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Exendin-4: Orchestrating Molecular Signals with Cellular Responses in Vascular Homeostasis

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Abstract Exendin-4, a potent glucagon-like peptide-1 receptor (GLP-1R) agonist, has emerged as a critical modulator of vascular homeostasis beyond its established role in glucose metabolism. This review explores the multifaceted effects of Exendin-4 on vascular endothelial cells (ECs), vascular smooth muscle cells (VSMCs) and the surrounding immune microenvironment. We examine the ultrastructural and signaling pathways-including AMPK/SIRT1, PKA/Epac1 and Akt/eNOS- through which Exendin-4 preserves barrier integrity, inhibits pathological VSMC remodeling and attenuates atherosclerotic progression. By integrating evidence from recent clinical trials and basic cell biology, we highlight the therapeutic potential of Exendin-4 in treating vascular-related complications such as atherosclerosis, hypertension and ischemic injury (Figure 1).

Key Words Exendin-4, GLP-1R, Vascular Homeostasis, Atherosclerosis, Hypertension, Ischemic Injury

INTRODUCTION

The vascular system serves as more than a mere conduit for blood; it is a dynamic organ system regulated by complex cellular interactions between the endothelium and the underlying smooth muscle layers. Disruptions in vascular function, often manifested as endothelial dysfunction or pathological vascular smooth muscle cell (VSMCs) proliferation, are hallmarks of diabetes and cardiovascular diseases [1].

Exendin-4, a 39-amino acid peptide originally isolated from the venom of the Gila monster (*Heloderma suspectum*), shares approximately 53% sequence homology with human glucagon-like peptide-1 (GLP-1). Unlike endogenous GLP-1, Exendin-4 is highly resistant to degradation by dipeptidyl peptidase-4 (DPP-4), leading to a significantly prolonged half- life [2]. While primarily used to treat type 2 diabetes (T2D) via its insulinotropic effects, emerging research demonstrates that Exendin-4 exerts direct, glucose-independent protective effects on the vasculature [3].

Cellular Localization of GLP-1 Receptors in the Vasculature

A prerequisite for the direct action of Exendin-4 is the expression of the canonical GLP-1 receptor (GLP-1R). Extensive immunohistochemical and mRNA analysis has confirmed GLP-1R expression across various cardiovascular cell types:

- **Endothelial Cells:** GLP-1R has been identified in microvascular and macrovascular ECs, where it regulates barrier function and nitric oxide (NO) production [4]
- **Vascular Smooth Muscle Cells:** VSMCs in the aorta, mesenteric arteries and renal afferent arterioles express robust levels of GLP-1R, mediating vasodilation and phenotypic switching [5,6]
- **Monocytes and Macrophages:** High expression in these cells facilitates the anti-inflammatory and anti-atherogenic properties of GLP-1R agonists [7]

Exendin-4 and Endothelial Function

Endothelial dysfunction is characterized by reduced NO bioavailability and increased permeability. Exendin-4 acts as a potent stabilizer of the endothelial barrier and a promoter of vasodilatory signals.

Preservation of Endothelial Barrier Integrity

Exendin-4 enhances the endothelial barrier through the activation of protein kinase A (PKA) and exchange protein

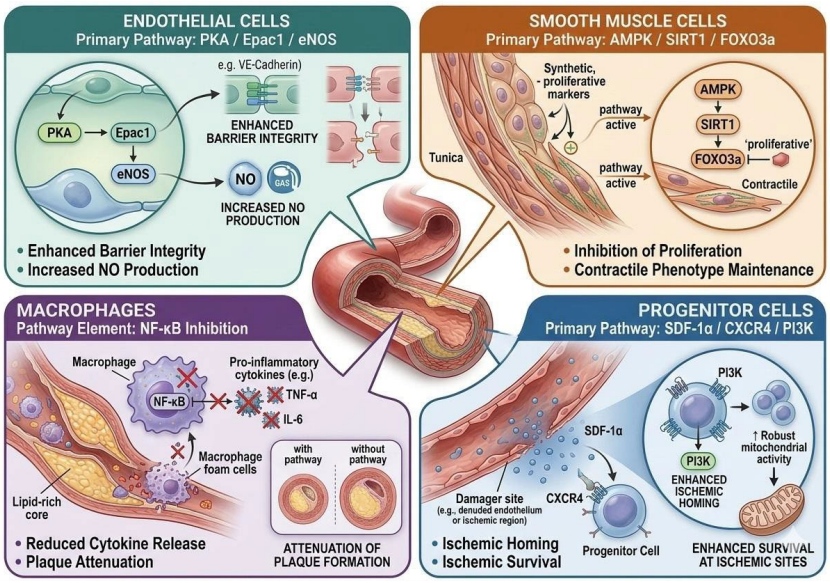

Figure 1: Graphical Abstract

directly activated by cAMP 1 (Epac1). These pathways lead to the activation of Rac1, a small GTPase that promotes the assembly of adherens junctions and stabilizes the actin cytoskeleton [8]. In models of acute lung injury and subarachnoid hemorrhage, Exendin-4 has been shown to reduce vascular hyperpermeability by upregulating tight junction proteins such as Occludin and Claudin-5 [4].

Modulation of Nitric Oxide and Vasodilation

Activation of GLP-1R in ECs stimulates the Akt/eNOS pathway, increasing the production of nitric oxide. This not only promotes vasodilation but also inhibits the adhesion of inflammatory cells. Studies in renal vasculature indicate that Exendin-4 reduces the autoregulatory response in afferent arterioles, thereby increasing renal blood flow and exerting a protective effect in hypertensive models [5].

Vascular Smooth Muscle Cells: Phenotype and Proliferation

Under pathological conditions such as hypertension or injury, VSMCs undergo a "phenotypic switch" from a quiescent, contractile state to a synthetic, proliferative state. This transition is a key driver of neointimal hyperplasia and atherosclerosis.

Inhibition of Proliferation and Migration

Exendin-4 suppresses VSMC proliferation and migration induced by factors such as Angiotensin II (Ang II) and high phosphate. Mechanistically, this is achieved through the inhibition of extracellular signal-regulated kinase 1/2 (ERK1/2) and c-Jun N-terminal kinase (JNK) signaling [2,9].

Promotion of VSMC Re-Differentiation

Research into the AMPK/SIRT1/FOXO3a axis has revealed that Exendin-4 can actively promote the re-differentiation of synthetic VSMCs back to a contractile phenotype. By increasing the expression of contractile markers like Calponin and SM22α, Exendin-4 maintains the structural integrity and functional tone of the vessel wall [6].

Anti-Inflammatory and Anti-Atherogenic Effects

Atherosclerosis is fundamentally a chronic inflammatory disease of the vascular wall. Exendin-4 exerts powerful anti-atherosclerotic effects by targeting both the endothelium and infiltrating immune cells.

Reduction of Macrophage Infiltration

Exendin-4 reduces the expression of adhesion molecules such as VCAM-1 and E-selectin on the endothelial surface, which significantly decreases monocyte adhesion [7]. Furthermore, it limits the progression of plaque development by reducing macrophage infiltration into the vessel wall [10].

Plaque Stability and Calcification

Recent studies highlight that Exendin-4 not only reduces plaque size but also improves plaque stability. It attenuates vascular calcification -a major risk factor for cardiovascular events- by inhibiting phosphate-induced VSMC osteoblastic differentiation [9,11].

Angiogenesis and Ischemic Recovery

Exendin-4 plays a crucial role in promoting revascularization following ischemic events, such as myocardial infarction (MI) or stroke.

VEGF Production and Stem Cell Homing

In infarcted myocardium, Exendin-4 increases the production of vascular endothelial growth factor (VEGF) and stimulates the MKK3/Akt-1 signaling pathway to promote angiogenesis [12]. Additionally, it enhances the

homing and survival of adipose-derived stem cells (ADSCs) to ischemic sites via the PI3K/Akt-SDF-1α/CXCR4 axis, facilitating tissue repair [13].

Clinical Perspectives and Future Directions

Clinical trials, such as the EXSCEL study, have confirmed the cardiovascular safety of Exendin-4-based therapies. While initially focused on T2D patients, the broad vascular protective properties of GLP-1RAs suggest potential applications in non-diabetic populations suffering from atherosclerosis or chronic kidney disease [14].

Future research must address the development of long-acting formulations, such as PEGylated Exendin-4, which have shown superior cardioprotection and sustained bioactivity in preclinical models [15].

Deep Dive: Molecular Signaling Pathways in Endothelial Cells

The vascular endothelium is the primary sensor of blood-borne signals. Exendin-4 interacts with the GLP-1 receptor (GLP-1R), a G-protein- coupled receptor (GPCR), to trigger a cascade that preserves cellular health.

The cAMP-PKA/Epac1 Bifurcation

Upon Exendin-4 binding, GLP-1R activates adenylyl cyclase, leading to a rapid increase in intracellular cyclic adenosine monophosphate (cAMP). This second messenger acts through two primary effectors:

- **Protein Kinase A (PKA):** PKA phosphorylates several targets that inhibit the expression of pro-inflammatory cytokines and adhesion molecules (e.g., ICAM-1)
- **Epac1 (Exchange Protein Directly Activated by cAMP 1):** Epac1 serves as a Guanine Nucleotide Exchange Factor (GEF) for Rac1. Activation of Rac1 is vital for endothelial barrier function as it promotes the peripheral distribution of the actin cytoskeleton, effectively "zipping" the gaps between adjacent cells [8]

The Akt/eNOS Axis and Oxidative Stress

One of the most critical functions of Exendin-4 is the restoration of Nitric Oxide (NO) bioavailability.

- **eNOS Activation:** Exendin-4 triggers the PI3K/Akt pathway, which leads to the phosphorylation of endothelial Nitric Oxide Synthase (eNOS) at Serine-1177. This increases NO production, facilitating vasodilation and preventing platelet aggregation
- **ROS Scavenging:** Exendin-4 suppresses the activity of NADPH oxidase (NOX4) and enhances the expression of antioxidant enzymes such as Superoxide Dismutase (SOD) and Catalase. By reducing the production of reactive oxygen species (ROS), Exendin-4 prevents the "uncoupling" of eNOS, ensuring that the enzyme produces NO rather than harmful superoxide radicals [14]

Mitigation of NF-κB Mediated Inflammation

Exendin-4 exerts potent anti-inflammatory effects by inhibiting the translocation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) into the nucleus. This prevents the transcription of genes involved in vascular "activation," such as VCAM-1 and MCP-1, which are responsible for recruiting monocytes to the vascular wall during the early stages of atherosclerosis [4,7].

Clinical Evidence: The EXSCEL Trial

While basic science provides the "how," clinical trials provide the "if." The EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial is the landmark study investigating the long-term vascular safety and efficacy of Exendin-4 (Exenatide) [21].

Study Design

- **Participants:** 14,752 patients with Type 2 Diabetes (T2D), of whom 73.1% had previous cardiovascular disease
- **Intervention:** Patients were randomized to receive either once- weekly subcutaneous Exenatide (2 mg) or a matching placebo
- **Primary Endpoint:** A composite of Major Adverse Cardiovascular Events (MACE), including cardiovascular death, nonfatal myocardial infarction or nonfatal stroke

Key Findings

The trial concluded that once-weekly Exenatide was non-inferior to placebo regarding cardiovascular safety ($p<0.001$ for non-inferiority) (Table 1).

Interpretation and Clinical Impact

Although the primary MACE endpoint did not reach the threshold for statistical superiority ($p = 0.06$), there was a significant 14% reduction in all-cause mortality in the Exenatide group [16]. This suggests that while Exendin-4 is safe, its vascular protective benefits may require longer-term exposure or specific patient sub-grouping (e.g., those with existing high-risk atherosclerotic plaques) to demonstrate clear superiority in clinical outcomes.

Summary of Molecular vs. Clinical Correlation

The discrepancy between the robust vascular protection seen in *in vitro* endothelial models and the "neutral" (though safe) results of the EXSCEL trial highlights a critical gap. It suggests that while Exendin-4 stabilizes the endothelium at a molecular level, its systemic impact may be influenced by the severity of pre-existing vascular damage in diabetic populations [14].

Vascular Smooth Muscle Cells: Phenotypic Switching and the AMPK/SIRT1 Axis

In the healthy vessel, Vascular Smooth Muscle Cells (VSMCs) exhibit a contractile phenotype, characterized by low proliferative rates and the high expression of contractile proteins like α-smooth muscle actin (α-SMA), smooth muscle-22α (SM22α) and calponin. However, in response to vascular injury, inflammation or metabolic stress, these cells undergo phenotypic switching to a synthetic state. This

Table 1: Once-Weekly Exenatide was Non-Inferior to Placebo Regarding Cardiovascular Safety

Metric	Exenatide Group (%)	Placebo Group (%)	Hazard Ratio (95% CI)
Primary MACE	11.4%	12.2%	0.91 (0.83-1.00)
All-cause Mortality	6.9%	7.9%	0.86 (0.77-0.97)
CV Death	4.6%	5.0%	0.92 (0.79-1.08)

transformation is marked by increased migration, proliferation and the secretion of extracellular matrix proteins, which are fundamental drivers of neointimal hyperplasia and atherosclerotic plaque progression [6].

The Master Regulator: AMPK Activation

Exendin-4 acts as a powerful brake on this transition by activating the AMP-activated protein kinase (AMPK). Upon binding to the GLP-1R on the VSMC surface, Exendin-4 increases intracellular cAMP, which in turn activates the LKB1/AMPK pathway.

AMPK serves as a metabolic "master switch". In the context of the vasculature, phosphorylated AMPK (p-AMPK) inhibits the mTOR (mammalian target of rapamycin) signaling pathway. By suppressing mTOR, Exendin-4 effectively reduces the protein synthesis and cellular growth required for the synthetic phenotype, thereby maintaining the cell in its quiescent, contractile state [9].

The SIRT1 Connection and Deacetylation

A critical downstream effector of AMPK is Sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase. The relationship between AMPK and SIRT1 creates a robust cytoprotective loop:

- **AMPK increases NAD+ levels:** Which enhances SIRT1 activity
- **SIRT1 deacetylates FOXO3a:** A transcription factor that promotes the expression of antioxidant genes and contractile markers
- **SIRT1 inhibits NF-κB:** Further dampening the inflammatory signals that trigger VSMC proliferation

Recent studies have shown that Exendin-4 treatment significantly increases the expression of both SIRT1 and contractile markers in high- glucose-treated VSMCs, suggesting that it can "re-program" synthetic cells back toward a healthy contractile lineage [6,14].

Clinical Implications: Neointimal Hyperplasia

The ability of Exendin-4 to regulate VSMC behavior has profound clinical implications, particularly for restenosis following angioplasty or stent placement. In animal models of carotid artery injury, Exendin-4 administration markedly reduced neointima formation by suppressing the migration of VSMCs from the media to the intima. This suggests that GLP-1R agonists could serve as a systemic pharmacological "stent," protecting the vessel wall from the pathological remodeling that often follows mechanical intervention [2].

Impact on Vascular Calcification

Beyond phenotype switching, Exendin-4 addresses the "hardening" of the arteries-vascular calcification. This process occurs when VSMCs take on an osteoblast-like (bone-forming) phenotype in response to high phosphate levels or chronic kidney disease (CKD).

Exendin-4 inhibits this osteoblastic differentiation by activating the PKA signaling pathway, which prevents the expression of Runx2 (the master transcription factor for bone formation). By maintaining VSMC identity and preventing mineral deposition, Exendin-4 preserves vascular compliance and reduces the risk of systolic hypertension and arterial stiffness [9,11].

Ischemic Recovery and Angiogenesis: Repairing the Vascular Network

Beyond its protective role in chronic conditions like atherosclerosis, Exendin-4 plays a pivotal role in the acute phase of ischemic recovery. Following a Myocardial Infarction (MI) or an ischemic stroke, the primary therapeutic goal is the restoration of blood flow and the repair of damaged microvasculature. Exendin-4 facilitates this through the orchestration of angiogenesis and the recruitment of regenerative progenitor cells.

VEGF Expression and the MKK3/Akt-1 Pathway

Angiogenesis-the formation of new blood vessels from pre-existing ones-is essential for salvaging hibernating myocardium after an infarction. Exendin-4 has been shown to significantly increase the local production of Vascular Endothelial Growth Factor (VEGF), the primary mitogen for endothelial cells.

Mechanistically, this is mediated through the MKK3/Akt-1 signaling axis. Research by [12] demonstrated that Exendin-4 treatment in infarcted hearts leads to the phosphorylation of Akt-1, which not only promotes endothelial cell survival under hypoxic conditions but also drives the sprouting and migration necessary for new vessel formation. This "pro-angiogenic" environment significantly reduces the size of the final infarct and improves overall cardiac output.

Stem Cell Homing: The SDF-1α/CXCR4 Axis

One of the more sophisticated vascular functions of Exendin-4 is its ability to facilitate "stem cell homing." For effective tissue repair, circulating stem cells (such as adipose-derived stem cells or ADSCs) must be recruited to the site of injury.

Exendin-4 enhances this process by upregulating the SDF-1α/CXCR4 pathway:

- **SDF-1α (Stromal cell-derived factor-1α):** Exendin-4 increases the secretion of this chemokine from the damaged vascular endothelium
- **CXCR4:** It also enhances the expression of the CXCR4 receptor on the surface of progenitor cells

This creates a chemical "GPS" system, allowing stem cells to effectively navigate to and integrate into the ischemic tissue [17]. Once at the site, Exendin-4 provides additional survival signals via the PI3K/Akt pathway, ensuring that these regenerative cells are not lost to the hostile, inflammatory environment of the ischemic zone.

Protection of the Blood-Brain Barrier (BBB) in Stroke

In the context of cerebral ischemia (stroke), the "vascular function" of Exendin-4 extends to the preservation of the Blood-Brain Barrier (BBB). Endothelial cells in the brain are linked by specialized tight junctions. During a stroke, matrix metalloproteinases (specifically MMP-9) degrade these junctions, leading to cerebral edema.

Exendin-4 has been shown to inhibit MMP-9 activity by suppressing the NF-κB pathway, thereby "locking" the barrier and preventing the secondary damage associated with vascular leakage in the brain [4].

Comparative Discussion: Exendin-4 vs. Human GLP-1 Analogs

While all glucagon-like peptide-1 receptor agonists (GLP-1RAs) share the same primary target, they are not monolithic. Understanding the nuances between Exendin-4 (Exenatide) and human-based analogs like Liraglutide and Semaglutide is crucial for clinical decision-making and understanding vascular pathophysiology.

Structural and Pharmacokinetic Divergence

The most fundamental difference lies in their origin and molecular structure. Exendin-4 is a 39-amino acid peptide derived from the Gila monster, whereas Liraglutide and Semaglutide are synthetic analogs of human GLP-1 (>90\% homology) modified with fatty acid chains (e.g., a C16 palmitic acid in Liraglutide).

- **DPP-4 Resistance:** Both classes are resistant to dipeptidyl peptidase-4 (DPP-4) but Exendin-4's resistance is inherent to its primary sequence, whereas human analogs rely on steric hindrance from their lipid tails
- **Binding Kinetics:** Human analogs like Liraglutide bind extensively to albumin, resulting in a significantly longer half-life (approx. 13 hours for Liraglutide vs. 2.4 hours for standard Exenatide). This translates to more sustained GLP-1R activation in vascular tissues [14,18]

Molecular Potency in Vascular Protection

At the cellular level, both Exendin-4 and Liraglutide activate the AMPK/SIRT1 axis but their efficacy in specific vascular niches varies:

- **Endothelial VCAM-1 Suppression:** Both agents effectively reduce TNF-α-induced VCAM-1 expression, thereby limiting monocyte recruitment. However, Liraglutide has been noted in some murine models for a slightly more robust reduction in atherosclerotic plaque burden compared to short-acting Exendin-4, likely due to more stable plasma concentrations [19]
- **VSMC Phenotype Stabilization:** A head-to-head *in vitro* comparison demonstrated that Exendin-4, Liraglutide and Dulaglutide all significantly inhibit VSMC migration and proliferation via the inhibition of ERK1/2 and JNK. Interestingly, Exendin-4 showed a unique potency in promoting mitophagy -the targeted clearance of damaged mitochondria- which is a critical defense against high-glucose-induced vascular calcification [9]

Short Acting vs. Long Acting Vascular Impact

Exenatide is available in both twice-daily (short-acting) and once-weekly (long-acting) formulations. Short-acting agonists have a more pronounced effect on gastric emptying, leading to a reduction in postprandial glucose spikes. From a vascular perspective, this is significant because "glucose variability" (sharp peaks and valleys) is more damaging to the endothelium than steady-state hyperglycemia. Conversely, long-acting agonists (like Liraglutide or Exenatide ER) provide constant receptor stimulation, which may be more effective for chronic suppression of systemic inflammation and blood pressure [1].

Future Perspectives: Beyond Glucose Control

The future of Exendin-4 research is shifting away from its insulinotropic properties toward its role as a vascular stabilizer.

- **Direct-to-Plaque Delivery:** Emerging research into nanoparticle-encapsulated Exendin-4 suggests the possibility of delivering the drug directly to "vulnerable" atherosclerotic plaques, maximizing the anti-inflammatory effect while minimizing systemic gastrointestinal side effects
- **Non-Diabetic Indications:** Given its robust protection of the blood- brain barrier and its ability to homing progenitor cells, Exendin-4 is being investigated for non-diabetic conditions, including recovery from acute ischemic stroke and the prevention of vascular dementia [4]
- **Dual and Triple Agonists:** The next generation of therapies involves combining Exendin-4-like GLP-1R agonism with other incretins like GIP (e.g., Tirzepatide). These "twincretins" have shown even greater efficacy in reducing weight and improving lipid profiles, which may translate to even more profound vascular benefits in the years to come [20]

CONCLUSIONS

Exendin-4 stands as a cornerstone of incretin-based therapy, providing a unique bridge between metabolic regulation and vascular biology. Through the activation of the AMPK/SIRT1/eNOS network, it preserves the endothelial barrier, maintains the contractile identity of smooth muscle

cells and orchestrates the repair of ischemic tissue. While human analogs like Liraglutide have demonstrated superior cardiovascular "hard endpoints" in some clinical trials, the molecular versatility of Exendin-4-particularly its ability to regulate cellular mitophagy and stem cell homing-ensures its continued relevance in the fight against cardiovascular disease.

Consequently, Exendin-4 represents a paradigm shift in vascular pharmacology. By targeting multiple cell types within the vascular wall through highly conserved signaling nodes like AMPK and SIRT1, it provides a holistic approach to preserving vascular function. From stabilizing the endothelial barrier muscle remodeling, to preventing pathological smooth a robust therapeutic strategy for the Exendin-4 offers global burden of cardiovascular disease.

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