hexagonally packed cylinders for f_{PLA} = 0.20 (see the figure, middle). Cooling from high temperature allows for single-chain or collective diffusion over large length scales, so the system can stay near equilibrium and assemble into uniform domain sizes.

However, when samples were quenched from a disordered state and then heated to low or moderate temperatures, a different ordering mechanism drove these materials toward new states: liquid-like packing (LLP)→DDQC→C14 for f_{PLA} = 0.15 and LLP→σ→C15 for f_{PLA} = 0.20 (see the figure, bottom). The initial state of quenched disorder is composed of small, highly nonequilibrium micelles. With low-temperature annealing, these micelles adjust their sizes and shapes by local exchange of mass through fusion, fission, and chain exchange (*5*), similar to diffusionless transformations in low-temperature treatments of metal alloys. The Laves phases, like the σ phase, have large unit cells, multiple types of lattice sites, and high sphericity. However, it remains unclear why these structures are selected over other low-symmetry (metastable) states.

The surprising structures formed by spherical PI-PLA micelles resemble the rich phases displayed by metals and metal alloys, and offer further evidence that similar principles guide the development of order in soft and hard condensed matter. Beyond ultrafast thermal treatments (*5*, *10*), controlled chain dispersity (*11*) and thin-film confinement (*12*, *13*) could be useful tools for continued exploration of symmetry-breaking transitions in conformationally asymmetric block polymers. More broadly, the variety of structures that are now realized with linear diblock copolymers—the simplest of all block polymer architectures—suggests that there are still many opportunities to discover complex states of order in these deceptively simple materials. ■

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IMMUNOLOGY

Inflammation by way of macrophage metabolism

IL-10 controls macrophage inflammatory function by reprogramming metabolism

By **Agnieszka M. Kabat** *and* **Edward J. Pearce**

Although inflammation is an essential component of immunity, an excessive response can lead to tissue damage and autoimmune pathologies. In most cases, this is avoided with parallel, integrated regulatory responses that allow healing to commence. A central mediator of this regulatory response is the cytokine interleukin-10 (IL-10). IL-10 is particularly important in mucosal tissues, such as the intestine, where it limits macrophage proinflammatory functions. On page 513 of this issue, Ip *et al.* (*1*) report that IL-10 alters macrophage function by promoting the clearance of damaged mitochondria and modulating cellular metabolism to limit inflammation.

IL-10 inhibits inflammatory cytokine release from macrophages and the expression of major histocompatibility complex II (which presents antigens to T cells). Individuals bearing mutations in genes encoding IL-10 or the IL-10 receptor (IL-10R) suffer from severe, early onset inflammatory bowel disease. Deletion of either gene in mice leads to spontaneous intestinal inflammation. IL-10R ablation in macrophages alone recapitulates the intestinal inflammation phenotype of global IL-10R deficiency (*2*).

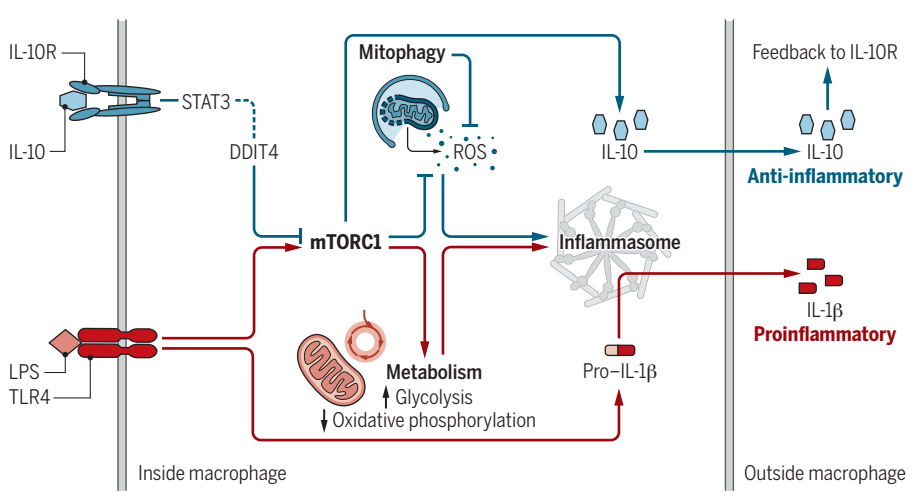
Metabolic reprogramming occurs in response to changes in nutrient or oxygen availability. In immune cells, such reprogramming is also regulated by ligation of receptors for pathogen-associated molecular patterns [e.g., Toll-like receptors (TLRs)] or damage-associated molecular patterns, antigens, and certain cytokines. Metabolic reprogramming also influences cellular fate and function and, consequently, immune response outcome.

When exposed to the TLR4 ligand bacterial lipopolysaccharide (LPS), macrophages produce proinflammatory cytokines and engage aerobic glycolysis to generate adenosine triphosphate (ATP) independently of mitochondrial oxidative phosphorylation (OXPHOS) (*3*, *4*). Ip *et al.* observed that macrophages from mice lacking IL-10 exhibited increased glycolysis in response to LPS. By contrast, OXPHOS was decreased. This is consistent with the effect of IL-10 on dendritic cells—minimizing the LPS-induced shift to glycolytic metabolism, which ultimately inhibits cell activation (*3*).

After stimulation with LPS, IL-10–null macrophages had low cellular ATP and accumulated damaged mitochondria due to a failure of mitophagy, a process that targets mitochondria for autophagic recycling. Damaged

Macrophage control of inflammation

Release of pro- and anti-inflammatory factors involves mTORC1, mitochondria, and metabolic processes.



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mitochondria generate increased amounts of reactive oxygen species (ROS), a product of OXPHOS, which can be damaging. Previous findings implicated ROS (made by complex I of the electron transfer chain) in the activation of the transcription factor hypoxia-inducible factor–1α (HIF-1α) and in downstream events, including proinflammatory IL-1β production (*5*). Overall, the findings of Ip *et al.* are consistent with impaired mitophagy in skeletal muscle in IL-10–deficient mice (*6*), but contrast with studies that associate IL-10 with blocking autophagy (*7*). This disparity may reflect distinct events in mitophagy compared to starvation-induced autophagy that are regulated by IL-10. Upstream events linked to mitochondrial fission, which is necessary for mitophagy to proceed, or proteins that target mitochondria for mitophagy, may be important in this context.

Many signals that control autophagy converge on mammalian target of rapamycin complex 1 (mTORC1), a signaling hub that regulates anabolic pathways such as glycolysis. Inhibition of mTORC1 promotes catabolism through processes including autophagy. Indeed, Ip *et al.* found that lack of IL-10 signaling in LPS-treated macrophages resulted in sustained mTORC1 activation, which would explain decreased mitophagy. The inhibitory effect of IL-10 on mTORC1 required signal transducer and activator of transcription 3 (STAT3) and could be recapitulated by addition of the mTORC1 inhibitor rapamycin. IL-10 has not previously been considered to mediate its effects by inhibiting mTORC1 activity in myeloid cells.

> ***"Metabolic reprogramming also influences...immune response outcome."***

To find out how IL-10 controls mTORC1 signaling, Ip *et al.* analyzed the expression of genes encoding known negative regulators of the mTORC1 pathway. The authors identified the expression of DNA-damage-inducible transcript 4 protein (DDIT4) in a STAT3-dependent manner early after LPS treatment in macrophages, only when IL-10 was present. Loss of DDIT4 in macrophages recapitulated key features of IL-10 deficiency, including increased mTORC1 activation, glycolysis, and the accumulation of damaged mitochondria after LPS treatment. IL-10 did not suppress mTORC1 activation or glycolysis in LPS-stimulated DDIT4-null cells, but interestingly, it rescued the decline in OXPHOS. Thus, much of the metabolic change observed in IL-10–null macrophages is due to a failure to both induce DDIT4 expression and block mTORC1. Moreover, macrophages isolated from patients with mutations in the IL-10R showed prolonged mTORC1 activation, decreased DDIT4 expression, and increased IL-1β secretion after LPS stimulation, indicating that IL-10 also engages the DDIT4-mTORC1 pathway in inflammatory human macrophages.

Implicated in autophagy in chondrocytes (*8*), DDIT4 is also involved in mTORC1 inhibition in the context of hypoxia (*9*). It also inhibits mTORC1 activation and glycolysis in hypoxic tumor–associated macrophages (*10*). Intriguingly, in hypoxia, DDIT4 transcription is induced by HIF-1α (*11*), but Ip *et al.* allude that IL-10–induced expression of this factor is HIF-1α–independent. Therefore, it is possible that pathways such as hypoxia that normally regulate DDIT4 expression in macrophages (and other cells) are rewired to become controlled by IL-10 and STAT3 after LPS stimulation.

The findings of Ip *et al.*, suggest that through induced mitophagy, IL-10 reduces LPS-induced IL-1β production by preventing excessive ROS release from complex II in damaged mitochondria and limiting inflammasome activation (see the figure). However, IL-10 also decreases expression of inflammasome components (*12*), suggesting that there may be overlapping mechanisms of IL-10–driven inflammasome inhibition.

Does IL-10 have the same effect on other immune cell types? For example, does it support regulatory T (T_{reg}) cell development by inhibiting mTORC1 activation? It seems plausible because mTORC1 inhibition promotes T_{reg} cell differentiation (*13*) and because mTORC1 activity is modulated in T_{reg} cells upon TLR activation (*14*). Moreover, decreased autophagy suppresses T_{reg} cell responses, particularly within the intestinal mucosa (*15*). A role for DDIT4 in T_{reg} cells will be interesting to explore. ■

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GENE EXPRESSION

Transcription factors read epigenetics

Many homeodomain transcription factors can bind methylated DNA

By **Timothy R. Hughes**[1,2] *and* **Samuel A. Lambert**[2]

Decoding precisely how sequence-specific DNA binding proteins (called transcription factors) recognize, access, and act at their genomic binding sites is challenging. One shortcoming is the lack of knowledge about DNA binding specificities (motifs) for hundreds of the estimated ~1600 human transcription factors. Another is how transcription factor binding is modulated by "epigenetics"—a contentious term that refers to heritable states of both cells and organisms, as well as the covalent chemical modifications of DNA and protein that often provide the underlying mechanism (*1*). DNA methylation at cytosine and guanine dinucleotides (mCG) satisfies most views of epigenetics, as it is inherited across cell divisions and functions in imprinting (parent-of-origin–dependent gene expression). On page 502 of this issue, Yin *et al.* (*2*) provide a comprehensive look at the extent to which human transcription factor binding is affected by mCG, and make a striking finding: Many homeodomain transcription factors—perhaps the best-characterized developmental regulators in biology (*3*)—can bind to specific methylated DNA sequences.

Most CG dinucleotides in mammalian cells are methylated, but mCG is depleted at active regulatory sequences (*4*). mCG is generally thought to occlude transcription factor binding, as the methyl groups protrude into the major groove (see the figure), where many transcription factors bind. There are dedicated CG and mCG binding factors (CXXC and MBD domain–containing proteins, respectively), and on page 503 of this issue, Takahashi *et al.* (*5*) allude to their importance in regulating de novo

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Science

Inflammation by way of macrophage metabolism

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