JIM
JIM 2025; 2 (1): e714
DOI: 10.61012_20252_714
Category: *Editorial*

METABOLIC REPROGRAMMING: INNATE METABOLISM IS THE KEYSTONE FOR ETIOPATHOGENETIC INTERPRETATION OF MANY DISEASES

A. PESSION[1,2]

• • •

[1]Full Professor of Pediatric Alma Mater Studiorum, University of Bologna, Bologna, Italy
[2]President of Italian Society for Inherited Metabolic Disease and Neonatal Screening, Bologna, Italy

Corresponding Author
Andrea Pession, MD PhD; e-mail: andrea.pession@unibo.it

Keywords: Metabolic reprograming, Cancer, Allergic diseases, Autoimmune diseases, Diabetic kidney disease, Ischemia-reperfusion injury, Bone regeneration.

Nothing is really difficult if you divide it into many small pieces

Henry Ford

Innate metabolism consists of a network of biochemical reactions that convert nutrients into small molecules called metabolites. Through this series of reactions and the resulting metabolites, cells generate macromolecules (proteins, lipids, nucleic acids), redox equivalents, and the energy they need to maintain cellular functions under normal circumstances. Under pathological conditions, cells undergo reprogramming of their metabolism to survive this change in their homeostasis.

The term “metabolic reprogramming” thus refers to a change in the metabolic processes of a cell or organism in response to induced homeostatic alterations. This process involves the modification of the use of energy resources, such as sugars, lipids, and proteins, by cells to adapt to new conditions that are classically pathological as well as physiological or environmental.

“Metabolic reprogramming” is a concept that has been developed and is particularly relevant and current in contexts, such as cancer, where cancer cells alter their metabolism to promote growth and survival, even under stressful conditions, such as hypoxia (low oxygen availability) or nutrient deficiency. It is well known that normal cells obtain their energy via first glycolysis in the cytosol, which is followed by mitochondrial oxidative phosphorylation under aerobic conditions. When oxygen is scarce, the cells rely on glycolysis rather than oxygen-consuming mitochondrial metabolism for energy supply. However, the metabolic pattern of tumors is different from that of normal cells. As first observed by Otto Warburg[1], the phenomenon that cancer cells prefer to carry out glycolysis in the cytosol, even in the presence of oxygen, is known as the “Warburg effect” or “aerobic glycolysis”.

Because the infinite proliferation of tumor cells requires a faster energy supply, the ATP production rate of glycolysis is much faster than that in oxidative phosphorylation. However, efficiency in ATP production per molecule of glucose is much lower via glycolysis. In fact, various central metabolic pathways can be dysregulated in cancer cells. This process can also involve the metabolism of fatty acids, proteins,

and other molecules (urea cycle) and can be mediated by genetic factors, epigenetics, and environmental signals. Metabolic reprogramming is thus a key mechanism for cellular plasticity and adaptation to changing conditions[2].

More importantly, emerging evidence indicates that cancer cells are able to suppress the anti-tumor immune response by competing for and depleting essential nutrients or otherwise reducing the metabolic fitness of tumor-infiltrating immune cells.

Both the innate and adaptive immune systems have now established roles in the host defense against cancers through various mechanisms, which are raising an unprecedented development of modern cancer immunotherapies. The innate immune system consists of different populations of immune cells, including macrophages, neutrophils, monocytes, eosinophils, basophils, and natural killer cells, which are responsible for innate immunity against pathogens to maintain homeostasis of the host. Indeed, immune cells are capable of sensing various signals in the microenvironment and turning on specific immune functions in response. More and more evidence has pointed out that the immune response is associated with dramatic modifications in tissue metabolism, including the depletion of nutrients, increased oxygen consumption, and the generation of reactive nitrogen and oxygen intermediates. Similarly, many metabolites in the tumor microenvironment, in turn, also influence immune cell differentiation and effector function. However, recent work has shown that immune cells compete with cancer cells and other proliferating cells in the microenvironment for nutrients. This suggests that metabolic interventions hold promise for improving the effectiveness of immunotherapies.

Previous studies showed that the modifications of cancer cell metabolism are, in part, due to the recruitment of many inflammatory and immune cells. Subsequently, more and more researchers have found that the aberrant metabolites or intermediates of cancer metabolism may play an important role in regulating the proliferation, differentiation, activation and function of immune cells. Recent studies have shown that our immune system is closely related to other metabolic functions (also in cancer cells) in a way that has never been realized before. Moreover, it is described as a new field called immune-metabolism. However, the actual process of how metabolic reprogramming and cancer immune response affect each other has not been completely understood[3].

However, after decades of cancer research, we can now say that metabolic reprogramming is also a hallmark of great interest in many other pathological conditions and beyond.

Allergic diseases are a group of chronic inflammatory disorders driven by abnormal immune responses. Extensive progress has been made in characterizing the crucial roles of metabolic reprogramming in the regulation of immune cell functions. Dendritic cells (DCs) play a key role in the initiation and progression of allergic diseases by modulating T-cell responses. As critical upstream regulators and effectors of allergic responses, the activation, migration, and function of DCs depend on metabolic reprogramming, and understanding the functional alterations of DCs during allergic responses and the mechanisms underlying their metabolic regulation is critical for the development of effective strategies for the prevention and treatment of allergic diseases[4].

Autoimmune diseases occur when the immune system abnormally attacks normal body tissues, causing inflammation and damage. Each autoimmune disease also has peculiar immune and metabolic dysfunction in terms of etiopathogenesis. In rheumatoid arthritis (RA), immune cells exhibit different metabolic patterns and peculiar and specific mitochondrial/lysosomal dysfunction at different stages of the disease. In systemic lupus erythematosus, metabolic dysregulation of immune cells caused by type I interferon (IFN) causes activation of metabolic alterations that can worsen the disease. In primary Sjögren's syndrome, immune cell metabolism is altered, and mitochondrial damage can lead to cell and tissue damage. In systemic sclerosis, mitochondrial alterations affect fibroblast metabolism and immune response. Finally, alterations attributable to metabolic and mitochondrial problems are also known to occur in patients with idiopathic inflammatory myopathies. Metabolic reprogramming links cellular energy requirements and immune dysfunction, causing inflammation, damage, and symptoms in these diseases. It also affects immune cell functions such as differentiation, proliferation, and secretion. Therefore, the enormous potential of targeting metabolic pathways is evident[5].

Mitochondrial metabolic reprogramming also appears crucial in diabetic kidney disease (DKD). DKD, known as a glomerular disease, arises from a metabolic disorder that impairs renal cell function. Recent studies indicate that mitochondrial metabolic reprogramming has a significant impact on the pathophysiological progression of DKD. Alterations in renal metabolism led to abnormal expression of signaling molecules and activation of pathways, inducing oxidative stress-related cell damage, inflammatory

responses, apoptosis, and autophagy irregularities, culminating in renal fibrosis and functional insufficiency. Therapeutic interventions targeting renal metabolic reprogramming can potentially delay DKD progression[6].

Metabolic reprogramming in arginine methylation is relevant in various diseases, including cancer, cardiovascular diseases, chronic obstructive pulmonary disease, neurodegenerative disorders, viral infections and respiratory disease. Arginine methylation, a vital post-translational modification, plays a pivotal role in numerous cellular functions such as signal transduction, DNA damage response and repair, regulation of gene transcription, mRNA splicing, and protein interactions. Central to this modification is the role of protein arginine methyltransferases, which have been increasingly recognized for their involvement in the pathogenesis of various respiratory diseases and revealed an enormous potential as therapeutic targets[7].

Metabolic reprogramming is a process that involves the upregulation of different metabolic pathways in cells to balance energy, alter their phenotype and produce differentiation requirements. In this light, the role of metabolic reprogramming is particularly suggestive in the case of astrocyte function. Astrocytes are crucial for the maintenance of neuronal activity, and their activation occurs within minutes of the onset of ischemic stroke and subsequent inflammatory damage, that is, cerebral ischemia-reperfusion (I/R) injury. Activated astrocytes, also known as reactive astrocytes, are divided into two different phenotypes: astrocytes A1 (pro-inflammatory) and A2 (anti-inflammatory). A1 astrocytes have neurotoxic effects, whereas A2 astrocytes support the survival of neurons and promote tissue healing. A1 and A2 astrocytes show different metabolic reprogramming, such as glycolysis, glycogenolysis and glutamate uptake. Numerous scientific evidence suggests that manipulation of energy metabolism homeostasis can induce astrocytes to switch from the A1 to the A2 phenotype, highlighting how metabolic reprogramming in reactive astrocytes in the pathophysiological context of cerebral I/R may be a potential therapeutic target for cerebral I/R injury[8].

Finally, metabolic reprogramming is also relevant in skeletal and dental cell differentiation. Skeletal remodeling is a process that requires enormous amounts of energy and is associated with altered metabolic activities. Metabolic pathways of bone and dental tissue cells show fluctuating activities during bone loss and defects, suggesting regulated metabolic plasticity. These metabolic changes are often associated with epigenetic modifications, including changes in the expression or activity of enzymes modified by epigenetic mechanisms, which have a direct or indirect impact on cellular metabolism. Metabolic reprogramming induced by bone and dental conditions alters the epigenetic landscape by modulating the activities of DNA- and histone-modifying enzymes at the metabolite level. Epigenetic mechanisms, in particular acetylation and methylation, modulate the expression of metabolic genes, thereby influencing the metabolome. The interplay between epigenetics and metabolomics is crucial for the maintenance of bone and dental homeostasis, preserving cell proliferation and pluripotency. Metabolic therapies based on enzymes that modify chromatin metabolism, as well as dietary compounds that are active as epigenetic modulators, are envisaged as clinical treatments for bone and dental diseases[9].

Metabolic pathways are extremely complex and very often redundant. It is, therefore, appropriate to ask why nature has chosen such complex solutions for sometimes solving simple biochemical transformations. One possible answer stems from the considerations outlined above in relation to metabolic reprogramming. Indeed, it seems that evolution has ensured boundless possibilities for recovery and reorganization of functions under conditions of physiological stress or actual pathological alteration that can ultimately be traced back to complex metabolic disease.

Artificial intelligence-assisted technologies:
No artificial intelligence-assisted technologies were used in the production of this article.

Conflict of interest:
The author declares that he has no conflict of interest to disclose.

Ethics approval and informed consent:
Not required due to the nature of the study.

ORCID ID
Andrea Pession – https://orcid.org/0000-0002-0379-9562

REFERENCES

1. Warburg O. On the origin of cancer cells. Science 1956; 123: 309-314.
2. Mao Y, Xia Z, Xia W, Jiang P. Metabolic reprogramming, sensing, and cancer therapy. Cell Rep 2024; 43: 115064.
3. Huang K, Han Y, Chen Y, Shen H, Zeng S, Cai C. Tumor metabolic regulators: key drivers of metabolic reprogramming and the promising targets in cancer therapy. Mol Cancer 2025; 24: 7.
4. Ouyang C, Huang J, Huang G, Wang Y. Dendritic cell immunometabolism-a potential therapeutic target for allergic diseases. Int J Med Sci 2025; 22: 417-431.
5. Chen Y, Lin Q, Cheng H, Xiang Q, Zhou W, Wu J, Wang X. Immunometabolic shifts in autoimmune disease: Mechanisms and pathophysiological implications. Autoimmun Rev 2024; 24: 103738.
6. Fan X, Yang M, Lang Y, Lu S, Kong Z, Gao Y, Shen N, Zhang D, Lv Z. Mitochondrial metabolic reprogramming in diabetic kidney disease. Cell Death Dis 2024; 15: 442.
7. Zhang B, Guan Y, Zeng D, Wang R. Arginine methylation and respiratory disease. Transl Res 2024; 272: 140-150.
8. Lu W, Wen J. Metabolic reprogramming and astrocytes polarization following ischemic stroke. Free Radic Biol Med 2025; 228: 197-206.
9. Chen X, Huang X, Zhang X, Chen Z. Metabolism-epigenetic interaction-based bone and dental regeneration: from impacts and mechanisms to treatment potential. Bone 2024; 192: 117382.