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mTOR trains heightened macrophage responses

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Abstract

The ability of a primary challenge to protect against secondary infection (e.g. during vaccination) *independent* of the adaptive immune system is mediated in part by macrophage “training”. Two new studies show that macrophage training is associated with genome-wide epigenetic changes and is regulated by the mTOR pathway and metabolic reprogramming.

Spotlight

Immunological memory, defined as increased resistance to a re-infection, is a hallmark feature of adaptive immunity. Intriguingly, available evidence indicates that the innate immune system is also capable of memory, which has been referred to as “trained” immunity. Exposure to a primary infection enhances resistance to a subsequent infection in plants and invertebrate animals, as well as vertebrate models lacking components of the adaptive immune system (e.g. athymic mice). In vertebrates, training can be conferred by innate cells such as NK cells and macrophages, but otherwise the cellular and molecular underpinnings remain little understood(1). Two recent studies(2, 3) now shed light on the epigenetic reprogramming, signaling pathways, and metabolic processes that mediate macrophage training.

The two studies(2, 3) used a model of macrophage training in which monocytes are primed with the *Candida albicans* product β -glucan during macrophage differentiation; subsequent challenge 6–7 days later elicits enhanced cytokine production indicative of training (Fig 1). Saeed and colleagues(3) focused on the genome-wide gene expression and epigenetic changes that occurred during macrophage training. They showed that macrophage training was associated with increased expression of multiple gene modules compared to naïve/untrained macrophages correlating with epigenetic remodeling at promoters and enhancers of these genes. This suggested that priming reinforced specific gene expression programs of naïve macrophages, allowing for increased induction upon a second challenge (Fig 1). H3K27Ac at promoters and enhancers correlated closely with dynamic levels of gene expression, while enhancer H3K4me1 was more stable and may serve as an epigenetic “memory” of enhancer activity. Additionally, the expression of many transcription factors changed dynamically upon training. Comparing such changes to changes in gene expression

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and epigenetic modifications, together with analysis of transcription factor binding motifs, the authors implicated bZIP transcription factors and the glucocorticoid receptor in control of training. Finally, the cAMP signaling pathway was identified as a key regulator of training. Prompted by the observation that cAMP signaling components were transcriptionally and epigenetically induced in trained macrophages, the authors showed that perturbing this pathway reduced in vitro training as well as the ability of a non-lethal dose of *C. albicans* to protect mice against a subsequent lethal challenge. The study also performed similar analyses of monocytes and tolerant macrophages (in which LPS priming leads to a state of reduced responsiveness to a second challenge), and provides a valuable resource for the molecular and epigenetic features associated with macrophage differentiation, training, and tolerance.

In similar epigenome profiling analyses, Cheng et al(2) noted that in trained macrophages, promoters of genes encoding components of immune signaling pathways are induced (relative to naïve macrophages), likely contributing to increased responsiveness to secondary challenge. Intriguingly, this was also true of genes regulating the mTOR and glycolysis pathways. The mTOR signaling pathway is a key regulator of cellular metabolism, and particularly anabolic processes that promote cell growth and proliferation(4), prompting the authors to investigate the metabolic basis of macrophage training. Of note, recent studies indicate that appropriate macrophage activation/polarization requires metabolic reprogramming-towards glycolytic and oxidative metabolism in M1 and M2 macrophages respectively. (5). Moreover, the mTOR pathway has been implicated in control of macrophage activation(6). Indeed, Cheng et al showed that macrophage training is associated with a shift from oxidative metabolism to glycolysis, and that inhibiting glycolysis diminished the responses of trained macrophages. Importantly, pharmacological block of mTOR activity during β -glucan priming reduced the effects of training, indicating a critical role for the mTOR pathway. Similarly, inhibiting Akt, which mediates mTOR activation by β -glucan, or HIF1 α , a mTOR target and master regulator of glycolysis, attenuated macrophage training. The mTOR-HIF1 α pathway could also regulate trained immunity in vivo. Administration of metformin, an indirect mTOR inhibitor (through effects on AMPK), abrogated the ability of a non-lethal dose of *C. albicans* to protect against disseminated candidiasis. Trained immunity was also impaired in mice with myeloid-specific deletion of HIF1 α , correlating with defects in metabolic reprogramming in HIF1 α deficient macrophages. The authors concluded that the Akt-mTOR-HIF1 α pathway critically mediates training by triggering a shift towards glycolytic metabolism that prepares the macrophage for mounting heightened responses during secondary challenge (Fig 1).

Increased glycolysis is likely to contribute to the trained phenotype by supporting effector functions, similar to its role in M1 macrophages. For example, upregulating glycolytic metabolism should enhance phospholipid synthesis and ER and Golgi expansion to facilitate enhanced cytokine production(7). Additionally, it is tempting to speculate that increased glycolysis may directly regulate epigenetic reprogramming during training. Consistent with this idea, maintaining glycolytic flux during priming is necessary to establish training(2). Indeed, metabolites are essential coenzymes for several classes of epigenetic regulators, including α -ketoglutarate in the case of Jumonji C histone demethylases and Tet DNA hydroxylases and FAD for the histone demethylase LSD1. Moreover, metabolites are

precursors of epigenetic modifications, including S-adenosylmethione for DNA and histone methylation and Acetyl-CoA for histone acetylation(8). It is highly likely that mTOR, a key metabolic hub, would regulate metabolite levels and other metabolic processes to control epigenetic events underlying the long-term effects of macrophage training (Fig 1).

Macrophages contribute critically to multiple in vivo models of trained immunity(1, 2), and the findings of these two studies indicate that these effects are due at least in part to epigenetic reprogramming of individual macrophages during their differentiation from monocytes. However, other mechanisms could play a role in macrophage-dependent trained immunity. Embryo-derived macrophages constitute a major macrophage population in many tissues and are maintained by self-renewal, thus epigenetic reprogramming of this population may be relevant(9). Monocytes and macrophages can proliferate in some settings, so selective expansion of certain cells within a heterogeneous population may contribute to increased responsiveness during rechallenge(9). Finally, long-term effects of trained immunity could involve changes to bone marrow myelopoiesis(10).

While the memory response of the adaptive immune system is exquisitely specific, trained immunity provides cross-protection to heterologous infection, as demonstrated in experimental models and by the effects of vaccination(1). How broadly macrophage training can confer cross-protection is an important question to pursue, and mechanistic insights are likely to be revealed in further analyses of the underlying epigenetic and metabolic changes.

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Figure 1. Mechanisms underlying macrophage training

Macrophage training, triggered by a priming stimulus such as β -glucan, is characterized by increased responsiveness to a second challenge and contributes to trained immunity in vivo. Macrophage training requires the Akt-mTOR-HIF1 α pathway, increased glycolysis, and epigenetic reprogramming. In response to the priming stimulus, activation of the mTOR pathway promotes glycolytic metabolism. In addition, mTOR activity may directly control epigenetic remodeling, via activation of HIF1 α and likely other transcription factors. A speculative role for mTOR-mediated metabolic processes in control of epigenetic reprogramming is shown with a dashed arrow. In the trained macrophage, epigenetic changes reinforce increased glycolysis and mTOR signaling.