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Exendin-4 Emerging Therapeutic Potential in Dermatology

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Abstract: Exendin-4 is a synthetic analogue of the glucagon-like peptide-1 (GLP-1) that has a potent GLP-1 receptor agonist activity primarily approved for the treatment of Type 2 Diabetes Mellitus. Beyond its well-established metabolic actions, research has increasingly revealed the pleiotropic effects of Exendin-4, particularly in regulating inflammation, cellular proliferation, and tissue repair. Given that many dermatological conditions, including psoriasis and chronic wounds, share underlying pathogenic mechanisms such as systemic inflammation and impaired healing, the role of Exendin-4 in skin disorders presents a promising avenue for therapeutic exploration. This review examines the current evidence, primarily from *in vitro* and animal studies, regarding the direct and indirect influence of Exendin-4 on skin pathology, focusing on its impact on inflammatory dermatoses, wound healing and potential anti-cancer effects.

Key Words: Exendin-4, Psoriasis, Skin Pathology, Wound Healing, Skin Malignancies

INTRODUCTION

Exendin-4 and the GLP-1 Receptor Axis

Excendin-4 -a 39-amino-acid peptide found in an exocrine secretion which has endocrine activity- was firstly discovered as a venom of Gila monster “Heloderma lizard”; a poisonous lizard from the deserts of Arizona [1].

Exendin-4 and GLP-1 are both peptide agonists for GLP-1 receptors. Natural and synthetic exendin-4 stimulate a monophasic increase in cAMP, this effect is inhibited progressively by exendin receptor antagonist. Also, exendin-4 does not stimulate a second rise in acinar cAMP, does not stimulate amylase release, and does not inhibit the binding of vasoactive intestinal peptide to acini [2].

Comparing the insulinotropic effect, paradoxically, excendin-4 has higher affinity to GLP-1 receptors with longer half-life and abundant amount of secreted cAMP [3].

In the pancreatic β-cells, the extracellular N-terminal domain (NTD) of the GLP-1 receptor is initially contacted by the helical portion of exendin-4 when it targets pancreatic β-cells, and its binding affinity is further increased by the C-terminal extension that contains the tryptophan cage. Following its binding to the receptor's NTD, it may cause the receptor to transition from its auto-inhibited to auto-activated state. Exendin-4 lowers plasma glucose levels via improving β-cell physiological functioning and upregulating GLP-1 receptors. Therefore, Exendin-

4's therapeutic application is based on its capacity to decrease stomach emptying, inhibit glucagon release, and increase glucose-dependent insulin secretion [4].

Furthermore, Exendin-4 is known for its efficiency in regulating the capillary tone and restoring microvascular patency after ischemia-reperfusion injury [5].

GLP-1 Receptors in Peripheral Tissues

The significance of Exendin-4 in dermatology stems from the fact that GLP-1 receptors (GLP-1Rs) are not restricted to the pancreas; they are expressed in various peripheral tissues, including the skin, where they are found on keratinocytes, fibroblasts, and immune cells [6]. Activation

of these cutaneous receptors by Exendin-4 initiates signaling cascades of PI3K/Akt and anti-NF-κB pathways that regulate cell proliferation, migration, and the secretion of pro- inflammatory cytokines, making it a target for managing chronic skin diseases [7].

Exendin-4 in the Inflammatory Skin Disorders: Psoriasis and Beyond

Inflammatory skin disorders like psoriasis and hidradenitis suppurativa (HS) are intimately linked to systemic inflammation, obesity, and insulin resistance- conditions Exendin-4 is approved to treat. The anti-inflammatory and immunomodulatory actions of GLP-1RAs have shown clinical promise in these areas [8].

Psoriasis is an inflammatory skin disorder that mainly depends on genetic predisposition and ageing. However, there are some environmental risk factors, such as trauma (e.g., Koebner phenomenon), infection, and drugs, that have been proposed to influence the development of this inflammatory skin disease. This pathology affects around 2% of the population worldwide, but it shows some variability, depending on the type of skin. Psoriasis is considered to be T cell- mediated disease characterized by hyperproliferation of keratinocytes and a strong inflammatory infiltrate driven by cytokines like IL-17, IL-23, and TNF-α [9].

Clinical observations and small studies report a rapid and significant improvement in Psoriasis Area and Severity Index (PASI) scores following the initiation of Exendin-4 (exenatide) or other GLP-1RAs, this improvement appears to be mediated by a direct action on the immune system, independent of weight loss or glycemic control in some cases [10, 11].

Possible underlining mechanistic action includes, Exendin-4 has been shown to inhibit cytokine secretion from invariant natural killer T (iNKT) cells, which are key players in psoriasis pathogenesis, and redistribute these cells away from psoriatic plaques [11]. It also reduces the number of dermal γδ-T cells and decreases IL-17 mRNA expression within psoriatic lesions [8]. In addition, Exendin-4 has been approved to suppress pro-inflammatory cytokine production (TNF-α and IL-6) from peripheral blood mononuclear cells (PBMCs) by inhibiting pathways like NF-κB [12].

Exendin-4 and Wound Healing

Approximately, about 25% of people with diabetes mellitus are thought to have poor wound healing, which frequently leads to lower limb amputation and has significant financial and psychological repercussions. Because the hyperglycemic environment encourages the growth of biofilms, diabetic wounds are challenging to treat. Impaired angiogenesis, neuropathy, a suboptimal chronic inflammatory response, decreased fibroblast/keratinocyte activity, and a consequent polymicrobial infection are the primary pathophysiological factors of diabetic wounds [13].

Studies on diabetic rat and mouse models have shown that topical administration or subcutaneous injection of Exendin-4 accelerates excisional wound closure via a cellular mechanism involves direct action on proliferative cells and the local environment. Exendin-4 is targeting the fibroblast and keratinocyte Modulation, it stimulates the proliferation and migration of fibroblasts (which differentiate into myofibroblasts) and keratinocytes, accelerating the transition into the proliferative phase of healing [14].

On the other hand, Exendin-4 enhances the promotion of angiogenesis as it mobilizes circulating endothelial progenitor cells and enhances the expression of proangiogenic factors like Vascular Endothelial Growth Factor (VEGF). In addition, Exendin-4 has a potent anti-inflammatory and anti-Oxidative effects, so, helps to resolve the prolonged inflammation typical of diabetic wounds by suppressing pro-inflammatory cytokines (IL-6) and reducing oxidative stress (superoxide anions) [15].

Potential Role in Skin Malignancies

The application of GLP-1RAs in oncology is an emerging field, driven by observations that these drugs can attenuate tumor growth in certain cancers, which may be relevant to cutaneous malignancies. Exendin-4 shows an anti-proliferative and anti-tumor immunity to suppress the growth of various human cancer cell lines like breast and prostate those express the GLP-1R [7].

The anti-cancer effects are theorized to occur through multiple pathways relevant to skin cancer. One of these pathways is inhibition of proliferation; Exendin-4 can decrease cancer cell proliferation by inhibiting signaling pathways, such as the NF- κB and ERK-MAPK cascades. The second pathway is immunomodulation; in diabetic animal models, Exendin-4 suppressed tumor growth and improved the anti-tumor immune response by enhancing the ratio of cytotoxic T lymphocytes (CTLs) to regulatory T cells (Tregs) [16].

CONCLUSION AND FUTURE DIRECTIONS

Exendin-4, a GLP-1RA, is far more than an anti-diabetic agent; it is a potent pleiotropic molecule with demonstrated anti-inflammatory, pro-angiogenic, and anti-proliferative activities that translate directly to beneficial effects in the skin. Current evidence strongly supports its potential in: (1) Modulating chronic inflammatory disorders like psoriasis by directly targeting key immune cells, and (2) Accelerating the healing of chronic wounds, especially in metabolically compromised patients, through enhanced angiogenesis and cell proliferation. While preclinical data is compelling, larger clinical trials focused on non-diabetic and non-obese dermatologic populations are required to fully elucidate the therapeutic potential and establish Exendin-4's safety and efficacy as a dermatological agent.

Conflicts of Interest

The authors declare no conflict of interest.

REFERENCES

[1] Eng J. *et al.* "Purification and structure of exendin-3, a new pancreatic secretagogue isolated from *Heloderma horridum* venom." *The Journal of Biological Chemistry*, vol. 265, no. 33, 1990, pp. 20259–20262.

[2] Eng J. *et al.* "Isolation and characterization of exendin-4, an exendin-3 analogue, from *Heloderma suspectum* venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas." *The Journal of Biological Chemistry*, vol. 267, no. 11, 1992, pp. 7402–7405.

[3] Figat M. *et al.* "Beneficial influence of exendin-4 on specific organs and mechanisms favourable for the elderly with concomitant obstructive lung diseases." *Brain Sciences*, vol. 12, no. 8, 2022, pp. 1090.

[4] Yap M.K.K. and Misuan N. "Exendin-4 from *Heloderma suspectum* venom: from discovery to its latest application as type II diabetes combatant." *Basic & Clinical Pharmacology & Toxicology*, vol. 124, no. 5, 2019, pp. 513–527.

[5] Chung C.H. *et al.* "RETRACTED: Long-lasting exendin-4-loaded PLGA nanoparticles ameliorate cerebral ischemia/reperfusion damage in diabetic rats." *Journal of Personalized Medicine*, vol. 12, no. 3, 2022, pp. 390. (Retraction published 2024).

[6] Fu X. *et al.* "Dermatologic implications of glucagon-like peptide-1 receptor agonist medications." *Skin Appendage Disorders*, vol. 11, no. 1, 2025, pp. 1–8.

[7] Iwaya C. *et al.* "Exendin-4, a glucagon-like peptide-1 receptor agonist, attenuates breast cancer growth by inhibiting NF-κB activation." *Endocrinology*, vol. 158, no. 12, 2017, pp. 4218–4228.

[8] Faurschou S. *et al.* "GLP-1RAs in patients with psoriasis." *International Journal of Molecular Sciences*, vol. 26, no. 4, 2025, pp. 3396.

[9] Samotij D. *et al.* "Pathogenesis of psoriasis in the 'omic' era. Part I. Epidemiology, clinical manifestation, immunological and neuroendocrine disturbances." *Postepy Dermatologii i Alergologii*, vol. 37, no. 2, 2020, pp. 135–153.

[10] Buysschaert M. *et al.* "Improvement of psoriasis during exenatide treatment in a patient with diabetes." *Diabetes Care*, vol. 33, no. 11, 2010, pp. e135.

[11] Hogan A.E. *et al.* "Glucagon-like peptide-1 (GLP-1) and the regulation of human invariant natural killer T cells: lessons from obesity, diabetes and psoriasis." *Diabetologia*, vol. 54, no. 10, 2011, pp. 2664–2674.

[12] Lin H. *et al.* "Anti-inflammatory effects of exendin-4, a glucagon-like peptide-1 analog, on human peripheral lymphocytes in patients with type 2 diabetes." *Experimental and Therapeutic Medicine*, vol. 12, no. 6, 2016, pp. 3907–3912.

[13] Burgess J.L. *et al.* "Diabetic wound-healing science." *Medicina (Kaunas)*, vol. 57, no. 10, 2021, pp. 1072.

[14] Monroy L. *et al.* "Effects of exendin-4 on diabetic wounds: direct action on proliferative phase of wound healing." *Biochimica et Biophysica Acta (BBA) – Molecular Basis of Disease*, vol. 1871, no. 1, 2025, pp. 166946.

[15] Hao H. *et al.* "Exendin-4 in combination with adipose-derived stem cells promotes angiogenesis and improves diabetic wound healing." *Journal of Surgical Research*, vol. 212, 2017, pp. 19–28.

[16] Sun Y. *et al.* "Exendin-4 exhibits enhanced anti-tumor effects in diabetic mice." *EBioMedicine*, vol. 19, 2017, pp. 130–139.