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Dichotomous Roles of Smooth Muscle Cell–Derived MCP1 (Monocyte Chemoattractant Protein 1) in Development of Atherosclerosis

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Dear ATVB Editors,

We thank Dr. Wang and colleagues for their kind remarks and further insights regarding our Owsiany et al. 2022 ATVB paper (1). We fully agree with virtually all their comments including there being multiple possible cellular sources of MCP1 and secondary responses to it's knockout in smooth muscle cells (SMC) including activating other cytokines. As is the case with any gene knockout study, the phenotype observed is a function not only of the initial gene knockout but also any downstream adaptive and maladaptive responses. Our observation that SMC heterozygous, but not homozygous MCP1 knockout mice, showed a paradoxical increase in plaque size and macrophage content is consistent with this idea since the homozygous SMC MCP1 knockout mice are more likely to undergo compensatory changes. Moreover, these results unveiled an unexpected beneficial role of SMC-derived MCPI in a Western diet fed $Apoe^{-/-}$ mouse model. We present evidence, but certainly not proof, that this phenotype may be the result of systemic monocytosis secondary to loss of SMC-derived MCP1 causing increased release of monocytes from hematopoietic stem cell niches. However, as indicated by Dr. Wang and colleagues there are numerous other possibilities that remain to be tested. One interesting possibility is that initial production of MCP1 by SMC is beneficial because it promotes recruitment of monocytes-macrophages to early-stage atherosclerotic lesions as a means to remove oxidized lipids and apoptotic cells. However, as suggested by Gwen Randolph (2), the process may only be effective for a short time before the macrophages are overwhelmed, become engorged with lipids, fail to egress to the lymphatics, and give rise to foam cells and contribute to a chronic inflammatory state.

We also agree with their comment that there is stage-specific regulation due to the different cellular sources of MCP1 at different stages of atherosclerosis. In support of this idea, we observed that mice with MCP1 knockout in the subset of SMC that have transitioned through an *Lgals3* state exhibit a phenotype virtually opposite to that of mice with MCP1 knockout in all SMC. SMC-Lgals3 dual recombinase MCP1 knockout mice had lesions with an increased $ACTA2^{+}$ 2 fibrous cap and decreased investment of Lgals3-transitioned SMCs, consistent with increased plaque stability. That is, MCP1 expression by this subset of SMC appears to be detrimental.

Finally, we wish to caution readers to be careful in directly comparing results of cell specific conditional gene knockout to global conventional gene knockout studies given the many undefined variables between such models including the timing of gene knockout and complex differences in the phenotypic state of lesion cells at any given time point. Our SMC-specific conditional MCP1 knockout mouse models provide valuable mechanistic insights regarding the contributions of SMC-derived MCP1 to lesion pathogenesis. However, these models are not intended or likely to predict overall effects of systemic MCP1 inhibitors.

Reference List

1. Owsiany KM, Deaton RA, Soohoo KG, Tram NA, Owens GK. Dichotomous Roles of Smooth Muscle Cell-Derived MCP1 (Monocyte Chemoattractant Protein 1) in Development of Atherosclerosis. Arterioscler.Thromb.Vasc.Biol. 2022 Aug;42(8):942–56. [PubMed: 35735018]
2. Randolph GJ. Emigration of monocyte-derived cells to lymph nodes during resolution of inflammation and its failure in atherosclerosis. Curr.Opin.Lipidol. 2008 Oct;19(5):462–8. [PubMed: 18769227]