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Metabolic Regulation of Inflammation and Its Resolution: Current Status, Clinical Needs, Challenges, and Opportunities

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Abstract

Metabolism and inflammation have been viewed as two separate processes with distinct but critical functions for our survival: metabolism regulates the utilization of nutrients, and inflammation is responsible for defense and repair. Both respond to an organism's stressors to restore homeostasis. The interplay between metabolic status and immune response (immunometabolism) plays an important role in maintaining health or promoting disease development. Understanding these interactions is critical in developing tools for facilitating novel preventative and therapeutic approaches for diseases, including cancer. This trans—National Institutes of Health workshop brought together basic scientists, technology developers, and

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clinicians to discuss state-of-the-art, innovative approaches, challenges, and opportunities to understand and harness immunometabolism in modulating inflammation and its resolution.

The "Metabolic Regulation of Inflammation and Its Resolution" virtual meeting (https://www.eventbrite.com/e/metabolic-regulation-of-inflammation-and-its-resolution-tickets-141464507149), organized by the Trans-NIH (National Institutes of Health) Chronic Inflammation Working Group, was held on June 2830, 2021. Metabolic changes in the immune system play a central role in multiple diseases. In obesity, nutrient overload activates inflammatory responses in adipose tissue, skeletal muscles, and other organs, contributing to systemic insulin resistance and diabetes (1). Interest in immunometabolism as a source of new cancer therapeutics has exploded recently, largely fueled by studies of tryptophan catabolism mediated by indoleamine-2,3-dioxygenase and tryptophan-2,3-dioxygenase enzymes and their roles in immunosuppression. Data suggest indoximod (an indoleamine-2,3-dioxygenase/tryptophan-2,3-dioxygenase inhibitor) safely enhances chemotherapy, chemoradiotherapy, immune checkpoint therapy, and vaccines (2). During the workshop, participants addressed major questions in the field by providing their research insights, and they identified common gaps and challenges to advance the field.

Trained immunity and chronic inflammation

George Hajishengallis opened the meeting with a keynote on trained immunity. Growing evidence supports the concept of long-term, innate immune memory during which an inflammatory challenge elicits an enhanced response upon a secondary challenge. Such responses have been observed in invertebrates and plants that lack adaptive immunity. Innate memory is associated with changes in intracellular metabolism and the epigenetic landscape (3). However, the short life span of circulatory myeloid cells presents a paradox in that it appears to be inconsistent with the long-term effects of trained immunity on circulating myeloid cells. Although trained immunity includes multiple beneficial outcomes, the increased production of myeloid cells with robust immune responsiveness may enhance inflammation and exacerbate diseases (4) in response to high-fat diets (5) and periodontitis-associated comorbidities (3).

Metabolic effects on immune cells

Metabolic modulation can affect phenotypes and functions of immune cells. Partha Biswas explained that neutrophils are critical for antifungal immunity, and neutropenia is a significant risk factor for disseminated candidiasis, a common hospital-acquired infection in patients with kidney disease (6). Neutrophils are metabolically unique, short-lived, and terminally differentiated. They rely on glycolysis and pentose phosphate pathways for their function. Neutrophil glycolysis is disrupted under uremic conditions, leading to lower cellular production of nicotinamide adenine dinucleotide phosphate (NADPH), disrupting their reactive oxygen species (ROS) production and fungicidal activities in kidneys. Neutrophil function can be restored using lithium chloride, a glycogen synthetase kinase 3b inhibitor that allows for ROS production (6). Bart Everts described how dendritic cell (DC) activation and T cell priming require a switch from catabolic to anabolic states. Glycolysis supports the anabolic demands of proinflammatory DC function (7), which is

required for potent T cell priming; DC catabolism is linked to priming of regulatory T cells. Key upstream regulators of DC metabolism are mammalian target of rapamycin and AMP-activated protein kinase, which promote anabolism and catabolism, respectively (8). Munir Akkaya explained how the metabolic clock controls B cell function in balancing its defensive versus self-preservation act. B cells play a critical role in producing protective Abs. When challenged by Ags binding to BCR, B cells activate a metabolic program that leads to mitochondrial dysfunction and cell death. Increased glucose import and oxygen consumption rate are critical in supporting B cell activation (9); however, the precise mechanism by which these metabolic pathways influence B cell stimulation remains unknown (10). Jan Van den Bossche investigated how metabolic reprogramming regulates macrophages in pathological conditions. Metabolic enzymes such as ATP citrate lyase (ACLY) link carbohydrates to lipid metabolism and are essential regulators of macrophages during atherosclerosis and inflammation (11). Mice with ACLY-deficient myeloid cells develop a more stable atherosclerotic plaque, and targeting ACLY in macrophages may have therapeutic potential for cardiovascular diseases (CVDs) (12).

Metabolic effects on inflammatory pathways

Speakers highlighted how metabolic modulation in inflammation can affect signaling pathways associated with and responsible for disease progression and treatment response. Jennifer Estall reported the impact of mitochondrial dysfunction on metabolic disease via organ cross-talk. Transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator-1α is the master regulator of mitochondrial biogenesis and function, coordinating the balance between metabolism and apoptosis during hepatic inflammation. Peroxisome proliferator activated receptor-γ coactivator-1α controls nutrient metabolism gene programs and mitochondrial biology and attenuates hepatocyte apoptosis in response to TNF-α or LPS (13). Santosh Vardhana examined the relationship between T cell exhaustion and metabolic stress. He noted that metabolites regulate immune cell homeostasis within the tumor microenvironment (14). Overstimulation by pathogens or malignant tumors renders exhausted T cells unable to clear infections or tumors. Changes in T cell metabolism in the tumor microenvironment reverse T cell exhaustion (15). Heather Francis described how mast cells may promote nonalcoholic fatty liver disease (NAFLD), a disease that increases risks for nonalcoholic steatohepatitis (NASH). Mast cells infiltrate the liver during cholestatic injury and cause liver damage, leading to increased serum histamine levels in patients with NAFLD or NASH. miR-144–3p/ALDH1A3 might be responsible for transition of NAFLD to NASH (16). Juhi Bagaitkar presented how leukocyte NADPH oxidases regulate neutrophilic inflammation at the oral mucosal barrier (17). NADPH oxidase deficiency promotes G-CSF–regulated neutrophilic responses and prolonged inflammation, whereas NADPH-derived ROS are essential in regulating various aspects of neutrophil functions (18).

Role of immunometabolism in disease

Keynote speaker Gokhan Hotamisligil opened the second day by discussing the role of immunometabolism in disease and how common metabolic mechanisms may determine outcomes of obesity, diabetes, fatty liver disease, CVDs, and some cancers. Homeostasis

is the result of highly integrated interactions between metabolic and immune responses, and maladaptation of these responses results in disease. In 1983, Pekala et al. (19) connected inflammatory cytokines with insulin resistance and showed that products of activated macrophages blocked insulin action. Genetic models of obesity reveal that blocking inflammatory cytokines inhibits inflammatory responses and restores insulin action in tissues. Macrophages in adipose tissue of obese animals produce TNF-α and other inflammatory mediators, leading to insulin resistance. TNF-α contributes to insulin resistance by inducing phosphorylation of the insulin receptor substrate 1, which converts insulin receptor substrate 1 into an insulin receptor inhibitor. TLR and cytokine receptor signaling induce stress signals that interfere with insulin action (20).

Nutrient overload and excess cholesterol induce stress in the endoplasmic reticulum (ER), the immunometabolic hub of the cell (20). Failure of the ER's adaptive capacity causes activation of the unfolded protein response, which induces an inflammatory cycle resulting in organelle failure during diabetes and NAFLD/NASH. Other specialized molecules in the ER are dedicated to organelle metabolic homeostasis. Nrf1, a transcriptional mediator, protects the ER against intracellular cholesterol accumulation by sensing and binding to excess cholesterol in the liver and brown adipose tissue, and pathway dysfunction leads to metabolic deterioration and disease (21, 22). Obesity and stress disrupt cellular architecture because chronic excess of nutrients leads to abnormal ER morphology and organization in tissues. The ER functional disruption centers around calcium homeostasis. These molecular mechanisms at the interface of immune response and adaptive metabolism may be targeted for prevention and treatment approaches for obesity, diabetes, and related metabolic diseases.

Novel immunometabolic approaches in combating coronavirus disease 2019

This session focused on the roles of metabolic and inflammatory pathways in coronavirus disease 2019 (COVID-19) pathogenesis and explored potential interventional and therapeutic strategies. Gary Patti described a metabolic signature of blood biomarkers from patients with early COVID-19 that could be better predictive markers than body mass index and age for development of serious illness. Using untargeted metabolomics analysis of plasma samples from hundreds of patients over the course of their illness, combined with machine learning tools, Patti found that a group of 25 lysophosphatidyl cholines could predict the probability of a patient's admission to the intensive care unit (23). Similarly, Bruce Hammock (24) used metabolomic analysis to study lipids in the arachidonic acid cascade with roles in the initiation and resolution of inflammation in blood samples from patients with COVID-19. He stated that although the cyclooxygenase and lipoxygenase pathways and their mediators are proinflammatory, the P450 pathway produces anti-inflammatory mediators that might be therapeutic targets (24). Monitoring lipid mediators, chemokines, and cytokines closely associated with the development of adult respiratory distress syndrome in the blood of patients with COVID-19, Hammock and colleagues (25) identified a signature of four highly elevated molecules: two leukotoxins and two regioisomeric leukotoxin diols of linoleic acid. Detecting plasma linoleate diols

identified patients with COVID-19 at high risk for early adult respiratory distress syndrome (26). Reducing diols by reducing linoleate in the diet or by blocking the epoxide hydrolase enzyme that forms inflammatory leukotoxin diols might have therapeutic value. Anne Marie Schmidt described how the receptor for advanced glycation end products (RAGE) pathway may explain increased COVID-19 severity among patients with obesity, patients with diabetes, and elderly patients. High levels of a soluble form of RAGE in plasma of patients with COVID-19 correlates with severe lung injury and decreased survival (27) and could be a therapeutic target (28). RAGE is expressed on macrophages and type 1 lung epithelial cells and is elevated in adipocytes and vascular tissues by obesity. Deletion of the *Ager* gene coding for RAGE protects mice from weight gain, insulin intolerance, and inflammation when exposed to a high-fat diet (29) and accelerates regression of atherosclerosis in Ldlr null mice, potentially via reduced expression of IRF7 in macrophages (30). RAGE is involved in both metabolism and the innate trained immune response. RAGE signaling is initiated via binding to Diaphanous 1 (31), which can be blocked with newly developed small molecules, a strategy being tested for treating patients with COVID-19. Marvin Slepian focused on the importance of thromboemboli in causing COVID-19related tissue ischemia, infarction, morbidity, and mortality. In patients with COVID-19, there is extensive local and systemic inflammation with tissue damage and release of prothrombotic mediators and hypercoagulability, leading to reduced blood flow and embolism. Around 20–30% of patients with COVID-19 experience development of clinically important thrombosis causing damage in many tissues (32). Platelets release cytokines that lead to a spiral of immune activation and cytokine storm (33, 34) and fuel the nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain (NLRP) inflammasome activation of innate immune cells and IFNs, central to the response to severe acute respiratory syndrome coronavirus 2 (35).

Therapeutic and clinical implications of immunometabolism

Speakers shared their research findings illustrating how tissue microenvironment, nutrition, and lipid metabolism modulate immune cell behaviors and may be potential therapeutic targets. Greg Delgoffe described the metabolic profile of tumor-infiltrating T lymphocytes (TILs) and strategies for improving antitumor immunity. The metabolic landscape of the tumor microenvironment is a barrier to immunotherapy and causes TIL exhaustion. TILs experience overwhelming metabolic deficiencies, such as insufficient oxygen, when stimulated by persistent Ag in solid tumors (36, 37).

Naomi Taylor discussed metabolic regulation of T cell effector function and hematopoietic stem cell differentiation. Hematopoietic cells can acquire energy from different fuels, such as glucose or glutamine, with shifts in metabolites regulating the differentiation of erythroblasts and T cells. Inhibiting the alanine serine cysteine transporter 2 (ASCT2) glutamine transporter or downstream glutaminolysis diverts erythropoietin-signaled human hematopoietic stem cells to a myeloid cell fate (38, 39). T cell effector function and differentiation are regulated by nutrient transporters and utilization, allowing lymphocytes to meet increased energetic and biosynthetic demands (40).

Ira Goldberg discussed the role of blood lipids in heart metabolism, with triglycerides (TGs) being the primary fuel for the heart. A human heart obtains most of its energy from the oxidation of long-chain fatty acids (FAs) from the hydrolysis of TG-rich lipoproteins via lipoprotein lipase and via uptake of albumin-bound FAs that originated from adipose TG stores. FAs derived from lipoprotein TGs are essential for cardiac lipid metabolism and gene regulation (41, 42).

Lev Becker discussed metabolic-epigenetic regulation of macrophage function through histone lactylation. Inflammation is needed for resolution of pathogen infection but must be resolved for homeostasis; otherwise, it leads to chronic inflammation. Early in the inflammatory process, proinflammatory M1-type macrophages are activated, and later, anti-inflammatory M2 macrophages promote tolerance and tissue regeneration. M1 macrophages perform glycolysis that results in lactate accumulation. Lactate plays a crucial role in gene transcription and cell function in immune cells and modifies histones to directly influence gene transcription from chromatin during infection. Lactate production during M1 activation promotes a transition to the M2 phenotype and helps limit the duration of the M1 state. Defects in this “lactate clock” may promote the transition to chronic inflammation. Histone lactylation represents an opportunity to improve our understanding of the role of lactate in diverse pathophysiological conditions and translate it in developing therapeutics across a spectrum of human disease (43).

Harnessing immunometabolic checkpoints of inflammation

Vishwa Deep Dixit, the third keynote speaker, discussed the concept of harnessing immunometabolic checkpoints of inflammation and aging. Visceral or ectopic fat that accumulates (despite a normal body mass index) in aging is associated with a cluster of cardiometabolic risk factors and chronic inflammation (inflammaging). In diet-induced obesity, adipose B cells in visceral fat promote inflammation and insulin resistance. Aging adipose B cell expansion and fat-associated lymphoid clusters formation are controlled by NLRP3 inflammasomes. Inhibiting NLRP3-dependent adipose B cell accumulation may reverse age-related metabolic impairment (44, 45). Although obesity and aging induce distinct adipose immune responses, both increase inflammation and decrease thermogenesis (45). Dietary or pharmacological approaches to lower NLRP3 may reduce multiple chronic diseases. Ketone bodies inhibit NLRP3, which may have clinical implications as mice under ketogenic diet show inhibition of aging-induced exacerbation of COVID-19 infection (46). Calorie restriction increases the life span in multiple species perhaps through reduced inflammaging (47). These examples suggest immunological-metabolic interactions may reveal targets to reduce inflammation and enhance life span.

Metabolic biomarkers

Maxim Artyomov discussed macrophage activation and itaconate as a possible biomarker of metabolic reprogramming during innate immune responses. Itaconate is an endogenous regulatory metabolite in macrophages that indirectly limits NLRP3 activation via caspase-1 after prolonged stimulation (48). Frank Hu discussed epidemiological studies identifying blood biomarkers of inflammation that improved prediction of CVD combined with

traditional risk factors (49). In addition, Hu described a system to measure dietary inflammatory potential with a food-based empirical dietary inflammatory pattern (EDIP) score determined from levels of systemic inflammatory biomarkers and food intake. High EDIP scores and a Mediterranean diet were significantly associated with increased and decreased risk for CVD, respectively (50, 51). Hu suggested that diets with high EDIP scores promote serum inflammatory biomarkers or gut microbial metabolism, resulting in increased CVD risk. Multiomics platforms and machine learning can facilitate the identification of robust inflammatory markers/ metabolic signatures of inflammation, diet, and CVD risk. Ronald Summers described using automated computerized tomography (CT)-based algorithms and radiological imaging to supplement clinical biomarkers to provide accurate information about body composition for diagnosing metabolic syndrome in clinically asymptomatic individuals. Automated CT image analysis permits measurement of five biomarkers of body composition and related pathology: bone mineral densitometry, muscle, adipose tissue, liver fat, and abdominal aortic atherosclerotic plaque (52). Combinations of these metrics and others improve diagnostic prediction in metabolic syndrome (53). Similar techniques can be used to screen for other diseases and conditions at a reasonable cost (54, 55). Melissa Skala showed how dynamic and quantitative imaging with cellular-level resolution can identify abnormal cellular metabolism, while labelfree optical imaging technologies and quantitative analysis tools can be used to study metabolic heterogeneity in cancer, stem cell function, and immune cell behavior. Fluorophores such as NADPH and flavin adenine dinucleotide already present in the cells can be used to monitor metabolism with single-cell resolution. These metabolic imaging tools allow rapid cellular-level assessment of metabolic phenotypes in tumors and immune cells, permitting examination of cellular metabolic heterogeneity and its effects on patient outcomes (56, 57).

Tools for interrogating immunometabolism

Russell Jones presented in vivo studies on cellular metabolism modulated by environmental factors and how whole-body metabolism filters down to cellular levels. He described a technique combining stable isotope labeling of carbons, cell sorting, and mass spectrometry for metabolomic analysis to trace the metabolic activities in cells (58). Jones showed that activated lymphocytes engage in metabolic reprogramming to support growth and proliferation independent of serine metabolism (58). Josh Mattila investigated glucose metabolism in granulomas associated with tuberculosis (TB) as an indicator of response to therapy. Elevated glucose metabolism caused by the presence of *Mycobacterium tuberculosis* resulted in increased uptake of [^{18}F]-FDG and elevated positron-emission tomography (PET) imaging signals. A cynomolgus macaque model of TB with serial PET imaging of [^{18}F]-FDG uptake showed dynamic changes in granuloma inflammatory profiles over time with each TB granuloma having its own trajectory (59). Damian Tyler described a hyperpolarized magnetic resonance imaging tool to study metabolism in vivo with significantly increased magnetic resonance signals from metabolites for a better understanding of the inflammatory response after myocardial infarction. Hyperpolarized magnetic resonance imaging also was used to assess physiological and pathological changes in cardiac metabolism (pyruvate dehydrogenase) in human type 2 diabetic hearts (60). Kylie Kavanagh focused on radiation-induced immunometabolic dysfunction in nonhuman

primates (NHPs). NHPs that received irradiation exhibited metabolic changes consistent with diabetes (61). Although the exact changes were unclear, it was thought that radiation exposure might epigenetically remodel fibroblasts, similar to that seen with aging and overnutrition, increasing risk for type 2 diabetes. These irradiated NHPs also had adipocyte hypertrophy, with large adipocytes and more macrophages in the fat without being obese (62).

Future directions

Metabolic modulation occurs in immune cells at all stages of inflammation depending on the immune cell type. Metabolic cellular changes do not follow a typical inflammatory time frame and can occur early in the cell cycle and lead to longer-term consequences. Although acute inflammation is typically protective early, targeting metabolic changes in chronic inflammation requires consideration of steady-state maintenance and the return to homeostasis from the chronic inflammatory state. Speakers discussed the cross-talk of metabolism and immunity among different levels of metabolic and signaling pathways across disease conditions, such as obesity, diabetes, CVDs, cancer, and COVID-19. Some of the main concepts from the workshop discussion are summarized in the following section.

Metabolic biomarkers of inflammation and immunometabolism-based therapeutic strategies have clinical potential

From a preclinical perspective, the discovery and utility of inflammatory or metabolic biomarkers will depend on the model system and intended use. Metabolic by-products, such as trimethylamine *N*-oxide and ceramides, are independent predictors of diabetes and CVD but are difficult to study clinically because of lack of assay standardization. Importantly, one needs to consider what the biomarker is intended to “mark”: is it a marker of disease, predictor of risk for development of a disease, indicator of a patient’s prognosis, predictor of treatment effects, and/or indicator of biological activity? For instance, ceramide accumulation resulting from cellular death could activate macrophages, potentially making ceramides an indicator of biological activity along with a marker of disease. Other metabolites of interest, including arginine, glutamine, pyruvate, lactate, and lipid mediators, affect immune cell functions, cardiac cell recovery, and tumor progression. Imaging metabolic changes using CT and PET scans has potential in clinical practice. However, there must be a balance between biomarkers and imaging, with both approaches being useful in different circumstances.

Many immunometabolism-based therapeutic studies at the preclinical stage show promise. Pilot studies using nanoparticles to deliver immunometabolism-modulating agents preferentially to bone marrow cells of atherosclerotic patients result in resolution of chronic inflammation via downregulating trained immunity. Many over-the-counter medications, such as antihistamine and immunomodulatory drugs, have been used to treat chronic inflammation and autoimmune conditions, highlighting the promise of repurposing drugs to address chronic inflammation. Immunomodulation of the metabolome by harnessing microbial metabolites is another avenue with a bright future.

Challenges in studying immunometabolism

The main challenges identified during the discussion sessions involved identifying how findings in vitro may be applicable in vivo. Novel tools, approaches, and technologies for examining metabolism and inflammation in in vivo–like systems such as organoids, single cells from freshly isolated tissues, among others, are needed. Furthermore, standard operating procedures are needed to improve reproducibility and accuracy. Metabolic changes occur faster than current technologies can discern. Mass spectrometry using fresh-frozen tissue to get special cellular resolution of metabolites is improving our resolution to studying these rapid changes. As an alternative and complementary approach, single-cell analyses may be useful given the complexity of cell types and metabolites that are involved.

Some of the other challenges identified include development of metabolic biomarkers and blood tests, machine learning algorithms, and quantitative matrices to adopt in clinical evaluation. In addition, tools are needed to facilitate the translation of imaging and biomarker results into information for patients. There is a critical need for databases that include imaging data, along with other associated data (epidemiological, clinical, -omics, etc.). Such databases would allow improving specificities of immunometabolic biomarker detection and clinical diagnoses.

Lastly, aging should be an important consideration when designing animal-, clinical-, or population-based immunometabolism studies with the caveat that biological and chronological age are different. Accessible technologies for assessing metabolites and inflammation are needed. The interplay between metabolism and inflammation affects the whole body, and it is important not to keep clinical practices in silos and train medical students to be thinking about the big picture.

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Abbreviations used in this article:

ACLY	ATP citrate lyase

COVID-19	coronavirus disease 2019
CT	computerized tomography
CVD	cardiovascular disease
DC	dendritic cell
ER	endoplasmic reticulum
FA	fatty acid
NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NHP	nonhuman primate
NIH	National Institutes of Health
NLRP	nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain
PET	positron-emission tomography
RAGE	receptor for advanced glycation end product
ROS	reactive oxygen species
TB	tuberculosis
TG	triglyceride
TIL	tumor-infiltrating T lymphocyte

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