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Editorial overview: Intrinsically tied: metabolism and immune cell function

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Dr Karsten Hiller is a Professor of Biochemistry and Bioinformatics at the University of Braunschweig. He obtained his diploma in Biology and Computer Science and performed his PhD in Bioinformatics and Microbiology at the University of Braunschweig, Germany and focused on the development of algorithms for the analysis of metabolomics data. From 2008 to 2010, he had an appointment as a postdoctoral fellow in the group of Gregory Stephanopoulos at the Department of Chemical Engineering, MIT where he worked on stable-isotope assisted metabolomics and cancer metabolism. In 2010 he moved to the Luxembourg Center for Systems Biomedicine where he became the head of the Metabolomics Group. In 2016 he was promoted to Associate Professor in Cellular Metabolism at the University of Luxembourg. A few months later he moved with his team to the University of Braunschweig and became a Full Professor of Biochemistry and Bioinformatics. Since 2016 he is the director of the Department of Biochemistry and Bioinformatics and since 2018 deputy director of the Braunschweig Integrated Center of Systemsbiology (BRICS). Dr Hiller is an expert in stable-isotope assisted

A key element during the beginning of life was the establishment of a metabolic homeostasis that enabled the operation of simultaneous anabolic and catabolic processes to setup a highly organized structure and thus to reduce entropy within a cellular system. From the beginning on, such systems were confronted with and had to act against predators competing for nutrients. This is the reason why these initially fragile systems quickly developed mechanisms to sense and adopt or respond to environmental stimuli. From early on, cellular systems had to establish defense mechanisms to achieve an advantage for growth. Because of the long history of host-pathogen interaction, initially simple mechanisms evolved to incredibly complex systems with the only goal to protect and foster cellular homeostasis. This became even more complex with the emergence of multi-cellular organisms requiring systems to detect self and repel foreign. Without any doubt metabolism and immune function arose simultaneously and their relation or interaction is essential to sustain a robust homeostasis and thus a living system.

Most likely because of the high complexity of both, biochemical reaction networks and immune function, research in both fields has often been conducted independently and resulted in atomistic views on highly intermingled systems. Nowadays it is clear that metabolism provides more than ATP to immune function and vice versa that immune function directly modulates metabolic homeostasis to achieve an situational advantage for the host under danger conditions.

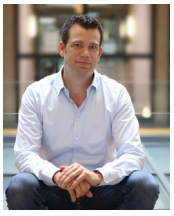
Metabolic defense mechanisms

A very ancient metabolic pathway is the TCA or Krebs cycle which forms an integral part of metabolism in many taxa. It serves as origin or end point for various anaplerotic or cataplerotic pathways and is thus directly or indirectly involved in immune function. Ryan *et al.* discuss in high detail the evolutionary origin of this key pathway and the role of mitochondria for the eukaryotic cell. The authors highlight how TCA cycle metabolites such as succinate, 2-oxoglutarate and acetyl-CoA (derived from citrate) have evolved to cellular regulators. Immune regulatory processes induced by metabolites can be immediate by directly interfering with enzymes or transcription factors such as HIF1α or NRF2 or act on the long-term via epigenetic modifications such as histone acetylation.

The TCA cycle is also the origin of the anti-microbial metabolite itaconate, a metabolite that called attention in several more recent studies. Cordes and Metallo elaborate on the evolution of itaconate synthesis and its role in mammalian metabolism. Besides its anti-microbial function, derivatives of

metabolic profiling and metabolism. His current work focuses on cellular and mitochondrial metabolism in the context of inflammation and neurodegeneration.

Dirk Brenner[1,2,3]



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this metabolite have been shown to exert an anti-inflammatory activity in mammalian macrophages. This context is also taken up by Wei *et al.* who discuss the activation of macrophages through various metabolic intermediates including itaconate. Citrate and succinate support the formation of inflammatory macrophages. He *et al.* put a special focus on the complexity of macrophage metabolism during an infection. Upon recognition of foreign material, different pattern recognition receptors (PRRs) trigger a specific macrophage activation. Cellular metabolism is tightly linked to the function and polarization state of the cells. Moreover metabolic processes are directly involved in innate immune function such as NO or ROS production and itaconate synthesis. In this regard, transmitters of danger signals are intracellular inflammasomes which are involved in cytokine processing and pyroptosis. Neuwirt *et al.* highlight the role of the NLRP3 inflammasome as a metabolic danger sensor. After an initial trigger the NLRP3 inflammasome needs to be activated and this activation can be performed by intracellular metabolic or mitochondrial signals. In case of a chronic dysbalance of metabolic homeostasis, NLRP3 activity can additionally cause stress through a continuous pro-inflammatory immune signaling that, on the long-term, promotes metabolic diseases such as type-2 diabetes or metabolic syndrome. Metabolic modeling studies can help to capture the full complexity of metabolism. Schuster *et al.* discuss different approaches to mathematically model energy metabolism of immune cells. Among others, the authors included models that describe macrophage polarization.

In addition to immediate immunological function, metabolites can indirectly modulate protein or enzyme activities involved in immune processes by post-translational modifications (PTM). Zhang *et al.* discuss several PTMs shaped by immune metabolites. The diversity of the PTM space is intriguing and includes modifications by lactate, itaconate, fumarate, succinyl-CoA, acetyl-CoA and malonyl-CoA. Except lactate all of these metabolites are intermediates or at least closely related to TCA cycle activity. Besides the role and space of these PTMs the authors discuss modern technologies to elucidate such modifications in cellular proteomes.

Role of metabolism in cells of the adaptive immune system

Apart from protection against pathogenic microorganisms, cellular defense mechanisms are challenged by viral infections. Once inside the cell, viruses try to manipulate host cell metabolism, thereby initiating an intracellular metabolic warfare with an always detrimental outcome for the infected cell; in the best case with halted virus replication. Thyrsted and Holm discuss which metabolic pathways are hijacked and exploited for replication by viruses. Besides nucleotide synthesis, fatty acid synthesis through citrate are essential for replication. Cellular defense mechanisms can sense metabolic reprogramming and virus production by increased cellular reactive oxygen species (ROS) and induce a NRF2-dependent antiviral response. In addition, the adaptive immune system can sense and eliminate virus infected cells. In this regard, T cells play a central role and can differentiate in CD8+ 'killer' or CD4+ 'helper' T cells. Kurniawan *et al.* highlight the critical role of folate mediated one carbon metabolism for T cell function. A dysbalance within this pathway has direct impacts on the subcellular cofactor balance, methylation, ROS scavenging and eventually T cell activation and polarization. Impaired T cell polarization is implicated in reduced anti-viral activity, autoimmune diseases and cancer progression. A broader view is given by Wei *et al.* on metabolic reprogramming of T cells. Manipulation of immunometabolism modulates effector T cell and T reg cell function and homeostasis and this can be used to enhance cancer immunity. Berod *et al.* discuss the current models that have been used to study dendritic cell (DC)

metabolism and put it in the context of recent single cell-based findings. Studies on DC metabolism may benefit from future single cell analyses in combination with the *in vivo* use of transgenic mouse models.

In addition to protecting against infection, T cells are heavily involved in the eradication of tumors. The anti-tumor responses are strongly influenced by the surrounding environment. In a comprehensive way Flerin *et al.* discuss different immune responses that occur in various cancer types. The tumor microenvironment (TME) induces metabolic stress on tumor infiltrating lymphocytes. Each cancer type has mutation-specific metabolic properties that affect the TME. These in turn affect T cell metabolism and their anti-tumor function. This should be taken into account in the development of therapeutic approaches that target T cell or cancer cell metabolism. A key mutation of various cancers is found in isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2), which leads to the formation of 2-hydroxyglutarate (2-HG). Leca *et al.* discuss the important effect of 2-HG on the TME. The focus here is on the non-cell autonomous influence of 2-HG on the immune system. IDH mutations can affect the metabolism, epigenetics, and functions of tumor-infiltrating immune cells. One of the features of cancer metabolism is the generation of ROS. The control of ROS by antioxidants is crucial for tumorgenesis, which is highlighted by Asantewaa *et al.* Of great importance in this context is glutathione (GSH), the main cellular antioxidant, which is synthesized from glycine, glutamate and cysteine.

Despite immune metabolism and cancer metabolism that regulate immune cell functions, the relationship between host and parasite can be significantly influenced by metabolism. Intracellular *Toxoplasma gondii* depends on its host and influences the host's cell metabolism. In contrast, the host adapts its metabolism in such a way that the parasite's access to important metabolites is restricted. Kloehn *et al.* describe the struggle between *Toxoplasma gondii* and the host cell for metabolites.