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LETTER

Transcriptome Changes of ACC in IBS Rats Induced by Electroacupuncture: Exploration of Mechanism and Clinical Significance [Letter]

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Dear editor

We read with great interest the excellent research recently published by Guo et al.[1] The authors provide compelling evidence that electroacupuncture Tianshu (ST25) and Tianshu (ST36) can reduce visceral hypersensitivity and anxiety-like behavior in irritable bowel syndrome (IBS) rats, accompanied by a unique transcriptome remodeling in the anterior cingulate cortex (ACC). The identification of glutamate metabotropic receptor 2 (GRM2), pyruvate dehydrogenase kinase 4 (PDK4), and serum/glucocorticoid-regulated kinase 1 (SGK1) as potential mediators of electroacupuncture (EA) therapeutic effects is a valuable contribution to the field. However, the original text has methodological limitations that are questionable in terms of both the neuroanatomical basis of acupoint specificity and the cellular heterogeneity of gene expression.

First, regarding the neuroanatomical basis of acupoint specificity. The authors report significant differences in the regulation of the ACC gene by EA at ST25 and ST36, and propose the hypothesis that they act through different pathways. ST36 activates the vagal-adrenal axis, while ST25 exerts its effects upward through the spinal brainstem. However, this hypothesis lacks any direct experimental verification in the original text, leading to a key break in the chain of argumentation.

Although the authors cited Liu et al 's study on ST36 activating the vago-adrenal axis in the introduction,[2] they did not verify in their own experimental system whether this pathway actually mediates the regulation of the ACC gene by ST36. More importantly, regarding the pathway of ST25, the authors only vaguely referred to the spinal-brainstem ascending projection, without identifying specific nuclei or verifying its functional necessity through any neural disappearance, knockout, or chemogenetic means. The authors attributed the differences in gene expression directly to the differences in pathways, but did not experimentally prove the existence of these two pathways, nor did they prove that they were, respectively, responsible for transmitting ST25 and ST36 signals.

The fundamental problem that would arise from this methodological gap is that the differences in gene expression between ST25 and ST36 induced by ACC could very well stem from other factors rather than the different upline pathways hypothesized by the authors. For example, the two acupoint stimulations may activate ACC through the same pathway but at different intensities, frequencies, or durations, and also produce differentiated transcriptome responses. In the absence of neural circuit evidence, the authors' conclusions about acupoint specificity can only remain on the surface of speculation and lack substantial mechanistic support. Future studies will definitely need to combine viral tracing, activity-dependent markers (such as TRAP2), and pathway-specific interventions (such as chemogenetic blocking) to directly verify at the neural circuit level whether the two acupoint stimulations activate different upward pathways and neuronal subpopulations in ACC.

Secondly, regarding cell type specificity of gene expression. The authors analyzed the transcriptome changes of ACC using bulk RNA-seq technology, a methodological choice that brings two levels of limitations.

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The first layer is the problem of information loss. The ACC itself is a highly heterogeneous brain region that contains a variety of excitatory pyramidal neurons, inhibitory pyramidal neurons, and non-neuronal cells such as astrocytes and microglia. Bulk RNA-seq mixes RNA from all cell types and presents an average signal, meaning that even if a certain gene is significantly upregulated in one cell subpopulation and significantly downregulated in another, the overall test may show no significant change; Conversely, the significant changes detected as a whole may reflect changes in only a few cell subpopulations. The author's reported variations in GRM2, PDK4, and SGK1 originated from cell types that the original text cannot answer.

The second layer is the ambiguity of functional interpretation. The three genes have distinct cellular distribution characteristics in ACC. GRM2 is mainly located at the synaptic endings of glutamatergic neurons, PDK4 is enriched in astrocytes and involved in energy metabolism, and SGK1 is widely expressed in neurons and glial cells and mediates stress signaling. This distribution difference means that even if the overall expression level changes are the same, the functional implications may be completely opposite. The original text categorizes the three genes as EA targets but fails to distinguish their cellular origins, leaving any inferences about their functional mechanisms lacking a cellular basis.

Mononuclear RNA sequencing of human ACC has revealed that it contains multiple subclasses of excitatory and inhibitory neurons with different transcriptome characteristics, providing an important reference for understanding the cellular targets of EA.[3] Future studies will need to re-evaluate electroneedle-induced transcriptome changes at cell resolution using single cell/single-cell RNA sequencing or multiplex in situ hybridization to determine whether there are differences in the cell types regulated by ST25 and ST36 and whether such differences correspond to their respective behavioral effects.

In summary, the study by Guo et al provides valuable transcriptome data on the central mechanism of EA for IBS, but there are significant methodological limitations in both acupoint-specific pathway validation and insufficient cell type discrimination If future studies can fill these gaps and further validate the correlation between the genes they discovered and the phenotypes of IBS patients in clinical cohorts, it will help advance acupuncture from empirical medicine to precision medicine.

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Disclosure

The authors declare there are no conflicts of interest in this communication.

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