miR-205 Suppression in Human Keratinocytes by *Leishmania braziliensis* Exposure Delays Skin Wound Repair Through Cell Adhesion Pathways

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ABSTRACT

In inflammatory skin diseases, keratinocyte migration plays a crucial role in re-establishing the epithelial layer, a fundamental process in wound healing. Cutaneous leishmaniasis (CL), a chronic inflammatory skin condition marked by ulcerated cutaneous lesions and persistent inflammation, lead to a reprogramming of host cell transcripts. This reprogramming facilitates the modulation of gene expression related to the response to the parasite. Consequently, post-transcriptional regulation mediated by microRNAs (miRNAs) can adjust the molecules involved in attenuating the damage caused by injury. Thereby, the aim of our study was to explore the role of miR-205 in the migration of human keratinocytes exposed to *Leishmania braziliensis* (Lb) within a 2-dimensional environment. Our research unveiled a consistent downregulation of miR-205 in bioinformatics analyses performed using transcriptomic data from biopsies of patients with various inflammatory skin diseases, including cutaneous leishmaniasis, psoriasis, lupus, and leprosy. Intriguingly, we found that, irrespective of the disease, miR-205 was consistently inhibited in inflammatory skin conditions. We validated these findings through biopsies from CL patients and by exposing human HaCaT keratinocytes to Lb. In both ex vivo and in vitro assays, the expression of miR-205 was downregulated in the presence of Lb, and our experiments showed that miR-205 promotes keratinocyte migration in a wound scratch model, while Lb delays wound healing. The scratch area was quantified, and the results revealed a dynamic interplay between miR-205 and Lb in wound closure. Additionally, we assessed cell adhesion molecules, observing a reduction in one of the essential proteins involved in adhesion complex formation, focal adhesion kinase (FAK), in response to parasite exposure. Furthermore, we noted alterations in actin dynamics in the groups exposed to Lb. Importantly, the inhibitions observed in the presence of Lb were reversed in groups treated with miR-205. Finally, Transwell assay

reinforces that Lb delays the migration of keratinocytes and that the presence of miR-205 reverses this effect. Our findings underscore the significance of regulating miR-205 in migrating keratinocytes, highlighting its fundamental role in the re-epithelialization process and a promising candidate for application in clinical practice.

Keywords: miR-205; wound healing; Cutaneous Leishmaniasis.

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