate β-catenin. This process leads to the dissociation of the VE-cadherin complex with β-catenin which triggers an increase in endothelial permeability (47). VE-cadherin destabilization also occurs through the VEGFR2-TSAd-Src pathway. Activation of VEGFR2 leads to recruitment of VE-cadherin to the intracellular domain of VEGFR2 which is followed by the formation of the VEGFR2/TSAd/Src complex. This condition activates Src which then phosphorylates VE-cadherin resulting in destabilization of VE-cadherin (41). Another mechanism of VEGF's effect on VE-cadherin is the formation of Nitric oxide (NO). The interaction between VEGF and VEGFR2 activates the PI3K/AKT pathway that stimulates endothelial Nitric Oxide Synthase (eNOS) to form NO (48). NO increase vascular permeability by decreasing VE-cadherin expression (49).

3.3.2 Vascular Endothelial Growth Factor in dengue virus infection

VEGF levels are increased in numerous viral infections, including DVI. In vitro experiments utilizing human mast cell lines KU812 and HMC-1 demonstrated that DENV infection in mast cells induces the production of VEGF (50). In DVI patients, VEGF levels in severe dengue are elevated compared to non-severe cases (51). It was further mentioned that

VEGF is associated with thrombocytopenia in patients with severe dengue (52).

Box 4. VEGF in Plasma Leakage and Dengue Virus Infection

- VEGF causes dissociation and decreased expression of VE-cadherin, which increases vascular permeability and causes plasma leakage.
- VEGF is upregulated in DVI, which is correlated with the severity of the condition.

3.4 Molecular Hypothesis of the Ang II-hnRNP K-VEGF Pathway in Triggering Plasma Leakage

Plasma leakage is the main clinical manifestation of severe dengue that contributes significantly to the occurrence of shock and mortality. The molecular mechanisms underlying this phenomenon are not yet fully understood, but recent evidence indicates that the Ang II–heterogeneous nuclear ribonucleoprotein K (hnRNP K)–vascular endothelial growth factor (VEGF) molecular cascade plays a significant function in the pathogenesis of plasma leakage.

Ang II, as a key component of the RAAS, experienced a significant rise in patients with severe dengue and showed a strong correlation with the degree of plasma extravasation. Activation of AT1R by Ang II directly activates hnRNP K through phosphorylation of Ser302 residues by the Src–PKCδ pathway, which leads to the translocation of hnRNP K from the nucleus to the cytoplasm. hnRNP K binds to VEGF mRNA in the CU-rich region of 3′-UTR, which plays a role in mRNA stabilization and accelerates the VEGF translation process. Furthermore, hnRNP K is also known to function as an activating factor of VEGF transcription through direct binding to the VEGF polypurine/polypyrimidine promoter (pPu/pPy) sequence. The increased expression and synthesis of VEGF induced by Ang II and mediated by hnRNP K has direct implications for increased VEGF levels in the blood.

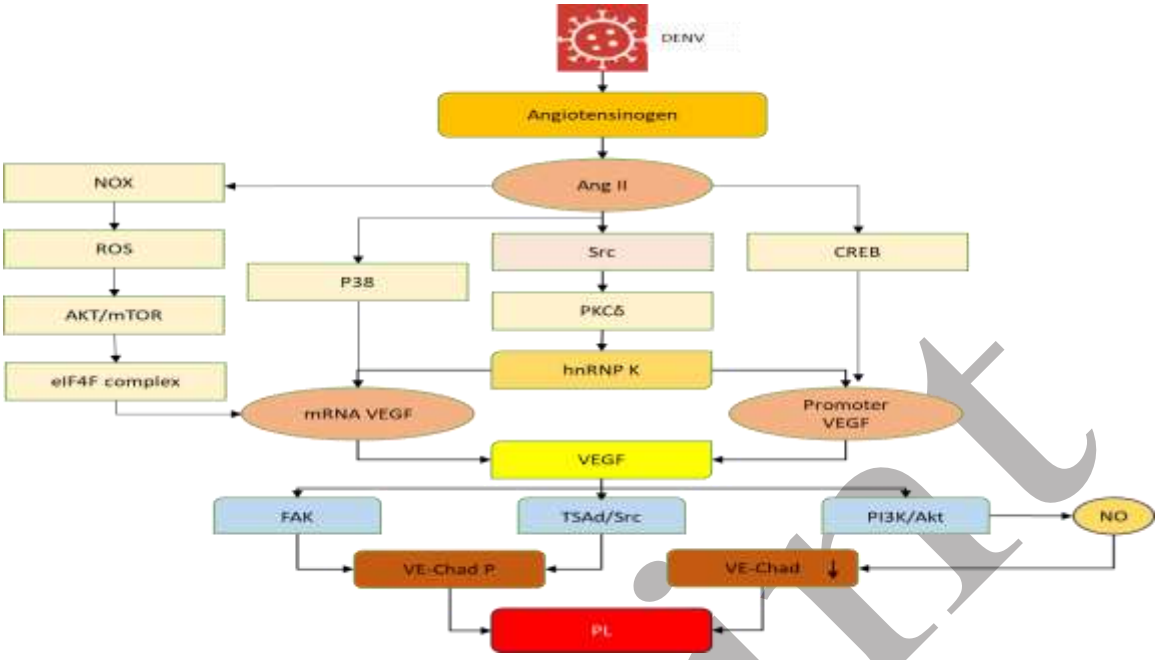

Figure 1. Hypothesis of the Ang II-hnRNP K-VEGF Pathway in Triggering Plasma Leakage. Path explanations can be seen in the text. Ang II (Angiotensin II), CREB (cAMP Response Element-Binding protein), DENV (Dengue Virus), eIF4F complex (Eukaryotic initiation factor 4F complex), FAK (Focal Adhesion Kinase), hnRNP K (Heterogenous Nuclear Ribonucleoprotein K), mTOR (mammalian targets of rapamycin), NO (Nitric Oxide), NOX (NADPH oxidase), PI3K (Phosphoinositide 3-kinase), PKCδ (Protein Kinase C δ), PL (Plasma Leakage), TSAd (T cell–specific adapter),VE-Chad P (phosphorylated VE-Cadherin), VEGF (Vascular endothelial Growth Factor).

The secreted VEGF then binds to VEGFR2 in endothelial cells and activates signaling pathways involving FAK, TSAd/Src, and PI3K/Akt, which collectively cause disruptions at inter-endothelial junctions, including the phosphorylation of VE-cadherin and the reduction of its expression through the production of nitric oxide (NO). These processes lead to the loss of endothelial barrier integrity and increased vascular permeability that is the basis for PL. To clarify the mechanism, Table 1 presents a summary of the main molecular role along with the literature evidence and its clinical implications.

Table 1. Summary of the Molecular Pathways Contributing to Plasma Leakage in Dengue Infection

Molecule/Pathway	Main Mechanism	Reference	Potential Clinical Implications
Ang II	Ang II activates hnRNP K through PKC signaling following its binding to AT1R	(8,10)	Potential use of ARB (losartan)
hnRNP K	hnRNP K increases VEGF gene expression	(8,10,35)	Potential use of hnRNP K inhibitors to prevent PL in DVI
VEGF	VEGF increases endothelial permeability & tight junction damage	(41,47,49)	Target of VEGF inhibitor therapy

Based on this, we propose that the Ang II–hnRNP K–VEGF pathway constitutes a critical pathogenic axis in the development of plasma leakage during dengue virus infection. Beyond integrating complex molecular mechanisms, this pathway highlights novel clinical implications: Ang II, hnRNP K, and VEGF may serve as predictive biomarkers of plasma leakage and disease severity (8,10,53–55), while existing agents such as RAAS inhibitors or anti-VEGF therapies could be repurposed as adjunctive treatments to mitigate vascular dysfunction in severe dengue (27).

The immunological paradigm linking Ang II, hnRNP K, and VEGF in dengue may share conceptual similarities with immunotherapeutic strategies in allergic diseases and cancer, where dysregulated immune tolerance and cytokine networks contribute to pathogenesis. As highlighted in recent reviews, molecules such as VEGF, IL-10, and TGF-β have emerged as central mediators across these conditions, suggesting their potential relevance both as pathogenic drivers and as therapeutic targets. This possible convergence points to the broader, though still evolving, applicability of immunomodulation in infectious, allergic, and malignant diseases (56).

3.5 Future Direction

The II-hnRNP K-VEGF Pathway Hypothesis in Triggering Plasma Leakage is promising but still needs to be proven. Therefore, in the future, research is needed that tests the truth of this hypothesis. This is not only testing the hypothesis but will further improve understanding of the immunopathogenesis of PL in DVI so that it will facilitate its management in the future.

4. Conclusions

Severe dengue is marked by life-threatening plasma leakage (PL), driven by complex molecular pathways. This review consolidates evidence supporting the Ang II–hnRNP K–VEGF axis as a key mechanism underlying PL in dengue infection. Elevated Ang II in severe dengue activates hnRNP K phosphorylation, leading to VEGF upregulation. VEGF then disrupts endothelial integrity via VEGFR2 signaling, resulting in vascular hyperpermeability. This hypothesis integrates scattered molecular evidence into a cohesive pathogenic model, offering novel therapeutic targets (e.g., Ang II inhibitors, hnRNP K modulators, or VEGF blockers). Experimental studies are urgently needed to validate this pathway *in vivo* and explore its clinical relevance. Unraveling this mechanism could transform the management of severe dengue, reducing mortality and global disease burden.

Acknowledgement

Thanks to the Universitas Muhammadiyah Surakarta for facilitating the process of preparing the narrative review from start to finish.

Authors' Contribution

Study concept and design: SWJ, RTT, and RA. Acquisition of data: SWJ, RTT, DAF, KAA, and RA. Analysis and interpretation of data: SWJ and RA. Drafting of the manuscript: SWJ, RTT, and RA. Critical revision of the manuscript for important intellectual content: RTT and RA. Administrative, technical, and material support: DAF and KAA. All authors have read and Approve to the content of the article.

Ethics

We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors have declared no conflicts of interest.

Funding

Article writing funded by Directorate of Research and Community Service (DPPM), Directorate General of Higher Education, Research, and Technology, Ministry of Higher Education, Science, and Technology of Indonesia with contract number: 127/C3/DT.05.00/PL/2025.

Data Availability

The data that underpins the findings of this study are available upon request from the corresponding author. No artificial intelligence (AI) tools were used in the preparation of this manuscript.

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