Adrenomedullin: A Multifunctional Regulator in Health and Disease

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Abstract

Adrenomedullin (ADM) is a multifunctional peptide hormone first recognized for its potent vasodilatory activity but now understood as a key regulator in diverse physiological and pathological processes. Its functions extend to angiogenesis, immune modulation, and tissue repair, placing it at the intersection of oncology, gastroenterology, and infectious diseases. Within the tumor microenvironment, ADM promotes cancer progression by facilitating immune evasion, stimulating angiogenesis, and contributing to chemotherapy resistance. In the gastrointestinal system, ADM and its related peptide PAMP act as essential regulatory hormones, supporting gastric motility, maintaining epithelial integrity, modulating mucosal immunity, and promoting repair—functions that underline their protective roles in inflammatory bowel diseases. Beyond these contexts, ADM has gained importance as a prognostic biomarker in critical care, with elevated circulating levels correlating strongly with disease severity in bacterial sepsis and emerging viral infections, where it may influence immune dysregulation and neurological complications. This review summarizes the multifaceted roles of ADM, highlights its dual protective and pathogenic actions, and discusses the therapeutic potential of selectively targeting the ADM pathway through precision strategies such as tumor-specific inhibitors and bi-specific antibodies.

Keywords: Adrenomedullin; PAMP; Angiogenesis; Tumor microenvironment; Immune modulation; Gut barrier; Sepsis biomarker; Therapeutic targeting

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Introduction

Adrenomedullin a versatile peptide hormone first isolated in 1993, has emerged as a critical regulator of homeostasis and a key player in pathophysiology (Kitamura *et al.,* 1993; Kangawa *et al.,* 1996). Initially characterized as a potent vasodilator, subsequent research has revealed its profound influence on vascular integrity, inflammation and tissue repair (Ihara *et al.,* 2021; Qian *et al.,* 2022; Spoto *et al.,* 2024). These diverse physiological effects are mediated through complex formation between the calcitonin receptor-like receptor (CRLR) and receptor activity-modifying proteins (RAMPs) (Van *et al.,* 2021). A particularly rich site of ADM expression and action is the gastrointestinal (GI) tract. Produced locally by epithelial, neuroendocrine, and smooth muscle cells, ADM and its co-derived peptide PAMP are essential for maintaining GI mucosal health, modulating immune response, and promoting healing in conditions like inflammatory bowel diseases (Martínez-Herrero and Martínez, 2016; Ashizuka *et al.,* 2019).

Paradoxically, the very mechanisms that confer protective benefits in the GI tract like promoting angiogenesis and suppressing immune activation can be co-opted in disease states line cancer. Within the tumor microenvironment (TME), hypoxia-driven ADM expression facilities tumor progression by stimulating neovascularization, enhancing cancer cell survival, and fostering immune evasion (Nakayama *et al.,* 2022; Zhao *et al.,* 2024). This dual nature cyto-protective in one context and pathogenic in another underscores the complexity of ADM signaling. Furthermore, its dynamic release in response to systemic stress, including sever infection, has positioned ADM as a promising biomarker for disease like viral meningitis and encephalitis, which demand improved diagnostic and prognostic tools (Solé-Ribalta *et al.,* 2022; Trojan *et al.,* 2024).

Beyond its physiological functions, ADM expression is markedly unregulated in various pathological states. This is especially evident in the context of cancer, where ADM acts as a key factor in the tumor microenvironment (Ashizuka *et al.,* 2021). Facilitated by hypoxic conditions via the HIF-1 pathway. ADM promotes tumorigenesis by stimulating angiogenesis, enhancing tumor cell proliferation, and enabling immune evasion (Takei *et al.,* 2004). This multifaceted involvement in disease pathogenesis extends beyond oncology and gastroenterology. There is a growing recognition of the need for robust biomarkers to manage complex diseases, particularly viral illnesses, which pose a persistent threat to global health due to their rapid transmission and potential for severe outcomes like meningitis and encephalitis (Baker *et al.,* 2022; Granerod *et al.,* 2023). The dynamic regulation of ADM in response to stressors such as infection and inflammation positions it as a molecules of interest in this diagnostic arena.

The expanding roles of ADM, from a gut-derived homeostatic peptide to a

central mediator in cancer and a potential clinical biomarker, highlight the need for a synthesized overview. This review will therefore comprehensively examine the multifaceted biology of ADM. We will try to explore its protective mechanisms and its emerging potential as a biomarker in systemic stress responses. By integrating these perspective, this review seeks to provide a comprehensive theoretical foundation for understanding ADM's diverse actions and its promise as a target for novel therapeutic strategies.

Physiological functions of adrenomedullin (ADM)

ADM is a pleiotropic hormone integral to maintaining systemic homeostasis. Its primary physiological roles encompass the regulation of vascular tone, the preservation of endothelial barrier integrity, immunomodulation, and the control of fluid and electrolyte balance. A schematic overview of these functions, and the specific mechanisms underlying each are detailed in the following subsections.

Vasodilation and cardiovascular regulation

The inaugural and one of the most significant physiological functions identified for ADM is the induction of potent vasodilation. This action reduces systemic vascular resistance and lowers blood pressure, subsequently triggering a compensatory increase in cardiac output (Otao *et al.,* 2021; Bonura *et al.,* 2023). The hypotensive effects of ADM are mediated through a sophisticated interplay of direct and indirect signaling pathways.

The primary mechanism involves the direct action of ADM on vascular smooth muscle cells. Upon binding to its receptor complex comprising the calcitonin receptor like (CRLR) and receptor activity modifying protein 2 or 3 (RAMP2/3), ADM activates adenylyl cyclase (AC). This activation catalyses the production of cyclic adenosine monophosphate (cAMP), a key second messenger. The elevated cAMP levels activate protein kinase A (PKA), which in turn promotes the opening of potassium channels (K-ATP and K-Ca) on the smooth muscle cell membrane. This leads to membrane hyperpolarization a reduction in intracellular calcium concentration, and ultimately, smooth muscle relaxation and vasodilation (Passaglia *et al.,* 2014; Ihara *et al.,* 2021).

Concurrently, ADM orchestrates an endothelium-dependent vasodilatory pathway. By stimulating endothelial cells, ADM activates the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt/PKB) pathway, which phosphorylates and activates endothelial nitric oxide synthase (eNOS). The resulting increase in nitric oxide (NO) production allows NO to diffuse into adjacent smooth muscle cells. Within these cells, NO activates guanyly cyclase, elevating levels of cyclic guanosine monophosphate (cGMP) and promoting vasodilation (Van *et al.,* 2021). This dual pathway

mechanism ensures robust and redundant control over vascular tone.

Beyond these peripheral actions, ADM also exerts central nervous system-mediated control over cardiovascular function. Studies in obese hypertensive (OH) rat models have shown that ADM acts within the periventricular nucleus (PVN) of the hypothalamus. There, it attenuates the adipose afferent reflex (AAR), a process that typically enhances sympathetic nerve activity and elevates blood pressure. This central effect is mediated through ADM receptor-activated pathways involving NO and γ-amino butyric acid type A (GABA-A) receptors. Leading to reduced sympathetic outflow and a consequent decrease in blood pressure (Wang *et al.,* 2023). Thus ADM's vasodilatory capacity is a result of integrated peripheral and central mechanisms, highlighting its critical role in cardiovascular homeostasis.

Amelioration of endothelial barrier function

Beyond its vasodilatory effects, ADM plays a critical role as a key regulatory agent in stabilizing endothelial barrier function (Hupf *et al.,* 2020). The endothelial forms a semi-permeable barrier that is crucial for vascular homeostasis, and its dysfunction characterized by increased permeability is a hallmark of numerous pathological conditions. A substantial body of evidence from experimental models underscores the potent protective of ADM in preserving this barrier integrity. The efficacy of ADM in enhancing endothelial barrier function has been demonstrated across diverse disease models. As in diabetic macular edema, ADM treatment significantly reduced rental vascular permeability and inflammation, thereby protecting the rental endothelial barrier (Imai *et al.,* 2017). Similarly, in experimental sepsis, ADM administration improved endothelial barrier function, inhibited vascular leakage minimized organ damage, and consequently increased survival rates (Spoto *et al.,* 2024; Trojan *et al.,* 2024). This protective effect extends to lung injury, where ADM significantly mitigated pulmonary edema and leukocyte extravasation in a lipopolysaccharide (LPS)-induced model (Interdonato *et al.,* 2022).

The molecular mechanisms underlying ADM's barrier-stabilizing effects are primarily mediated through the cAMP signaling pathway, which diverges into two principal branches: the protein Kinase A (PKA) pathway and the Exchange protein directly activated by cAMP (Epac)-Rap1 pathway. Activation of these pathways by ADM leads to the strengthening of intracellular junctions. Specifically, ADM promotes the assembly and stability of tight junctions and adherens junctions by regulating the expression of key proteins like vascular endothelial (VE)-cadherin and reducing their phosphorylation, which minimizes the formation of intercellular gaps and decreases paracellular permeability (García-Ponce *et al.,* 2016).

Furthermore, ADM reinforces the endothelial barrier through potent anti-inflammatory and anti-apoptotic actions. It attenuates inflammatory mediator-induced damage by suppressing the expression of critical pro-inflammatory cytokines, like as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL - 1β) (Dai *et al.,* 2021). The specific roles of its receptor components have been elucidated in models of acute respiratory distress syndrome (ARDS), where both RAMP2 and RAMP3 are crucial for ADM's inflammatory modulation (Kasahara *et al.,* 2024). Genetic studies highlight a functional dichotomy between these RAMPs ADM signalling through the RAMP2 receptor is particularly vital for protecting endothelial cells from apoptosis, as evidenced by increased pulmonary cell apoptosis in RAMP2-deficient mice (Cui *et al.,* 2021). In contrast, RAMP3 appears to be more specialized in regulating the resolution of inflammation, with RAMP3 knockout mice showing a marked down regulation of inflammatory mediators like inducible nitric oxide synthase (iNOS), TNF-α, and the NLRP3 inflammasome during later, chronic staged of inflammation.

In summary, ADM serves as a multifaceted guardian of endothelial integrity, employing a combination of junctional stabilization, anti-inflammatory, and anti-apoptotic mechanisms, with its receptor components RAMP2 and RAMP3 mediating distinct temporal and functional aspects of this protection.

Immunomodulation

In addition to its vascular effects, ADM functions as a crucial endogenous immunomodulation factor with significant anti-inflammatory properties. This role is supported by the widespread expression of ADM and its specific receptors on various immune cells including macrophages, monocytes, and T cells as well as within lymphoid organs and mucosal surfaces like the gastrointestinal tract (Nair, 2021). By influencing both the activity of these immune cells and their cytokine secretion profiles, ADM acts as a key modulator that attenuates excessive inflammatory responses, thereby preventing collateral tissue damage and promoting resolution (Simonetti *et al.,* 2021).

A principal mechanism of ADM's immunomodulatory action is its profound impact on macrophage polarization. Macrophages are plastic cells that can adopt either a pro-inflammatory (M1) or an anti-inflammatory (M2) phenotype. Empirical evidence indicates that ADM can skew this balance towards the MS state. In response to bacterial lipopolysaccharide (LPS), ADM facilities a phenotypic switch from M1 to M2 macrophages. This reprogramming in underpinned by a metabolic shift, wherein ADM promotes a transition from glycolysis (characteristic of M1 macrophages) towards mitochondrial oxidative phosphorylation, a metabolic signature associated with M2 phenotype (Wang *et al.,* 2021).

Furthermore, ADM directly suppresses the production of key pro-inflammatory mediators. This has been demonstrated in a model of interstitial cell inflammation, where ADM decreased the expression of the pro-inflammatory factor RANKL (Receptor Activator of Nuclear Factor-Kappa B Ligand), which is typically induced by IL - 1β and TNF-α. This suppression was mediated through the inhibition of the ERK and p38 MAPK signaling pathways (Hu *et al.,* 2015). By maintaining a critical balance between pro- and anti-inflammatory signals a balance essential for controlled and self-limiting immune responses ADM helps to preserve immune homeostasis under physiological conditions (Schröde *et al.,* 2022).

In summary, through its dual actions of directing macrophage polarization towards an anti-inflammatory state and directly inhibiting pro-inflammatory signalling cascades, ADM emerges as a central regulator of immune equilibrium, ensuring that inflammatory responses are effective yet appropriately constrained.

Adrenomedullin in the oral cavity

The oral cavity represents a significant site of ADM production and action. ADM is present in saliva, where it is secreted by oral keratinocytes and the salivary glands (Gröschl *et al.,* 2009). This local production is integral to oral innate immunity and tissue homeostasis. Functionally, salivary ADM exhibits a dose-dependent capacity to stimulate the growth of oral keratinocytes, which is crucial for maintaining the mucosal barrier, while simultaneously inhibiting the growth of specific oral bacteria (Gröschl *et al.,* 2009). Human oral keratinocytes mount a defense against bacterial infection by producing a broad spectrum of antimicrobial peptides, among which ADM is a key component, providing a robust, frontline response against pathogens (Hiroshima *et al.,* 2011). The physiological importance of ADM in oral health is further underscored by pathology, microarray profiling studies have identified an up regulation of the *Adm* gene in the context of dental caries and pulp disease (McLachlan *et al.,* 2005). This elevated expression likely represents a compensatory defensive mechanism aimed at combating infection and promoting tissue repair in the inflamed dental pulp.

Adrenomedullin and diabetes mellitus

Beyond local actions, ADM has emerged as a peptide of systemic significant in metabolic disease, particularly diabetes mellitus. ADM plays a fundamental, yet complex, role in maintaining insulin homeostasis and normoglycemia. Its known inhibitory effect on insulin secretion from pancreatic beta cells suggests a direct association with the disease's pathophysiology. Clinical observations consistently report elevated plasma levels of ADM in both type 1 (T1D) and type 2 (T2D) diabetic patients, with concentrations further increased in those suffering from extra-pancreatic

complications such as microangiopathy and nephropathy (Wong *et al.,* 2014).

In T1D, the elevation in ADM is generally considered a consequence of the disease process, specifically linked to the development of microvascular complication (Rullé *et al.,* 2012; Wong *et al.,* 2014). The relationship in T2D is less clear, it remains ambiguous whether increased ADM is a causal factor in the disease's pathogenesis or a secondary consequence of the associated metabolic and vascular disturbances, Nevertheless, elevated circulating ADM is a undeniable feature of T2D (Garcia-Unzueta *et al.,* 1998; Martınez *et al.,* 1999).

This strong association has spurred interest in ADM's diagnostic utility. Notably, ADM has emerged as a promising biomarker for the early detection of pancreatic cancer-induced diabetes, a paraneoplastic syndrome that often precedes the diagnosis of the malignancy itself (Martınez *et al.,* 1999). This highlights the potential of ADM not only as a marker of diabetic complications but also as a tool for differentiating etiologies of new onset diabetes.

Adrenomedullin as a biomarker in specific viral infections

The utility of ADM as a clinical biomarker is particularly evident in specific viral infections, where its plasma levels provide critical prognostic information that aids in patient management. Two prominent examples are influenza and dengue fever both of which can lead to severe life-threatening complications.

Prognostic value in influenza

Influenza is an acute respiratory illness caused by influenza viruses that can progress to severe pneumonia especially in vulnerable populations. Beyond its role in SARS-CoV-2 infection, Mid-Regional pro-Adrenomedullin (MR-proADM) has proven valuable in stratifying risk in influenza patients. Studies have determined that upon hospital admission, an MR-proADM level of 1.09 nmol/L serves as an optimal cutoff for predicting disease severity, especially the need of intensive care unit (ICU) admission, with a sensitivity of 73.53% and a specificity of 96% (Valenzuela *et al.,* 2015).

Initial MR-proADM levels are effective predictors of unfavourable outcomes, including ICU admission and mortality, in patients with influenza A virus pneumonia (Valenzuela *et al.,* 2015; Valenzuela-Sánchez *et al.,* 2016). When compared to other biomarkers like ferritin, C-reactive protein (CRP), and procalcitonin (PCT), MR-proADM demonstrated superior predictive power for survival. This strong prognostic capability is likely rooted in ADM's fundamental role in mitigating endothelial damage and organ dysfunction during severe systemic inflammation, making it a more direct marker of the host's compensatory response than generic markers of inflammation.

Role in dengue fever pathogenesis and severity

Dengue fever, a mosquito-borne viral disease caused by the dengue virus (DENV), is a major public health concern in tropical and subtropical regions. The clinical spectrum ranges from mild febrile illness to severe and potentially fatal dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), which are characterized by profound plasma leakage due to increase vascular permeability.

ADM is significantly implicated in the pathogenesis of severe dengue. As a key vasoactive hormone, ADM directly influences endothelial permeability and vascular tone. Elevated ADM levels have been observed in patients with DHF and DSS, underscoring its role in the vascular dysfunction that defines these severe complications. These elevated levels have been correlated with clinical signs of plasma leakage, such as low albumin levels and increased pleural effusion (Michels *et al.,* 2011). Therefore, ADM serves a dual purpose in dengue, it acts as a biomarker for diseases severity, helping clinicians assess patient status and predict outcomes, and it is an active participant in the pathophysiology, likely released as part of a compensatory mechanism to stabilize the endothelial barrier in the face of intense inflammatory activation.

Conclusion and future perspectives

Adrenomedullin (ADM) is a quintessential multifunctional peptide, with critical roles in vascular, immune, and metabolic homeostasis that extend to pathogenesis in cancer, diabetes, and severe infections. Its stable precursor, MR-proADM, has proven to be a valuable prognostic biomarker in these conditions. However, the therapeutic targeting of ADM, particularly in oncology, is complicated by a paradoxical duality, while it drives tumor progression through angiogenesis and immune evasion, its inhibition may not be universally beneficial, as its role is highly context dependent. Future research must therefore prioritize elucidating these complex mechanisms using advanced techniques like single-cell transcriptomics. The key challenge lies in developing precision therapies, such as tumor-selective delivery systems or bi-specific antibodies, which can inhibit ADM's pathogenic actions without disrupting its vital physiological functions. Ultimately, unlocking the full potential of the ADM system will require a nuanced approach to successful translate these insights into improved clinical outcomes.

Conflict of Interest: The authors declare no competing interests.

Ethical Approval: Ethical approval is not required

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