

# Hormonal control of trained immunity: aldosterone at the crossroad between activation of innate immunity and cardiovascular diseases

Giuseppe Matarese <sup>1</sup> and Giuseppe Danilo Norata <sup>2,3\*</sup>

<sup>1</sup>Treg Cell Lab, Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università di Napoli "Federico II" and Istituto per l'Endocrinologia e l'Oncologia Sperimentale, Consiglio Nazionale delle Ricerche (IEOS-CNR), Napoli 80131, Italy; <sup>2</sup>Department of Excellence of Pharmacological and Biomolecular Sciences (DisFeB), Università Degli Studi di Milano, via Balzaretti 9, Milan 20133, Italy; and <sup>3</sup>SISA Centre for the Study of Atherosclerosis, Bassini Hospital, Cinisello Balsamo 20092, Italy

**This editorial refers to 'Aldosterone induces trained immunity: the role of fatty acid synthesis', by C.D.C.C. van der Heijden *et al.*, doi: 10.1093/cvr/cvz137.**

The activation of the renin–angiotensin–aldosterone system, and the consequent increase in aldosterone levels promote atherosclerosis in animal models; similar results are observed after aldosterone infusion in apoE KO mice.<sup>1</sup> These effects are blunted by the inhibition of the mineral corticoid receptor (MR),<sup>1</sup> thus supporting a proatherogenic role for the aldosterone–MR axis in experimental atherosclerosis. The molecular mechanisms explaining the inflammatory response associated with increased aldosterone levels have been so far elusive. The work by van der Heijden *et al.*<sup>2</sup> sheds light on this topic by showing that aldosterone promotes the epigenetic reprogramming of monocyte-macrophages, thus supporting the instauration of immunological memory in innate immune cells also known as 'trained immunity',<sup>3</sup> via activation of the MR receptor (Figure 1). These effects were not mediated by either induction of glycolysis or oxidative phosphorylation as previously suggested for other inducers of trained immunity.<sup>4</sup> At structural level, while aldosterone treatment did not induce formation of foam cells, it significantly boosted fatty acids synthesis (FAS) via an epigenetic mechanism enriching H3 histones trimethylated at lysine 4 (H3K4me3) in the promoters of FAS genes.<sup>2</sup>

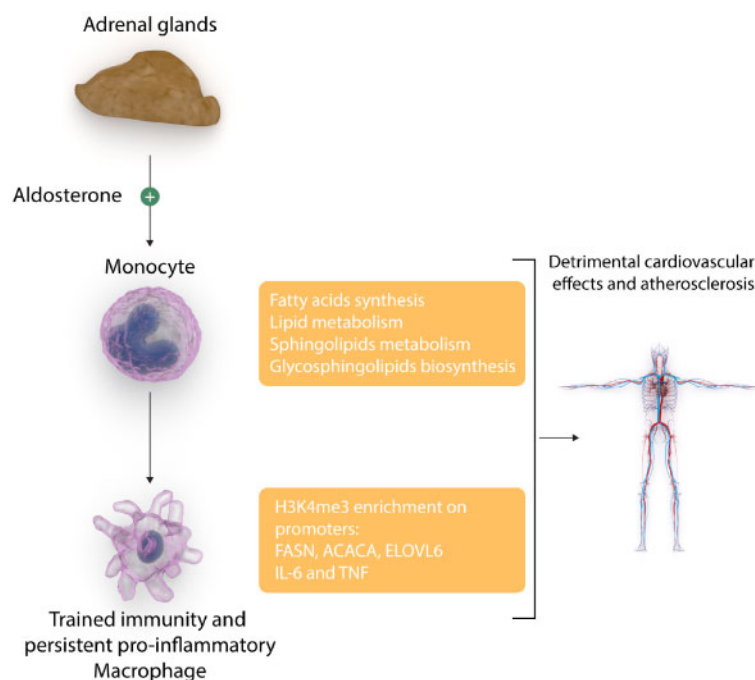
Trained immunity represents a recent acquisition in the field of immunological memory and identifies the ability of innate immune cells to retain 'memory' of a previous contact with an antigen (trained cells) and induce an increased responsiveness upon re-challenge with an insult similar or unrelated to the first one.<sup>3</sup> This process results in enhanced cytokine production and provides a more effective protection against re-infection. Epigenetic reprogramming is the key mechanism supporting the acquisition of trained immunity, with selective changes in histone methylation and acetylation associated with the acquisition of a trained phenotype.<sup>3,5</sup> Epigenetic reprogramming occurring during trained immunity is linked to profound changes in intracellular metabolism. Indeed, it is now established that immune cells, upon activation, adapt their cellular metabolism to cope with proliferation and/or differentiation.<sup>6</sup> These changes affect several metabolic pathways such as glycolysis,

tricarboxylic acid cycle, pentose phosphate pathway, fatty acid oxidation, fatty acid synthesis, cholesterol metabolism, and amino acid/tryptophan metabolism.<sup>7</sup>

Aldosterone activates macrophages towards a proatherogenic and proinflammatory phenotype, with similarities to the M1 macrophage phenotype.<sup>1</sup> At the molecular level, the activation of the aldosterone–MR pathway increases ROS production in macrophages, influences monocyte and macrophage migration, proliferation, and efferocytosis, and affects macrophage lipid accumulation.<sup>1</sup> Further, myeloid-specific knockout of the MR in low-density lipoprotein (LDL)-receptor KO mice suppressed atherosclerosis induced by a high-fat diet, and likewise reduced angiotensin II-induced atherosclerosis in ApoE KO mice, supporting a key role for the aldosterone–MR axis in innate immune cells.<sup>8</sup> This picture is reflected also in humans, where patients with primary hyperaldosteronism (PA) have substantially increased cardiovascular event rates compared with patients with similar blood pressure levels due to essential hypertension, and also show an increased carotid artery intima-media thickness and a higher aortic wall stiffness.<sup>1</sup>

Trained immunity has already been suggested to associate with induction of glycolysis, which leads to epigenetic remodeling mediated by the histone deacetylase sirtuin-1.<sup>4</sup> A similar metabolic reprogramming occurs when monocytes are exposed to oxidized LDLs and is associated with the induction of trained immunity,<sup>9</sup> further highlighting the link between cardio-metabolic diseases and trained immunity. Other additional cellular pathways have been linked to the induction of trained immunity, including glutamine and sterol pathways,<sup>3</sup> raising the possibility that targeting these biochemical ways might contribute to modulate trained immunity.

Interestingly, the report by van der Heijden *et al.*<sup>2</sup> adds a novel piece to the puzzle by demonstrating that glycolysis, which is fundamental for beta-glucan induced trained immunity, is dispensable for aldosterone-induced epigenetic reprogramming and induction of trained immunity. These events were instead abolished by FAS inhibition, suggesting a direct link between FAS and induction of the phenotype. Of note, a recent report in humans excluded the possibility that drugs targeting the mevalonate pathway, such as statins, although decrease the risk of cardiovascular events and improve patient's lipid profile, can affect the



**Figure 1** Aldosterone is produced by adrenal glands and target immune cells via activation of mineralocorticoid receptor, which in monocytes reprogrammes cellular metabolism towards increased fatty acid synthesis and lipid metabolism, thus contributing to macrophage trained immunity via H3K4me3 enrichment on several gene promoters. Trained macrophages might contribute to the detrimental effect of aldosterone on atherosclerosis and cardiovascular diseases.

trained immunity phenotype present in monocytes from patients with familial hypercholesterolaemia.<sup>10</sup> This observation raises the question on the proper strategies to revert *in vivo* 'trained immunity'; indeed, statins target mainly the liver and the latter observation supports the hypothesis that the chances that the drug could directly target 'trained immune cells' are limited.<sup>5,6</sup>

Interestingly, in humans a trained immune phenotype of circulating monocytes remains apparent even 3 months after vaccination with BCG.<sup>4</sup> Given the short circulating half-life of monocytes of only 1–4 days, it is likely that training already occurs at the level of myeloid progenitor cells in the bone marrow, as unequivocally demonstrated by recent reports, at least in mouse models.<sup>5</sup> From a translational point of view, these findings suggest the need to further characterize how metabolic drugs could be used to manipulate 'trained' immune cells. Moreover, it is possible that *in vivo* the effects of increased aldosterone levels could be blunted by other feedback mechanisms, and therefore the relevance of aldosterone on immune cells proinflammatory activation might be moderate-to-neutral. This could be easily tested by investigating whether patients with primary hyperaldosteronism present a 'trained' phenotype in innate immune cells.

In conclusion, van der Heijden *et al.* show that aldosterone induces innate immune memory and a persistent proinflammatory macrophage phenotype leading to cardiovascular consequences. These effects were mainly mediated by innate immune cells. Further studies are needed to assess the possible involvement of adaptive immune cells in this process, including effector and regulatory T cells.

**Conflict of interest:** none declared.

## References

1. van der Heijden CDCC, Deinum J, Joosten LAB, Netea MG, Riksen NP. The mineralocorticoid receptor as a modulator of innate immunity and atherosclerosis. *Cardiovasc Res* 2018;**114**:944–953.
2. van der Heijden C, Keating ST, Groh L, Joosten LAB, Netea MG, Riksen NP. Aldosterone induces trained immunity: the role of fatty acid synthesis. *Cardiovasc Res* 2019;doi:10.1093/cvr/cvz137.
3. van Tuijl J, Joosten LAB, Netea MG, Bekkering S, Riksen NP. Immunometabolism orchestrates training of innate immunity in atherosclerosis. *Cardiovasc Res* 2019;doi:10.1093/cvr/cvz107.
4. Cheng S-C, Quintin J, Cramer RA, Shepardson KM, Saeed S, Kumar V, Giamarellos-Bourboulis EJ, Martens JHA, Rao NA, Aghajanirofeh A, Manjeri GR, Li Y, Ifrim DC, Arts RJW, van der Veer BMJW, Deen PMT, Logie C, O'Neill LA, Willems P, van de Veerdonk FL, van der Meer JWM, Ng A, Joosten LAB, Wijmenga C, Stunnenberg HG, Xavier RJ, Netea MG. mTOR- and HIF-1 $\alpha$ -mediated aerobic glycolysis as metabolic basis for trained immunity. *Science* 2014;**345**:1250684.
5. Norata GD. Trained immunity and cardiovascular disease: is it time for translation to humans? *Cardiovasc Res* 2018;**114**:e41–e42.
6. Norata GD, Caligiuri G, Chavakis T, Matarese G, Netea MG, Nicoletti A, O'Neill LAJ, Marelli-Berg FM. The cellular and molecular basis of translational immunometabolism. *Immunity* 2015;**43**:421–434.
7. Yvan-Charvet L, Bonacina F, Guinamard RR, Norata GD. Immunometabolic function of cholesterol in cardiovascular disease and beyond. *Cardiovasc Res* 2019;doi:10.1093/cvr/cvz127.
8. Shen ZX, Chen XQ, Sun XN, Sun JY, Zhang WC, Zheng XJ, Zhang YY, Shi HJ, Zhang JW, Li C, Wang J, Liu X, Duan SZ. Mineralocorticoid receptor deficiency in macrophages inhibits atherosclerosis by affecting foam cell formation and efferocytosis. *J Biol Chem* 2017;**292**:925–935.
9. Bekkering S, Quintin J, Joosten LA, van der Meer JW, Netea MG, Riksen NP. Oxidized low-density lipoprotein induces long-term proinflammatory cytokine production and foam cell formation via epigenetic reprogramming of monocytes. *Arterioscler Thromb Vasc Biol* 2014;**34**:1731–1738.
10. Bekkering S, Stiekema LCA, Bernelot Moens S, Verweij SL, Novakovic B, Prange K, Versloot M, Roeters van Lennep JE, Stunnenberg H, de Winther M, Stroes ESG, Joosten LAB, Netea MG, Riksen NP. Treatment with statins does not revert trained immunity in patients with familial hypercholesterolemia. *Cell Metab* 2019;**30**:1–2.