Inflammatory Risk & Post-COVID Endothelial Dysfunction: The Role of Anti-ACKR1 Autoantibodies

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Introduction

The long-term effects of COVID-19 extend beyond the acute infection phase. Among these, endothelial dysfunction, characterised by impaired blood vessel health, has emerged as a significant concern due to its association with cardiovascular diseases.

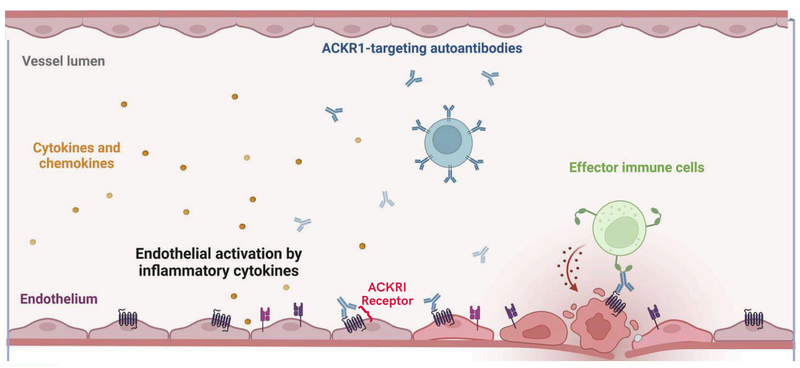

Figure 1: Role of the ACKR1 receptors and anti-ACKR1 autoantibodies in vessel endothelium

This study explores the intricate mechanisms by which chronic inflammation triggers anti-ACKR1 auto-antibody response and how this may potentially influence endothelial dysfunction amongst post-COVID individuals.

Methods

This study employed a cross-sectional design, investigating the long-term endothelial, haematological and cardiovascular complications amongst post-COVID patients without prior established cardiovascular diseases. Anti-ACKR1 autoantibody levels were quantified using flow cytometry-based assays, and individual ACKR1 genotypes were determined using Sanger sequencing.

Subsequently, the effects of human plasma immunoglobulin G (IgG) from participants on human vascular endothelial cells were analysed including apoptosis, barrier function and antibody-dependent cell cytotoxicity. Liposome ACKR1 recombinant protein and a blocking peptide were tested in their efficacy of negating the effect of anti-ACKR1 autoantibodies.

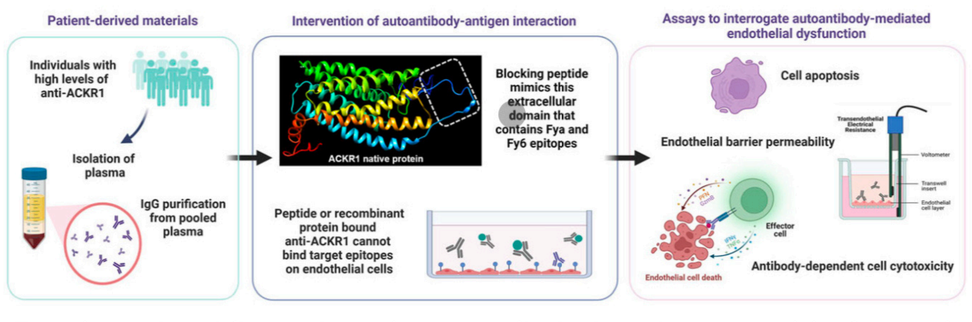

Figure 2: Experimental workflow to determine autoantibody-dependent cytotoxicity from patient plasma

Results

TNFα treatment, a surrogate mimicking long term inflammation due to COVID-19, revealed the expression of ACKR1, an atypical chemokine receptor, in both arterial and venular endothelial cells.

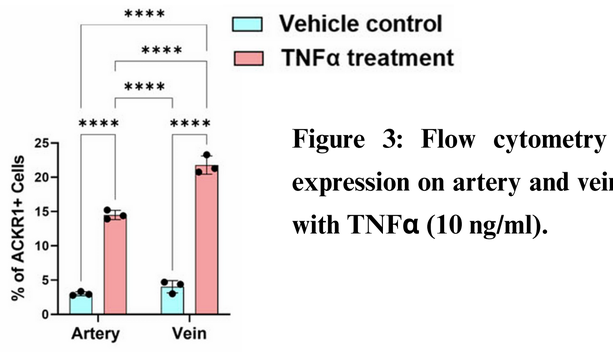

Figure 3: Flow cytometry analysis of ACKR1 protein expression on artery and vein cells after 48 h of stimulation with TNFα (10 ng/ml).

This study also revealed significant findings that underscore the role of anti-ACKR1 autoantibodies in post-COVID endothelial dysfunction.

Post-COVID survivors exhibited significantly elevated concentrations of anti-ACKR1 autoantibodies ($p<0.05$) correlating with increased systemic cytokine levels and damaged circulating endothelial cells as compared to their non-infected counterparts.

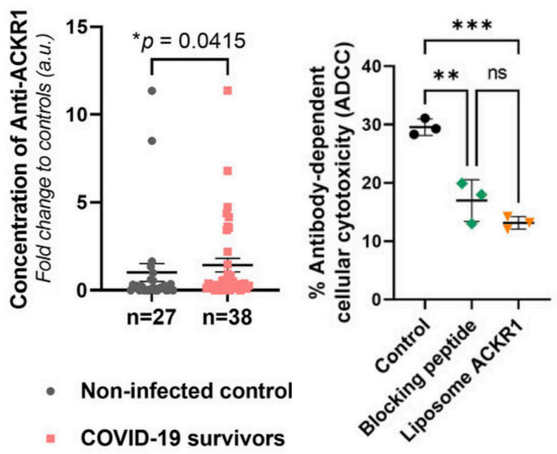

Figure 4a: Plasma levels of anti-ACKR1 autoantibodies in COVID-19 survivors and non-infected controls

Figure 4b: Degree of antibody-dependent cellular cytotoxicity in endothelial cells exposed to purified IgG and PBMCs. Purified IgG was pre-incubated with and without blocking peptide or liposome ACKR1.

Cell cytotoxic assays showed that both purified IgG and participants' peripheral blood mononuclear cells led to significantly higher levels of antibody-dependent and immune cell-mediated cytotoxicity respectively. Interestingly, this response was abrogated by the inclusion of blocking peptides and liposome ACKR1, with the latter significantly reducing levels of late-apoptotic cells as well as improving endothelial barrier tightness.

While it has yet to be proven in human subjects, literature showed high expression of ACKR1 in murine brain and soleus muscle venous endothelial cells potentially explaining site-specific compliacations like deep vein thrombosis when corroborated with our study.

Discussion & Outlook

The findings of this study highlight a novel pathogenic mechanism underlying post-COVID endothelial dysfunction. Elevated anti-ACKR1 autoantibodies appear to exacerbate vascular damage by amplifying systemic inflammation and impairing chemokine scavenging. Interventions such as neutralising antibodies or blocking peptides could offer a promising approach in therapeutics to mitigate chronic vascular inflammation. Additionally, the role of anti-ACKR1 autoantibodies in other inflammatory conditions warrants exploration.

Conclusion

This study identifies anti-ACKR1 autoantibodies as a key factor contributing to endothelial dysfunction in post-COVID patients. By linking these autoantibodies to inflammatory pathways, the findings provide a deeper understanding of endothelial dysfunction in chronic inflammatory conditions and open new avenues for targeted therapies. The results underscore the importance of addressing endothelial health in the management of post-COVID complications to reduce the burden of cardiovascular diseases.

Acknowledgements

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