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Interplay Between Metabolic Reprogramming and Immunity: A Key Role of Superfood as Sources of Vitamins and Antioxidants in Prevention of Different Pathologies and for Healthy Aging and Focus on NAD+ Prospectives

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Immune cell activation, differentiation, and effector functions are governed by tightly coordinated metabolic reprogramming involving a network of interconnected biochemical pathways. Glycolysis, the tricarboxylic acid (TCA) cycle, and the pentose phosphate pathway (PPP) constitute the core metabolic axes sustaining bioenergetic demands, generating biosynthetic intermediates, and preserving redox balance during immune responses. In parallel, lipid metabolic programs-including fatty acid oxidation (FAO) and fatty acid synthesis (FAS)-play critical roles in regulating cellular energy homeostasis, membrane remodeling, and signal transduction in immune cells. In this highly integrated metabolic landscape, amino acid metabolism emerges as a pivotal regulatory layer; notably, tryptophan catabolism exerts profound immunomodulatory effects by shaping immune cell fate decisions, functional polarization, and immunoregulatory signaling through its downstream metabolic pathways.

A growing body of evidence demonstrates that finely tuned alterations in metabolite availability and metabolic flux within these pathways directly influence immune cell activation, lineage commitment, and effector responses. Collectively, these findings underscore a dynamic and reciprocal interplay between metabolic reprogramming and immune function, adding a further conceptual dimension to immune system regulation in both physiological homeostasis and pathological states.

Nicotinamide/nicotinic acid mononucleotide adenylyltransferase (NMNAT) has long been recognized as the central, rate-limiting enzyme in nicotinamide adenine dinucleotide (NAD^+) biosynthesis, a role that has prompted extensive investigation into its biochemical properties and regulatory mechanisms. Beyond its canonical metabolic function, NMNAT has emerged as a multifunctional protein positioned at the interface between central metabolism and diverse cellular regulatory networks, including those implicated in neurodegeneration and stress resilience. The accumulation of biochemical and preclinical evidence has established a robust framework supporting the rational development of NMNAT-targeted therapeutic activators.

The SARS-CoV-2–driven COVID-19 pandemic has posed an unprecedented challenge to global health systems, economic stability, and societal organization. Although viral entry and initial infection primarily affect the respiratory tract, severe COVID-19 is now recognized as a systemic disease involving widespread multi-organ dysfunction, frequently progressing to systemic failure in vulnerable individuals. Despite intensive global research efforts, no universally effective therapeutic intervention has yet been identified. Pre-existing pathological conditions and comorbidities-particularly advanced age-remain major determinants of increased morbidity and mortality, substantially contributing to premature death.

Prolonged immobilization associated with hospitalization, together with sustained physical inactivity induced by quarantine and social distancing measures, can compromise organ system resilience and exacerbate dysfunction across immune, respiratory, cardiovascular, musculoskeletal, and central nervous systems. This review addresses the cellular mechanisms underlying these so-called "second-wave" effects of COVID-19, while critically examining the modulatory roles of aging, nutritional status, and regular physical activity.

Compelling evidence indicates that dietary behaviors are strongly influenced by psychological stress and emotional dysregulation, with elevated distress consistently associated with unhealthy eating patterns and reduced diet quality. At the individual level, the unifying principle underlying most nutritional strategies aimed at mitigating viral infections resides in the close and bidirectional relationship between diet and immune function. Substantial evidence demonstrates that dietary intake exerts a profound influence on immune competence and disease susceptibility. Specific nutrients and defined nutrient combinations modulate immune responses by regulating immune cell activation, cytokine production, and gene expression programs. Moreover, dietary components are key determinants of gut microbiota composition and metabolic activity, thereby indirectly shaping host immune responses.

Deficiencies in dietary energy, protein, and essential micronutrients are closely associated with impaired immune function and heightened susceptibility to infection. Adequate intake of fat-soluble vitamins A, D, and E, water-soluble vitamin C, and B-complex vitamins-including riboflavin, niacin, vitamin B6, and vitamin B12-together with sufficient bioavailability of iron and zinc, is essential for maintaining immune homeostasis. The preservation of an effective immune system critically depends on preventing deficiencies in nutrients required for immune cell activation, intercellular communication, differentiation, and execution of effector functions.

Nutritional status has long been regarded as a key indicator of individual resilience to physiological and systemic destabilization. Lockdown and confinement periods have promoted irregular eating behaviors and increased snacking frequency, patterns associated with excessive caloric intake and elevated obesity risk. Individuals affected by autoimmune diseases are particularly vulnerable to infection due to intrinsic immune dysregulation and the widespread use of immunosuppressive therapies. Although immunosuppressed patients may exhibit increased susceptibility to SARS-CoV-2 infection, treatment discontinuation is contraindicated owing to the risk of disease flare and secondary complications. By attenuating oxidative stress and supporting immune competence, appropriate nutritional interventions may contribute to reducing infection risk and mitigating COVID-19 severity.

At the cellular level, remodeling of Krebs cycle activity in macrophages supports the accumulation of bioactive metabolites capable of driving either pro-inflammatory or anti-inflammatory programs, although the underlying molecular mechanisms remain incompletely defined. Among these metabolites, itaconate has been shown to modulate the activity of the anti-inflammatory transcription factor NRF2. However, itaconate production entails a metabolic trade-off, as macrophages consequently lose the capacity to perform mitochondrial substrate-level phosphorylation.

Amino acids represent fundamental molecular building blocks essential for life. Beyond their role in protein synthesis, amino acids contribute to ATP generation, nucleotide biosynthesis, and redox homeostasis. Immune cells critically depend on amino acid-driven metabolic pathways to support activation-induced growth, proliferation, and effector functions. Accordingly, amino acid metabolism constitutes a central component of immune metabolic rewiring and plays a decisive role in sustaining immune responses under pathological conditions.

The long-term consequences of recent global disruptions for society, economy, and food systems remain incompletely understood. Academic researchers and food sector stakeholders face substantial challenges in ensuring food safety and security. The adoption of Industry 4.0 technologies offers promising strategies to reduce food loss and waste and to identify alternative, nutritionally adequate protein sources capable of meeting evolving population needs.

Concurrently, a new era in cancer therapy has emerged, grounded in the principles of 4P Medicine-Personalized, Predictive, Preventive, and Participatory approaches. Artificial intelligence is rapidly reshaping cancer research and personalized clinical care through the integration of high-dimensional datasets, high-performance computing, and advanced deep learning architectures. AI-driven applications now span cancer detection, tumor classification, molecular profiling, drug discovery, and prediction of treatment outcomes. These advances have been enabled by an improved understanding of cancer biology and the development of innovative biomarker technologies. Precision-based strategies are increasingly being explored across multiple disciplines, including neuroscience, immunology, and women's health.

Precision medicine integrates clinical and health record data with pan-omics approaches to enable deep phenotyping and individualized therapeutic decision-making. Lifestyle factors-particularly diet and physical activity-are becoming integral components of personalized and precision medicine frameworks. However, the global implementation of precision healthcare will require coordinated policy initiatives and sustainable economic strategies. In this evolving landscape, women continue to play a critical role in advancing precision health, biomedical innovation, and scientific leadership.

Finally, oxygen availability remains a fundamental determinant of cellular metabolic organization. Under normoxic conditions, energy metabolism is predominantly supported by the TCA cycle and oxidative phosphorylation, whereas hypoxic environments activate hypoxia-inducible factor 1α (HIF-1α), driving a metabolic shift toward glycolysis and adaptive metabolic reprogramming.

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