Trends in Biochemical Sciences

CellPress

Review

Intermediates of Metabolism: From Bystanders to Signalling Molecules

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The integration of biochemistry into immune cell biology has contributed immensely to our understanding of immune cell function and the associated pathologies. So far, most studies have focused on the regulation of metabolic pathways during an immune response and their contribution to its success. More recently, novel signalling functions of metabolic intermediates are being discovered that might play important roles in the regulation of immunity. Here we describe the three long-known small metabolites lactate, acetyl-CoA, and succinate in the context of immunometabolic signalling. Functions of these ubiquitous molecules are largely dependent on their intra- and extracellular concentrations as well as their subcompartmental localisation. Importantly, the signalling functions of these metabolic intermediates extend beyond self-regulatory roles and include cell-to-cell communication and sensing of microenvironmental conditions to elicit stress responses and cellular adaptation.

Trends

Metabolic intermediates of biochemical pathways are able to act as intra- and extracellular signalling molecules affecting immune cell responses.

The signalling effects of metabolites are concentration and localization dependent.

Their functions go beyond self-regulatory mechanisms and include cell-to-cell communication as well as sensing of microenvironmental conditions to elicit stress responses and cellular adaptation.

Metabolite Signalling in Immunity

The metabolic regulation of immune cells during health and disease has gained much attention as the active reconfiguration of immune cell metabolism enables these cells to sustain certain effector functions. The focus so far has been on the necessity of the main catabolic pathways glycolysis, fatty acid oxidation (FAO), the anaplerotic tricarboxylic acid (TCA) cycle, and oxidative phosphorylation as well as amino acid metabolism (Figure 1) during activation, proliferation, differentiation, and function as a response to extracellular signals.

It is now becoming increasingly evident that small-molecule intermediates of these metabolic pathways, besides their anabolic and catabolic function, can act as intra- and extracellular signals that influence the outcome of an immune response. The roles of metabolite signalling stretch from regulation of cytokine production via indirect effects on the cellular **redox state** (see Glossary) [1] or direct interaction with transcription factors binding the specific cytokine promoter elements [2] and modulating the activity of transmembrane ion channels [3], to interference with cell migration and differentiation. Interestingly, a few G protein-coupled receptors that are activated by intermediates of metabolism have recently been identified, supporting a role for metabolites as extracellular signals [4,5]. In this review we discuss the three well-known metabolites lactate, succinate, and acetyl-CoA in more detail, identifying their differences and similarities in signal transduction and effects on immunity and inflammation that define them as novel signalling molecules in physiology and pathology.

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Lactate is a Signalling Molecule

Lactate is a ubiquitous molecule whose presence in the mammalian body was first observed in muscle tissue at the beginning of the 19th century [6]. Since its discovery lactate has been intensely studied and has been shown to have numerous metabolic functions (Figure 2, Key Figure), including as a central metabolite in the Cori cycle (also known as the lactic acid cycle), which mediates metabolic crosstalk between liver and muscle. In the Cori cycle, muscle tissue metabolises liver-derived glucose to lactate, which in turn is shuttled back to the liver and acts as a fuel source for hepatic gluconeogenesis [7]. By contrast, in the brain lactate acts as a metabolic signal and fuel for oxidative metabolism, which is the basis of the neuron–astrocyte lactate shuttle [8]. Briefly, the neurotransmitter glutamate induces high glycolytic activity in astrocytes, which secrete lactate into the synaptic cleft. The increased availability of extracellular lactate enables neurons to import it and use it as an alternative fuel source.

Although lactate has been known to biochemists for over 200 years, it has been long neglected, seen as a byproduct or a biomarker at best rather than a bioactive molecule. As a consequence its potential functional effects have been underappreciated.

Recently, lactate has been rediscovered as an active signalling metabolite in multiple fields of biology and medicine with two main means of signal transduction: transporter and receptor mediated. Its direct regulation of global gene transcription [9,10], endothelial and cancer cell

Glossary

Fumarate hydratase (FH): TCA cycle enzyme responsible for the conversion of fumarate to malate.
Redox state: the cellular redox state is often described as the balance of reduced and oxidised glutathione (GSH/GSSG), nicotinamide dinucleotide (NAD^+/NADH), and nicotinamide dinucleotide phosphate ($NADP^+$/NADPH). These redox couples are central mediators for catabolic and anabolic reactions, acting as cofactors and regulators for enzymes, scavengers for ROS, or substrates for the mitochondrial electron transport chain (ECT).
Spare respiratory capacity: the extra capacity available in a cell to produce energy via mitochondrial respiration.

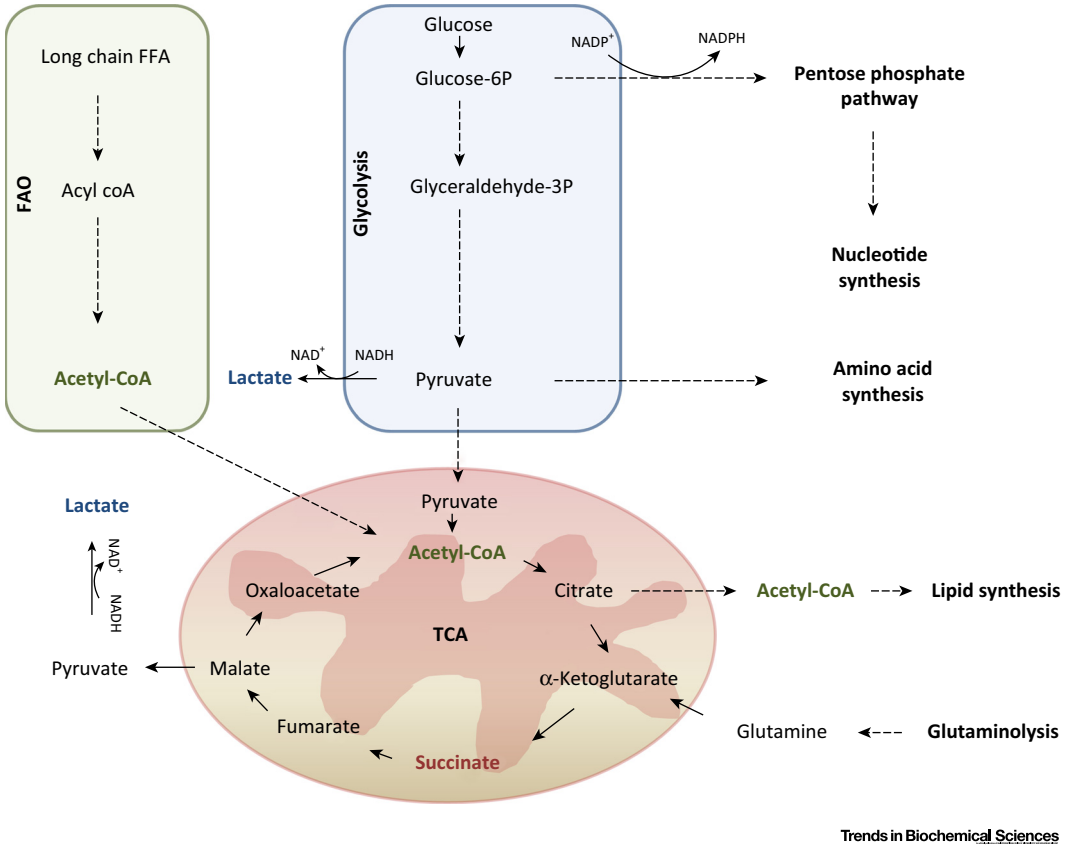

Figure 1. Metabolic Pathways and Regulatory Intermediates of Metabolism. The main cellular catabolic pathways [glycolysis, blue; tricarboxylic acid (TCA) cycle, red; fatty acid oxidation (FAO), green] produce not only ATP but also metabolic intermediates such as lactate, acetyl-CoA, and succinate, highlighted in colour. These are substrates for anabolic processes including lipid and nucleotide synthesis, but can also act as regulatory signalling molecules.