Are Macrophages the Foot Soldiers in the War Waged by Aldosterone Against the Heart?

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The mineralocorticoid receptor (MR) is present in a myriad of extrarenal tissues, including endothelial cells, vascular smooth muscle cells, and cardiac myocytes. The physiological role played by the MR in these tissues remains unclear because, as yet, aldosterone seems to have only deleterious effects at these receptors. The study by Rickard et al adds macrophages to the list of cells where aldosterone has pathophysiological effects. This group has shown that aldosterone, or MR activation, is intrinsically involved in cardiac fibrosis and that inflammation and macrophage infiltration are precursors to this. The latest article highlights the importance of macrophages in this process and assigns a key role to the MR in macrophages (Figure). This elegant study used macrophage-specific MR knockout mice. When treated with deoxycorticosterone (DOC), wild-type mice develop hypertension, cardiac fibrosis, and inflammation concomitant to macrophage infiltration. Knockout mice show macrophage infiltration but do not develop fibrosis or hypertension. This tells us 2 things. First, macrophages may infiltrate a tissue without having detrimental effects. Second, the macrophage MR is needed to mediate the blood pressure and fibrogenic responses but not for infiltration.

That is only one side of the story. The role played by aldosterone in the inflammatory response becomes complicated when one considers the infiltration process. The study by Rickard et al suggests the macrophage MR does little to control infiltration. However, studies by Caprio et al suggest that MR activation plays a key role, just in a different cell type. This group showed that aldosterone increases intracellular adhesion molecule 1 expression on endothelial cells; intracellular adhesion molecule 1 is required for macrophage attachment to the endothelium. Therefore, it appears that MR activation is responsible for both ensuring that the macrophages get to the appropriate destination and for controlling their activities on arrival.

The most thought-provoking finding in the current study is that deletion of the macrophage MR prevented the blood pressure increase normally observed with DOC treatment. This fits with studies showing that macrophage colony-stimulating factor–deficient mice do not develop mineralocorticoid-dependent hypertension. The study by Rickard et al adds an order of complexity to the process because it identifies the macrophage MR as a critical factor in blood pressure control. The problem is that, in their study, the MR has been knocked out in the entire macrophage population, so a key question remains: in which tissue is macrophage infiltration important for the increase in blood pressure? The most likely target is, of course, the kidney. However, it is difficult to imagine what role the macrophages play in the kidney that would be detectable over the powerful effects of mineralocorticoids on sodium channel expression and salt and water retention. MR activation in the brain also controls blood pressure, but it seems unlikely that peripheral macrophages are involved in this process. However, we cannot rule out the possibility that microglia could modulate blood pressure.

Preventing macrophage infiltration into specific tissues may help elucidate their role but will not determine the importance of the MR. For that to be possible, methods to knock down or inhibit the MR in individual cell types in particular tissues will need to be developed. This will be difficult, especially considering that macrophages have a habit of infiltrating into tissues where the MR is already expressed and causing deleterious effects. In the current study, blood pressure was measured by tail cuff. The increase in pressure in the DOC-treated wild-type mice is quite small (20 mm Hg). The knockout mice have an 8-mm Hg increase in pressure that is teetering on the brink of significance \( P=0.06 \). One has to wonder whether the improved resolution that would be obtained with the use of telemetry would tip the balance in favor of the knockout mice having a significant increase in blood pressure. The fact that the macrophage MR affects blood pressure would still hold, but the increases in blood pressure in response to DOC would be considered to be attenuated instead of prevented.

Rickard et al measured a cadre of inflammatory and oxidative stress markers. However, these were measured in total cardiac tissue, and no attempt was made to identify which cell types produce which markers or whether these markers are the cause or effect of macrophage infiltration. This does not detract from the importance of the work but highlights the complexity of the system. We do not know whether infiltrating macrophages are solely responsible for the upregulation of the proposed markers or whether something released from macrophages alters gene expression in other cell types. In reality, it is probably some combination of both. If the inflammatory response is to become a “druggable” target in cardiovascular disease, it is imperative that we better define the pathways involved.

The study by Rickard et al depicts the macrophage as the enemy, and we cardiovascular researchers have been more
than happy to assign this role. However, macrophages also have a good side, and, surprisingly, the MR is involved in that too. In coronary artery ligation studies, MR blockade increased the number of macrophages infiltrating into the infarcted tissue and increased the expression of inflammatory cytokines. This effect is opposite to that observed by Rickard et al, and it raises important questions. Why would the effects of MR activation on macrophages be different in the 2 systems? Does the cell death in the ligation model and the need for macrophages to clean up the debris change the signaling pathway? Is this a situation where the macrophage phenotype is key? Macrophages can be classically or alternatively activated. Rickard et al suggest that deletion of the macrophage MR affects the phenotype. The authors suggest that MR-deficient macrophages have lost the classical macrophage activation phenotype. However, they are very careful not to suggest the macrophages have become alternatively activated. This is an important point, because alternatively activated macrophages are generally thought to be involved in tissue remodeling.

Another question to consider is the ligand for the macrophage MR. Macrophages do not express the $11\beta$-hydroxysteroid dehydrogenase type 2. Therefore, cortisol is not converted to cortisone and is free to bind to and antagonize the MR. The same is true in cardiac myocytes, but the picture is more complicated than simple antagonism. Studies suggest that, in the heart, oxidative stress causes the glucocorticoids to activate the MR. This seems to be the reason why the MR antagonists, spironolactone and eplerenone, are effective drugs in situations where aldosterone levels are normal. It is unclear whether a similar situation occurs in macrophages. This effect may not be important in the model used by Rickard et al because of the high levels of exogenous mineralocorticoids, but it may be critical in models of hypertension that exhibit macrophage infiltration without markedly elevated aldosterone levels.

This raises another important point, which is the need to confirm the role of the macrophage MR in a model of hypertension that is not mineralocorticoid dependent. One thing is clear, the study by Rickard et al has the potential to change the way we look at macrophage infiltration. It also presents another reason why MR antagonists remain important therapeutic agents. It is amazing to consider the meteoric rise in interest in this once-forgotten hormone and its receptor. One has to wonder where the list of effects of aldosterone or MR activation will end.

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None.

**References**


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