conventional resonance is not substantially affected by parameter variations.

In practical optical resonators, the quality factors of BICs are fundamentally limited by inevitable fabrication defects, which scatter light out of the plane of the device. Any light wave that is scattered off a structural imperfection changes its wavevector. To prevent scattering losses, waves must remain trapped in the resonator even after these changes have occurred. In other words, the quality factor needs to be high both before and after scattering.

Jin and colleagues have suggested and demonstrated an innovative physical mechanism for achieving optical resonances that are extremely robust to out-of-plane scattering. They considered a structure called a photonic crystal slab, consisting of a submicrometre-thick dielectric (electrically insulating) membrane patterned with a square lattice of circular holes.

The authors first ran numerical simulations to study the optical resonances in their membrane. By carefully selecting the membrane's parameters, they achieved several simulated BICs that had different wavevectors. They then altered the periodicity of the lattice until the BICs had the same wavevector. This gave rise to a new type of optical resonance: a merging BIC (which one might refer to as a super-BIC; Fig. 1). The hallmark of a merging BIC is that it increases the quality factor of all waves that have nearly the same wavevector as the resonance, reducing scattering losses from the resonator.

Jin *et al.* then experimentally demonstrated their mechanism by fabricating a set of silicon membranes that had different lattice periodicities. Some of these membranes supported a merging BIC at telecommunication wavelengths (about 1,550 nanometres) and others were close to this merging-BIC regime. The authors used a tunable telecommunication-wavelength laser to measure the intensity of scattered light along different directions for each of the samples. They found that the membranes supporting a merging BIC had a quality factor that was about 10 times larger than that for the membranes not in the merging-BIC regime. Moreover, they showed that the observed increase in quality factor was robust by finding a similar level of enhancement in all of the fabricated samples that had a merging-BIC design.

The demonstration could have many consequences for engineering high-quality resonances in nanophotonics. The ability to convert light waves into BICs allows the realization of the supercavity regime, in which highly compact resonators can have extremely large quality factors[5]. Dielectric materials that have high refractive indices could be used to reduce the resonator dimensions and to combine individual BIC resonators that have high-quality resonances into structured arrays[6].

We predict that an electromagnetic theory will be developed for describing high-quality resonances in individual dielectric nanoparticles of high refractive index and arrays of such nanoparticles, and that they all will be expressed in terms of the mathematics used to study interference in quantum mechanics. In the real world, the engineering of quality factors in the BIC regime could lead to substantial enhancement of nonlinear and quantum effects, the development of lasers that consume little power, and the realization of nanoscale resonators that facilitate strong confinement of light and large boosts to its amplitude.

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Epigenetics

Lactate links metabolism to genes

Luke T. Izzo & Kathryn E. Wellen

Cells regulate gene expression in part through the chemical labelling of histone proteins. Discovery of a label derived from lactate molecules reveals a way in which cells link gene expression to nutrient metabolism. **See p.575**

Cellular metabolism involves the uptake, release and biochemical interconversion of nutrients to produce energy and synthesize complex molecules. The intermediates and end products of metabolism also have essential signalling functions, modulating cell signalling and gene expression in accordance with nutritional resources[1,2]. One way in which these metabolites signal is through the chemical modification of proteins such as histones. On page 575, Zhang and colleagues[3] describe their discovery of a previously unknown histone modification, lactylation, derived from the cellular metabolite lactate.

Histones are central components of chromatin — a complex of DNA and proteins that organizes and regulates the genome. They can be altered by cellular enzymes, which add chemical tags such as methyl, acetyl and phosphate groups; these epigenetic modifications to the genome affect processes such as gene expression and DNA replication and repair. Zhang *et al.* predicted that histones might also be altered by the addition of lactyl groups, and they began their search for lactylation by using a technique called mass spectrometry, which has enabled the identification of numerous protein modifications in the past few years[4]. By looking for shifts in the masses of amino-acid residues that make up histone tails, the authors deduced the presence of a modified lysine amino-acid residue, consistent with the addition of a lactyl group. Zhang *et al.* validated this finding by comparing synthetic peptides that had been chemically modified in this way with the corresponding peptides identified in cells.

The authors also used metabolic tracing with a form of lactate labelled with a stable isotope of carbon ($^{13}C_3$-lactate) to demonstrate that lactate is involved in histone lactylation. They further found that levels of lysine lactylation rose when cells were treated with increasing doses of lactate. So, histone lactylation is derived from lactate and is sensitive to lactate levels.

Lactate is an abundant metabolite produced during glycolysis — a central metabolic process in which glucose consumed by cells is broken down to generate energy. During glycolysis, glucose is converted into two pyruvate molecules; these can be either funnelled into lactate production or transported into the cellular power generators (the mitochondria), forming the intermediate acetyl coenzyme A (acetyl-CoA) and thence entering the Krebs cycle for energy production. Lactate is produced through glycolysis in various cell types, including cancer cells and immune cells. Its production is also enhanced under certain conditions, such as hypoxia (low oxygen levels), which suppresses pyruvate entry into the Krebs cycle. Zhang and colleagues' discovery that lactate is used for histone modification is intriguing both because of the metabolite's abundance and because its production, uptake and use are all subject to dynamic regulation[5].

One substantial question that the authors

aimed to address is whether lysine lactylation responds to metabolic alterations in cells. Other metabolite-derived protein modifications — such as lysine acetylation (derived from acetyl-CoA) — are metabolically sensitive[2], providing a precedent for this idea. Zhang *et al.* found that the amount of glucose available to cells grown *in vitro* dynamically regulates the lysine lactylation of histones in those cells. Furthermore, tracing of isotopically labelled glucose ($^{13}C_6$-glucose) showed that lysine lactylation depends on glycolysis. The authors used several perturbations to promote lactate production (including hypoxia and inhibitors of mitochondrial metabolism) and to suppress it (using inhibitors of pyruvate conversion to lactate). The cumulative data indicate that lysine lactylation is highly sensitive to lactate production through glycolysis.

Zhang *et al.* next sought to investigate the biological functions of lactylation, selecting macrophages as their model. Macrophages are immune cells that can take on pro-inflammatory (termed M1) or anti-inflammatory (M2) characteristics; they undergo metabolic changes that correspond to these functions[6]. For example, macrophages that encounter signs of bacterial infection activate inflammatory genes and upregulate glycolysis[6]. Zhang *et al.* stimulated macrophages with bacteria or with the bacterial component lipopolysaccharide (LPS) to induce M1 characteristics. They found that glycolysis increased and that intracellular levels of lactate rose progressively, parallelling an increase in histone lactylation (Fig. 1a). Notably, inflammatory genes typically associated with M1 characteristics were upregulated rapidly on exposure to LPS, but did not correlate with lactate levels or lysine lactylation (Fig. 1b). Instead, the increase in lysine lactylation was slower and correlated with the upregulation of homeostatic genes (those involved in maintaining a biological steady state).

The authors went on to investigate where lysine lactylation occurred in the M1 genome, as well as how the modification altered gene expression. They found that lysine lactylation was high in gene promoter regions (which mark the start points of gene transcription), and associated positively with the levels of messenger RNA produced from those genes. The authors also compared lysine lactylation and acetylation, finding lactylation at many genes that lack acetylation — suggesting distinct roles for the two modifications. Moreover, macrophages that could not produce lactate could increase the expression of inflammatory genes in response to stimulation with LPS, but could not upregulate lysine lactylation or the associated expression of homeostatic genes at later times. These temporal dynamics led the authors to propose that a delayed 'lactate timer' involving histone lactylation drives the activation of genes involved in resolving infections to help re-establish tissue homeostasis (Fig. 1b).

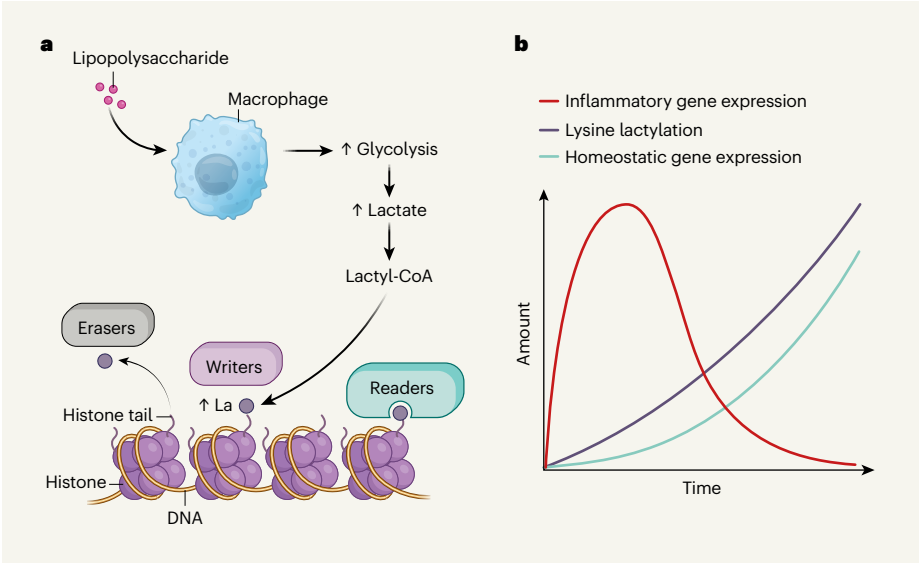

Figure 1 | A new epigenetic modification, histone lactylation. Zhang and colleagues[3] have discovered a chemical modification called lactylation — the addition of a lactyl (La) group to the lysine amino-acid residues in the tails of histone proteins. **a**, Stimulating immune macrophage cells with lipopolysaccharide molecules (mimicking bacterial infection) increases the conversion of glucose to energy through glycolysis. This, in turn, leads to increases in intracellular levels of the molecule lactate, and to lactylation of histones at promoter DNA sequences. However, it is unclear which enzymes generate the intermediate molecule lactyl-CoA, from which La is derived, or which enzymes deposit (writers), remove (erasers) or recognize and interpret (readers) histone lactylation. **b**, Zhang *et al.* report that the increase in lysine lactylation is delayed following macrophage stimulation. This delay correlates with changes in the expression of homeostatic genes involved in maintaining a biological steady state, but not with changes in inflammatory-gene expression. The authors therefore hypothesize that lactylation generates a 'lactate timer' to restore normal tissue function after infection.

These findings raise questions about the biochemistry of lactylation and its broader roles in physiology and disease. In terms of biochemistry, the authors show in a cell-free system that lactyl-CoA is a lactyl-group donor for lysine lactylation. So far, however, the enzymes that produce lactyl-CoA from lactate in the cell, as well as the cellular concentrations of lactyl-CoA, are unknown. Other unresolved questions concern the way in which lysine lactylation is regulated by the enzymes that deposit, read or remove this label. In the authors' cell-free system, an acetyltransferase enzyme known as p300 can catalyse the transfer of lactyl from lactyl-CoA to histones, but whether it does this in cells has yet to be tested.

"The findings raise questions about the biochemistry of lactylation and its broader roles in physiology and disease."

In terms of the broader roles of this modification, lactate is generated by cells both in physiological contexts — such as in skeletal muscle during exercise — and in the context of diseases such as cancer. In addition, lactate is taken up by cells of healthy tissues and tumours to feed the Krebs cycle[7]. So, as well as occurring in glycolytic cells, lactylation might also participate in communication between cells. On this note, high lactate levels in the environment around tumours are known to promote immunosuppression[8], and Zhang *et al.* found that histone lysine lactylation was greater in tumour-associated macrophages than in those from another tissue. All in all, the authors' discovery of histone lactylation provides a launch point for a deeper investigation into the roles and regulation of this modification, which links cellular metabolism to gene regulation and could have numerous implications for human health.

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