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Innate memory training

Immunological memory is a cardinal feature of the adaptive immune system, but there is a growing appreciation that innate immune cells can also show memory-like behaviour. Two studies in *Science* add to our understanding of this emerging field by detailing the epigenetic and cellular changes that underpin memory-like responses in monocytes and macrophages.

It has long been known that monocytes exposed to endotoxins can enter a tolerant state; more recently, the term 'trained immunity' was coined to describe how an initial infection can increase the responsiveness of monocytes to a secondary infection. Saeed *et al.* examined the epigenetic changes that occur in monocytes during their differentiation into macrophages, or following their acquisition of either a 'tolerant' state or a 'trained' phenotype. Monocytes from healthy humans were cultured in human serum to promote their differentiation into macrophages, and some monocyte cultures were also exposed for a short interval to lipopolysaccharide (LPS) to induce a tolerant macrophage phenotype or alternatively, they were primed with β-glucan from the fungus *Candida albicans* to induce a trained state. By comparing epigenetic markers and transcriptional profiles in these different cell populations, the authors identified core gene signatures that were associated with macrophage differentiation and with the acquisition of a tolerant or a trained phenotype.

In agreement with previous studies, many of the genes that were differentially expressed between monocytes and monocyte-derived macrophages were those with roles in wound healing or inflammatory responses. In addition, the authors found that monocyte–to–macrophage differentiation or the acquisition of a tolerant or a trained phenotype involved marked changes in cellular metabolism. Interestingly, cell fate was associated with changes in the levels of transcripts encoding regulators of cyclic AMP (cAMP) signalling, and the disruption of cAMP signalling prevented β-glucan-mediated training of human monocytes *in vitro* and also of mouse monocytes in an *in vivo* model of trained immunity.

> “trained immunity … is associated with epigenetic changes that affect immune signalling pathways and cellular metabolism”

Similarly to Saeed *et al.*, Cheng *et al.* used β-glucan to induce a state of trained immunity in human monocytes and found that this process is associated with epigenetic changes that affect immune signalling pathways and cellular metabolism. Notably, they showed that the β-glucan-mediated training of monocytes leads to epigenetic remodelling at genes involved in glycolysis. Accordingly, β-glucan-trained monocytes displayed reduced oxygen consumption and increased glucose consumption, which is consistent with a switch from oxidative metabolism to glycolysis.

Trained monocytes also showed epigenetic remodelling of genes involved in the mTOR pathway (which regulates glucose metabolism in activated lymphocytes) and inhibition of mTOR blocked β-glucan-mediated training of monocytes. In addition, trained immunity could not be induced in monocytes from patients deficient in dectin 1 (the receptor for β-glucan; also known as CLEC7A) or in monocytes treated with inhibitors of hypoxia-inducible factor 1α (HIF1α) or AKT, both of which are components of the mTOR pathway. Therefore, the switch to glycolysis that is necessary for monocyte training by β-glucan seems to depend on the activation of mTOR through a dectin 1–AKT–HIF1α-dependent pathway.

Cheng *et al.* assessed the relevance of this pathway *in vivo* using mouse models of trained immunity. An initial non-lethal infection with *C. albicans* normally protects against subsequent lethal disseminated candidiasis by reprogramming monocytes, but the authors found that administering an mTOR inhibitor to mice abolished the protective effect of the initial *C. albicans* challenge. Furthermore, in a model of β-glucan-induced protection against bacterial sepsis, trained immunity could not be induced in mice with a myeloid cell-specific deletion of HIF1α.

In summary, both studies identify key epigenetic and metabolic changes that are necessary for trained immunity in monocytes. As such, they add to our understanding of memory-like behaviour in the innate immune system.

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ORIGINAL RESEARCH PAPERS Saeed, S. *et al.* Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. *Science* http://dx.doi.org/10.1126/science.1251086 (2014) | Cheng, S.-C. *et al.* mTOR- and HIF-1α-mediated aerobic glycolysis as metabolic basis for trained immunity. *Science* http://dx.doi.org/10.1126/science.1250684 (2014)