

ARHGAP17 and VEGFB as Biomarkers for Electroacupuncture in Rheumatoid Arthritis: Potential and Unresolved Questions [Letter]

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Dear editor

We have read with great interest the study by Sun et al on the diagnostic biomarkers for rheumatoid arthritis (RA) treated with electroacupuncture. We are impressed by the rigorous study design and advanced methodologies employed in their research. In particular, the identification of ARHGAP17 and VEGFB as potential biomarkers through the integration of various machine learning algorithms, coupled with the validation of their regulatory effects on expression in animal models, offers new insights into the precise diagnosis of RA and the mechanisms of traditional Chinese medicine treatment.¹

Although the study has made significant progress in bioinformatics and experimental validation, we would like to offer comments on two points in the hope of further advancing discussions in this field.

The Bidirectional Regulatory Role of VEGFB in RA Remains Unclear

Sun et al found that electroacupuncture could upregulate the expression of VEGFB in the peripheral blood of both RA patients and CFA rats, suggesting a potential association with the anti-inflammatory effects of electroacupuncture. However, previous studies have indicated that members of the VEGF family primarily promote angiogenesis and inflammatory responses in RA. For instance, Kim et al observed a positive correlation between serum VEGF levels and RA disease activity.² In addition, Zhu et al reported that electroacupuncture could inhibit synovial angiogenesis in adjuvant-induced arthritis rats by downregulating the HIF-1 α /VEGF pathway.³ These studies suggest that VEGF primarily exerts a pro-inflammatory role in RA.

As one of the VEGF isoforms, the specific function of VEGFB in RA remains unclear. Although this study suggests that VEGFB may be involved in the anti-inflammatory process through the PI3K/AKT-FoxO3A signaling pathway,¹ there is currently a lack of direct evidence supporting the protective role of VEGFB in RA. We recommend that the authors further elucidate the specific role of VEGFB in the pathological process of RA, for example, by conducting in vitro cell experiments or using tissue-specific knockout models to clarify whether it exhibits biological functions distinct from those of VEGF-A.

The Mechanistic Study of ARHGAP17 in RA Is Still Insufficient

This study is the first to propose ARHGAP17 as a potential target for electroacupuncture in the treatment of RA, hypothesizing that it may exert anti-inflammatory and analgesic effects by inhibiting the activity of Rho GTPases, such as RAC1. However, current research on ARHGAP17 in RA is very limited, and its expression and function in immune cells or synovial tissues have yet to be reported. In our previous research, we found that RAC1 is highly expressed in the synovial tissue of RA patients and is closely associated with the infiltration of inflammatory cells. Additionally, Wan et al

reported that inhibiting spinal RAC1 could alleviate inflammatory pain,⁴ suggesting that the RAC1 signaling pathway plays a crucial role in RA-related pain.

Although Sun et al suggested that electroacupuncture may inhibit RAC1 by upregulating ARHGAP17, this hypothesis has not been directly validated in their study. We recommend further investigation of RAC1 activity changes in the CFA model, or the use of ARHGAP17 inhibitors/agonists, to clarify its specific mechanism in electroacupuncture-induced analgesia.

Summary and Recommendations

The study by Sun et al provides new candidate biomarkers for electroacupuncture treatment of RA and offers preliminary insights into the roles of ARHGAP17 and VEGFB in electroacupuncture modulation. However, the specific functions of these two genes in the pathogenesis of RA and their reliability as therapeutic targets still require further validation. We recommend the following:

- Conduct functional experiments to clarify the bidirectional regulatory mechanism of VEGFB in RA.
- Investigate the molecular pathway of the ARHGAP17-RAC1 axis in electroacupuncture-induced analgesia.

We look forward to the authors' follow-up research in these areas, which will also provide a more solid scientific foundation for personalized treatment of RA.

Acknowledgment

The bidirectional regulatory role of VEGFB in RA remains unclear.

Disclosure

The authors report no conflicts of interest in this work.

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