JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 9, NO. 5, 2024

EDITORIAL COMMENT

Dysregulation of IL-6/MCP-1/STAT3 Axis

A Promising Therapeutic Postinfarction Inflammation Strategy?*

Andreas Mitsis, MD, MSc, PhD(c),[a] Stergios Tzikas, MD, PhD,[b] George Kassimis, MD, PhD[c]

In recent decades, there has been a progressive understanding of the complex interplay between cytokines and chemokines released after an acute myocardial infarction (AMI) and their prognostic role during the post-myocardial infarction (MI) period.[1] The acknowledgment of inflammation's crucial role in prognosis has steered the scientific community's efforts toward identifying the optimal target, potentially through inhibition, to mitigate the extent of adverse outcomes resulting from inflammation after an AMI.

Various inflammatory pathways have been described to be used in the post-MI phase. From a pathophysiology viewpoint, these pathways can be separated into those acting via interleukin (IL)-6 and those operating independently of it.[2] IL-6 plays a pivotal role in the inflammatory signaling implicated in the initiation and progression of cardiovascular disease. IL-6 orchestrates the recruitment of immune cells to the damaged myocardium, while also stimulating the production of acute-phase proteins such as C-reactive protein, which act as inflammation markers. Furthermore, IL-6 influences the differentiation and activation of immune cells, thereby contributing to the inflammatory environment within the infarcted tissue. Increased levels of IL-6 are related to adverse clinical events following AMI,[3] while IL-6 inhibition with tocilizumab has been correlated with improved myocardial salvage index in patients with ST-segment elevation MI.[4] Similarly, monocyte chemoattractant protein (MCP)-1, a chemokine released by cardiac fibroblasts, contributes to the recruitment of monocytes and macrophages to the site of injury and promote inflammation. Of note, an elevated baseline MCP-1 level is linked to traditional atherosclerosis risk factors and an elevated risk for death or MI, regardless of baseline variables.[5]

One of the downstream pathways through which IL-6/MCP-1 can act is the Janus kinase protein/signal transducer and activator of transcription 3 (STAT3) pathway. Janus kinase protein/STAT3 plays a multifaceted role in AMI. Following an AMI, STAT3 activation has been associated with both cardioprotective and detrimental effects. On one hand, it can promote cell survival, reduce apoptosis, and facilitate cardiac repair and regeneration after injury. However, excessive STAT3 activation can contribute to adverse cardiac remodeling, fibrosis, and inflammation. The intricate balance of STAT3 signaling in AMI suggests its potential as a therapeutic target for modulating postinfarction outcomes.[6]

In a study reported in this issue of *JACC: Basic to Translational Science*, Paccalet et al,[7] examined the prognostic role of IL-6 and MCP-1 in patients with ST-segment elevation MI, showing that the levels of IL-6 and MCP-1 in the blood levels peak at 24 hours and positively correlate to worse outcomes, respectively. This knowledge might be already well recognized, but the investigators went a step further; using a murine model of MI and an in vitro coculture model, they proved that the production of IL-6/MCP-1 by the injured cardiomyocytes acts via the STAT3 pathway, and this signaling pathway is involved in worsening reperfusion injuries. The investigators found that the use of IL-6-neutralizing antibody led to a 32.1% reduction of anti-inflammatory macrophage recruitment by cardiac myocytes at 24 hours post-MI, without impairing proinflammatory macrophage

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Cardiology Department, Nicosia General Hospital, Nicosia, Cyprus; [b]Third Department of Cardiology, Aristotle University of Thessaloniki, Thessaloniki, Greece; and the [c]Second Department of Cardiology, Aristotle University of Thessaloniki, Thessaloniki, Greece.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2024.03.006

recruitment. Likewise, the MCP-1-neutralizing antibody led to a 44.2% reduction of anti-inflammatory macrophages ($P = 0.002$) and a 29.8% reduction of proinflammatory macrophages ($P = 0.005$). Furthermore, the inhibition of the STAT3 signaling pathways by the STATTIC antagonist reduced anti-inflammatory macrophage recruitment at 24 hours post-MI ($P = 0.044$), whereas it had no significant effect on proinflammatory macrophage recruitment.

The investigators conclude that these results suggest that IL-6- and MCP-1-mediated anti-inflammatory macrophage recruitment relies mostly on STAT3-dependent pathways. Finally, they report that reducing the recruitment and activation of anti-inflammatory macrophages at the onset of reperfusion, either by treatment with STATTIC or with the combination of neutralizing antibodies, the severity of the infarction decreases ($P = 0.0061$ and $P = 0.0081$, respectively).

The major advantage of this research is the use of the translational nature of research, merging preclinical and clinical studies. The investigators show that this is probably one of the ways to improve the translational aspect of research, as understanding the underlying mechanism using a preclinical model could massively accelerate therapeutic research. An additional benefit of this study compared with previous research is the examination of the secretion kinetics of the 2 cytokines, IL-6 and MCP-1, at 5 different sampling times, with the last one at 1 month, which allowed temporal distance from the acute event and a better understanding of these cytokines' secretion kinetics. Besides, the study demonstrates that the combination of IL-6 and MCP-1 has a more robust predictive power than either cytokine alone. A limitation of the study is the absence of a control group, while the complex phenotype of anti-inflammatory macrophage subtypes may require more refined characterization in future studies.

Finally, the big question that arises with this study is again the complexity of targeting inflammation in cardiovascular diseases. The study results challenge the traditional belief that anti-inflammatory macrophages are inherently advantageous, while proinflammatory ones are harmful, showing the dynamic shift in the role of the anti-inflammatory macrophages whereby their function during the early reperfusion phase differs from their role during the subsequent remodeling phase.

Undoubtedly, future areas of development remain, and further investigations are necessary to address unresolved inquiries. However, a significant conclusion from this study is that effectively targeting molecular inflammation mediators demands a thorough comprehension of the dynamic inflammatory process and the involvement of these mediators in its various stages. Despite significant advances, our understanding of cardiac immunity remains incomplete, highlighting a significant gap in achieving safe and effective treatments for patients with heart inflammation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Andreas Mitsis, Nicosia General Hospital, Cardiology Department, Limassol Old Road No. 215, 2029, Nicosia, Cyprus. E-mail: andymits7@gmail.com.

REFERENCES

1. Mitsis A, Kadoglou NPE, Lambadiari V, et al. Prognostic role of inflammatory cytokines and novel adipokines in acute myocardial infarction: an updated and comprehensive review. *Cytokine*. 2022;153:155848.

2. Ridker PM, Lüscher TF. Anti-inflammatory therapies for cardiovascular disease. *Eur Heart J*. 2014;35:1782-1791.

3. Tøllefsen IM, Shetelig C, Seljeflot I, Eritsland J, Hoffmann P, Andersen GØ. High levels of interleukin-6 are associated with final infarct size and adverse clinical events in patients with STEMI. *Open Heart*. 2021;8:e001869.

4. Broch K, Anstensrud AK, Woxholt S, et al. Randomized trial of interleukin-6 receptor inhibition in patients with acute ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2021;77:1845-1855.

5. de Lemos JA, Morrow DA, Sabatine MS, et al. Association between plasma levels of monocyte chemoattractant protein-1 and long-term clinical outcomes in patients with acute coronary syndromes. *Circulation*. 2003;107:690-695.

6. Zhang Q, Wang L, Wang S, et al. Signaling pathways and targeted therapy for myocardial infarction. *Signal Transduct Target Ther*. 2022;7:78.

7. Paccalet A, Badawi S, Pillot B, et al. Deleterious anti-inflammatory macrophage recruitment in early post-infarction phase: unraveling the IL-6/MCP-1/STAT3 axis. *J Am Coll Cardiol Basic Trans Science*. 2024;9(5):593-604.

KEY WORDS IL-6, inflammation, macrophages, MCP-1, myocardial infarction, STAT3