RESEARCH LETTER



# Glucagon-Like Peptide-1 Receptor Agonists as a Potential Mitochondrial Modulation Therapy for Hidradenitis Suppurativa

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*To the Editor,*

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease that is often associated with obesity, metabolic syndrome and mitochondrial dysfunction. The latter could lead to widespread inflammation and immune system dysregulation, resulting in the manifestations of metabolic syndrome and its influence on the skin (1). Gouvrion et al. (2) have recently reported that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are associated with improved HS treatment by reducing disease severity across multiple outcomes. This supports the growing interest in drug repurposing of these agents for indications other than glycemic control. Building on these clinical observations, the purpose of our study was to investigate unbiased transcriptomic data in order to evaluate how GLP-1 RAs may mechanistically influence pathways relevant to HS, beyond their established metabolic effects. This approach aims to link clinical outcomes with underlying molecular signatures, thereby contributing to a better understanding of the potential role of GLP-1 RAs in HS.

Two relevant RNA-seq datasets were retrieved from the NCBI's Gene Expression Omnibus (GEO) and analyzed: GSE245451, generated from the skin of patients with HS, and GSE262105 from a study on GLP-1 RA *in vivo*. For GSE245451, gene count matrices were obtained directly from GEO. For GSE262105, Raw sequencing files were obtained from the Sequence Read Archive (SRA) using the SRA Toolkit. RNA-seq data quality was assessed using FastQC, and reads were aligned to the respective reference genomes (GRCm39) using HISAT2, and featureCounts was used to obtain the gene counts. Gene expression of both datasets was normalized using DESeq2. Finally, pathway enrichment analysis was assessed by GSEA using Hallmark gene sets and standard permutation-based statistics. Clinical covariates were not consistently available in GSE245451 and were therefore not included in the analysis.

Analysis of GSE245451 (3) from lesional, non-lesional HS, and control skin samples revealed that the oxidative phosphorylation (OXPHOS) pathway was strongly downregulated in HS compared to control skin, regardless of lesional or non-lesional location (**Fig. 1**A). The reduced transcriptional signature associated with OXPHOS in HS patients may indicate mitochondrial impairment as a general characteristic of HS skin. The consistent suppression of this pathway in clinically unaffected (non-lesional) skin indicates that mitochondrial dysfunction is likely a systemic feature of HS rather than a local consequence of inflammation, raising the possibility that impaired mitochondrial metabolism contributes to disease susceptibility. On the other hand, analysis of GSE262105 (4) revealed that the OXPHOS pathway was enriched in the heart tissue of both control and transverse aortic constriction (TAC) mice treated with two different regimens of semaglutide (Sema), a GLP-1 RA (Fig. 1B). This suggests that GLP-1 RAs can enhance mitochondrial oxidative metabolism *in vivo*, which could potentially counteract the reduced OXPHOS signature observed in HS.

Our data analysis shows a consistent trend of reduction in OXPHOS in patients with HS, which was enriched upon GLP-1 RA treatment (Fig. 1). Together, these patterns suggest that GLP-1 signalling can restore mitochondrial transcriptional signatures that are deficient in HS. Beneficial effects of GLP-1 RA treatment on mitochondrial function across multiple biological contexts have also been reported and comprehensively reviewed in other studies (5). On the other hand, Palmer et al. discussed that mitochondrial dysfunction is linked to inflammation across skin disorders, including HS, providing skin-specific biologic context for an OXPHOS mechanism (1). Our findings show that OXPHOS suppression is present not only in lesional but also in non-lesional skin of HS patients. The consistent reduction in clinically unaffected tissue suggests that mitochondrial dysfunction is a systemic feature of HS and may act as a driver of inflammation, rather than merely a secondary consequence of local inflammatory processes. Taken together, the association of GLP-1 RAs with improved HS outcomes (2), OXPHOS deficit in HS skin (Fig. 1A), and evidence that GLP-1 RAs can restore OXPHOS (Fig. 1B), could support a role for GLP-1 RAs that act, at least partially, through systemic mitochondrial modulation in HS. Based on these observations, we hypothesized that hidradenitis suppurativa exhibits suppressed mitochondrial function

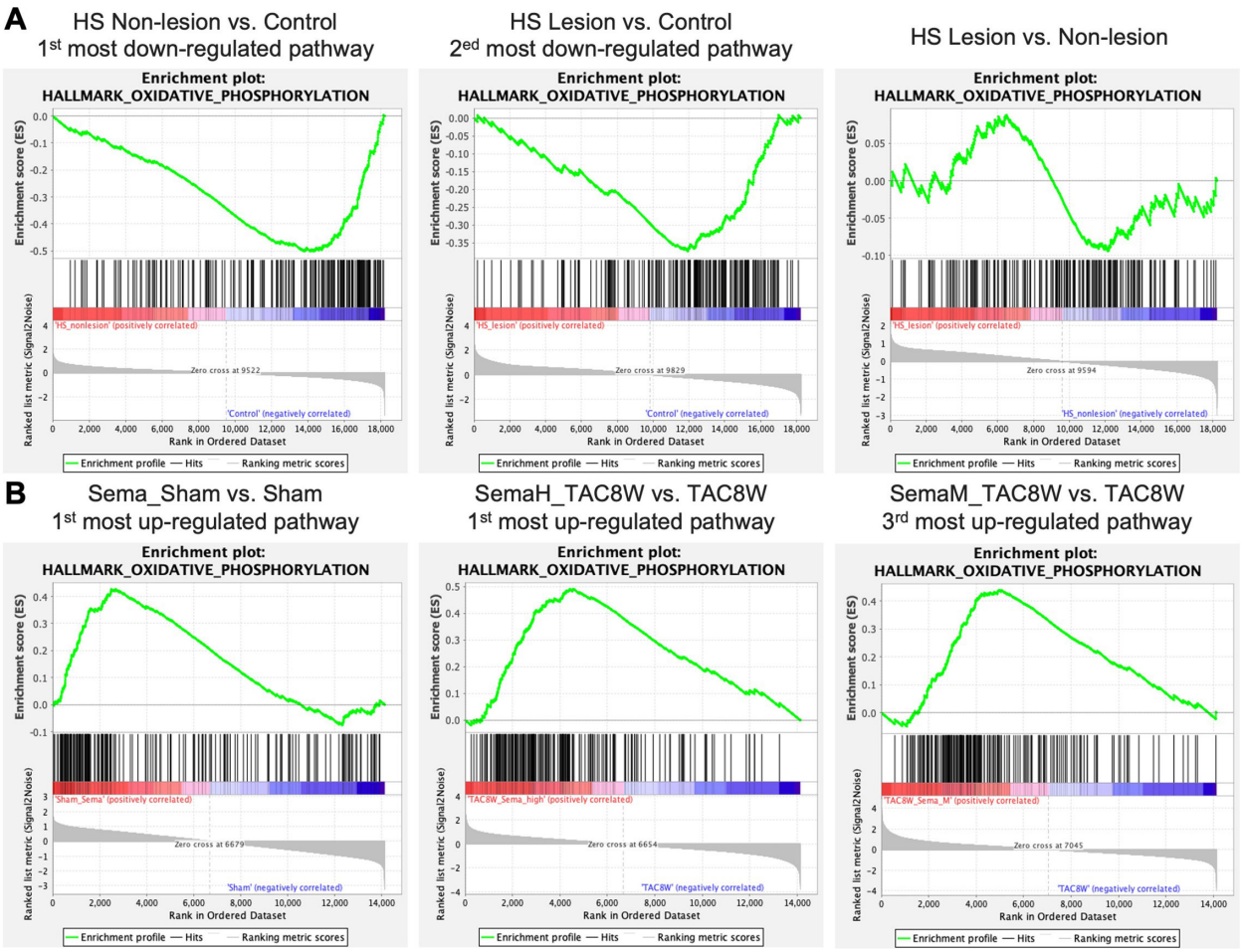


**Fig. 1. Dysregulation of the OXPHOS-associated transcriptional signature.** (A) Analysis of GSE245451 dataset showed dysregulation of the OXPHOS pathway in HS skin samples compared to healthy skin. NOM *p*-value from left to right: <0.001; <0.001; 1. (B) Analysis of GSE262105 dataset revealed that semaglutide (a GLP-1 RA) treatment enriched the OXPHOS pathway in different groups of mice. NOM *p*-value from left to right: <0.001; <0.001; <0.001. *GLP-1 RA*: glucagon-like peptide-1 receptor agonist; *HS*: hidradenitis suppurativa; *OXPHOS*: oxidative phosphorylation; *Sema*: semaglutide; *SemaH*: high semaglutide regimen; *SemaM*: medium semaglutide regimen; *Sham*: sham surgery (control); *TAC8W*: transverse aortic constriction for eight weeks.

and that GLP-1 RAs may improve mitochondrial function in this disorder.

Limitations of this study include the absence of human skin transcriptomic data upon GLP-1 RAs exposure and the lack of direct evidence that GLP-1 RAs reduce inflammation or restore mitochondrial function in HS. These gaps could be addressed by *ex vivo* studies evaluating the mechanism of action of GLP-1 RAs on skin and alongside a biomarker-anchored study on HS. In addition, a controlled, prospective trial is proposed to assess the clinical efficacy of GLP-1 RAs in treating HS, focusing on the key clinical and dermatographic elements of HS and metabolic syndrome, while considering various possible confounding factors, such as medication, that may affect mitochondrial dysfunction. If confirmed, GLP-1 RAs may provide a direct immunometabolic approach for HS management.

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*Conflict of interest:* CCZ has received disease relevant honoraria as a consultant for Almirall, Boehringer Ingelheim, CSL Behring, Eli Lilly and Company, Idorsia, Incyte, MSD, Novartis, Pfizer, Sanofi, ShiRhom, Takeda, UCB, and ZuraBio and lecture honoraria from Almirall, BMS, Novartis, and UCB. He is President of the EHSF e.V., President of the Deutsches Register Morbus Adamantiades-Behçet e.V., Board member of the International Society for Behçet's Disease, coordinator of the ALLOCATE Skin group of the ERN Skin, and chair of the ARHS Task Force group of the EADV. He is Editor of the EADV News, and co-copyright holder of IHS4 on behalf of the EHSF e.V. SMSJ: Advisory boards and speaker at educational events by LEO Pharma, Eli Lilly, Novartis and Pfizer.

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