Comment on "Human Adipose Tissue-Derived Stem Cells Inhibit Coronary Artery Vasculitis in a Mouse Model of Kawasaki Disease"

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To the Editor:

I read with great interest the recent article by Ryohei Fukunaga et al. entitled "Human Adipose Tissue-Derived Stem Cells Inhibit Coronary Artery Vasculitis in a Mouse Model of Kawasaki Disease", published in Journal of Nippon Medical School[1]. The authors present compelling data showing that human adipose tissue-derived stem cells (hADSCs) can attenuate coronary vasculitis in a CAWS-induced mouse model of Kawasaki disease (KD). Their findings provide valuable insight into the potential of mesenchymal stem cell-based therapies for immune-mediated vascular injury.

I found several aspects of this study particularly thought-provoking. As the authors noted, the immunological changes induced by hADSCs are of significant interest. Previous studies have reported that mesenchymal stem cells (MSCs) and adipose-derived stem cells (ADSCs) interact with various immune cells, including T cells and macrophages[2,3]. Furthermore, ADSCs have been shown to exert anti-inflammatory effects by suppressing $CD4^+$ T cells and macrophages[4]. In this regard, further identification and immunophenotyping of the inflammatory cells surrounding the coronary arteries—including their activation states—would be highly informative. Such analyses may elucidate how hADSCs interact with immune populations in situ.

Moreover, the authors' observation that CD44, a known surface marker of hADSCs, was not detected in the inflammatory lesions is intriguing. This raises the question of whether the hADSCs accumulate in specific remote tissues or act through paracrine mechanisms such as exosome secretion, growth factors, or anti-inflammatory mediators. Further exploration of these possibilities would greatly enhance our understanding of the underlying therapeutic pathways. Notably, recent studies have also highlighted the role of exosomes derived from MSCs in modulating immune responses[5]. In this context, administration of hADSC-conditioned media could also be a promising alternative to direct cell transplantation.

In addition, because long-term cardiovascular sequelae are a hallmark of KD, it would be of particular importance to evaluate pathological changes not only in the acute phase but also over short- to mid-term periods in this mouse model. Inflammation typically progresses through acute, subacute, and chronic stages, each with distinct immunological landscapes. Future studies examining how immune cell phenotypes shift across these phases in response to hADSC therapy will be critical for defining optimal treatment timing and understanding long-term efficacy.

The observation that hADSC transplantation suppressed the production of IL-1α, rather than IL-1β, is also highly intriguing. IL-1β production is tightly regulated by the inflammasome, whereas IL-1α is released during cell injury such as necrosis and functions as an alarmin that triggers inflammation[6,7]. IL-1α is a key trigger in various inflammatory diseases, and based on the present findings, hADSCs may have therapeutic potential not only for KD but also for other IL-1α-mediated inflammatory conditions.

In conclusion, we commend the authors for their

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important contribution to the field of vascular inflammation and pediatric immunology. We look forward to future studies that will further dissect the mechanisms of action and long-term implications of hADSC-based interventions in Kawasaki disease.

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