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A guide to immunometabolism for immunologists - Evidence review

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1. ABSTRACT

The analyzed publication is a review on immunometabolism, which is the study of how processes that produce and use energy within immune cells modify their function. The goal was to summarize six major metabolic pathways and explain how their products can influence immune responses. Since only the abstract is available, the full text does not allow for a detailed verification of literature selection methods, included studies, or quantitative results.In section 6.1 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the narrative that pro-inflammatory M1 macrophages favor glycolysis, while those activated by M2-type repair signals show greater mitochondrial respiration and fatty acid utilization. Independent studies confirm the link between glycolysis and pro-inflammatory activation and document the association between M2 programs and oxidative metabolism. However, genetic and pharmacological studies indicate that long-chain fatty acid oxidation is not always essential for M2 activation. The synthesis is therefore biologically consistent, but it should not be read as a rigid rule applicable to all tissues and conditions.

ONLINE ARTICLE

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MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The research question of the publication was how changes in intracellular metabolic pathways can modify the behavior of immune cells. The general hypothesis is that metabolism does not only serve to produce energy, but also contributes to deciding whether an immune cell initiates an inflammatory response, defends the organism, or promotes the repair and resolution of inflammation.This point is relevant to the book's paragraph because the cited sentence attributes different metabolic profiles to macrophages in relation to their functional state: higher glycolysis in the M1 profile and higher oxidative phosphorylation and fatty acid oxidation in the M2 profile. The publication subject to the Evidence Review is a narrative review, not a single clinical or laboratory experiment. It can therefore frame and interpret a body of knowledge, but it cannot, on its own, demonstrate a causal relationship in humans.In the available material, which consists only of the abstract, the authors describe immunometabolism as the set of changes in intracellular metabolic pathways that alter the function of immune cells. However, the abstract does not specifically report the M1-M2 comparison cited in the book. This passage is consistent with the general theme of the review, but its detailed discussion is not verifiable in the available material.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a narrative scientific review. The abstract indicates that the authors have organized the discussion around six main metabolic pathways: glycolysis, the tricarboxylic acid cycle or Krebs cycle (a series of reactions that derive energy from nutrients), the pentose phosphate pathway, fatty acid oxidation, fatty acid synthesis, and amino acid metabolism.No participant population, sample size, control group, intervention, follow-up, or clinical endpoint is described. This information is not provided in the available material. Furthermore, the bibliographic search criteria, databases consulted, study inclusion criteria, or a formal risk of bias assessment are not reported. For this reason, it cannot be considered a systematic review or a meta-analysis.The approach consists of presenting examples of how metabolites and energy pathways can influence the immune system response. The goal is conceptual and interpretive: to integrate knowledge derived from cellular and animal experiments and, when available, from human observations.

4. RESULTS

The central finding reported in the abstract is that immune function and cellular metabolism are closely interconnected. In simple terms, an immune cell does not just change the genes it activates when it receives a signal: it also changes the way it uses sugars, fats, and amino acids. These changes can help determine what type of response the cell carries out.The authors identify six relevant metabolic pathways and emphasize that specific metabolites can shape the immune response. The abstract does not report numerical values, effect sizes, statistical tests, the number of experiments, or separate results for M1 and M2 macrophages. Consequently, such data are not reported in the available material.For the book passage, the relevant point is the general concept of metabolic reprogramming: glycolysis is the pathway that rapidly transforms glucose into simpler compounds and can support immediate responses; oxidative phosphorylation is the mitochondrial process that uses oxygen to produce ATP, the cell's main energy molecule; fatty acid oxidation derives energy from fats. However, the available abstract does not allow for attributing specific experimental data on the prevalence of these pathways in the two macrophage phenotypes to the publication.

5. INTERPRETATION

The biological significance of this narrative is that macrophages can adapt their “feeding mode” to the task they are performing. A macrophage rapidly confronting microorganisms or damage signals may increase its reliance on glycolysis. A macrophage stimulated by interleukin-4, often used in the laboratory as a model of alternative or M2 activation, may instead increase mitochondrial activity and metabolic programs associated with tissue repair.The segment of the chain supported by the publication that is the subject of the Evidence Review is the general principle: changes in intracellular metabolic pathways contribute to modifying immune cell function. The sentence in the book applies this

principle to M1 and M2 macrophages. However, the M1 and M2 labels are experimental simplifications useful for describing functional extremes; in human tissues, macrophages can exhibit intermediate characteristics that depend on the local environment.The formulation stating that M1 predominantly uses glycolysis and M2 uses oxidative phosphorylation and fatty acid oxidation is a useful description of the classic model, but it does not equate to proving that a single metabolic pathway always causes a specific phenotype. The relationship can change based on the stimulus, the duration of activation, the tissue, the availability of nutrients, and the species studied.

6. INDEPENDENT SUPPORTING EVIDENCE

Direct confirmation of the pro-inflammatory aspect comes from Haschemi and colleagues, who studied primary murine macrophages, a macrophage cell line, and human cells exposed to inflammatory signals. Stimulation with lipopolysaccharide, a bacterial component used to induce an M1-like profile, increased extracellular acidification—an indirect indicator of glycolysis—and reduced oxygen consumption, an indicator of mitochondrial respiration. Interfering with specific steps of glucose metabolism reduced the production of the pro-inflammatory cytokines TNF-alpha and IL-6. This study confirms the passage in the book stating that the M1 profile is associated with a prevalence of glycolysis, although it remains primarily experimental evidence from cells and animals [1].Regarding the M2 aspect, Vats and colleagues analyzed macrophages stimulated with interleukin-4 and murine models. The reparative signal induced programs associated with mitochondrial biogenesis—that is, the formation and enhancement of mitochondria—and fatty acid oxidation. Experimentally increasing PGC-1beta, a regulator of mitochondrial energy production, promoted alternative activation characteristics and reduced the production of pro-inflammatory cytokines; conversely, hindering oxidative metabolism or reducing PGC-1beta attenuated this response. The result is consistent with the part of the book's sentence regarding oxidative phosphorylation and fat metabolism in the M2 program [2].Huang and colleagues reinforced the idea that M2 activation requires coordinated metabolic reprogramming, not just a single energy source. In mouse macrophages treated with interleukin-4, alternative activation was accompanied by increased fatty acid oxidation and oxidative phosphorylation, but also by greater glucose utilization. The loss of mTORC2, a protein complex that integrates growth and nutrient signals, reduced glycolysis and markers of M2 activation. This confirms that the M2 program can have a mitochondrial and lipid component, but it also shows that glucose remains important; the contrast between glycolytic M1 and exclusively oxidative M2 is therefore incomplete [3].Taken together, these works support a coherent chain: immune or repair stimulus metabolism reprogramming modification of macrophage functions. The confirmation is more robust in cellular systems and murine models than in humans. None of these studies demonstrate that modifying diet or a single metabolite automatically produces a useful conversion of macrophages in people with chronic diseases.

7. CONFLICTING EVIDENCE

The conflicting evidence primarily concerns the stronger claim implied in the book's statement: that fatty acid oxidation is necessary for the M2 phenotype. Divakaruni and colleagues tested this hypothesis in murine macrophages activated by interleukin-4, combining pharmacological inhibition and genetic inactivation of enzymes essential for the mitochondrial oxidation of long-chain fatty acids.At low concentrations, etomoxir inhibited the intended metabolic target without reducing M2 activation markers. Furthermore, macrophages lacking CPT1a or CPT2, enzymes required to utilize long-chain fatty acids in the mitochondria, maintained markers of interleukin-4-induced polarization. At high concentrations that blocked M2 activation, etomoxir also acted through non-specific effects, including the alteration of coenzyme A availability. The authors therefore concluded that the oxidation of long-chain fatty acids and oxidative phosphorylation were largely dispensable in their M2 activation model [4].This result does not deny that M2 macrophages can exhibit increased fatty acid oxidation or mitochondrial respiration. However, it indicates that an observed increase does not automatically demonstrate a causal necessity. The discrepancy also depends on the difference between measuring a metabolic profile

associated with a phenotype and demonstrating that a specific pathway is essential to produce it. Therefore, the part of the narrative relating to metabolic association remains well-supported, while the idea of an obligatory dependence on fatty acid oxidation requires caution.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the conceptual synthesis of the original study from independent research that confirms or defines the scope of the paragraph's narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature synthesis on immunometabolism	Describes the principle that intracellular metabolic pathways modify immune functions.	biologically consistent evidence	moderate
[1]	Cellular and experimental observational	Primary murine macrophages, RAW264.7 line, and human cells	M1-like stimulation increases glycolysis and reduces mitochondrial respiration; blocking glucose metabolism steps reduces TNF-alpha and IL-6.	direct confirmation	moderate
[2]	Cellular and animal	Interleukin-4 stimulated macrophages and murine models	The alternative activation program increases oxidative metabolism and fatty acid oxidation; hindering them attenuates M2 characteristics.	direct confirmation	moderate
[3]	Cellular and animal	Murine macrophages, mice with selective mTORC2 alteration	M2 activation increases fatty acid oxidation and oxidative phosphorylation, but also requires greater glucose use.	indirect confirmation	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication correctly frames the principle that metabolism and immunity are linked. Independent evidence confirms that glycolysis is closely associated with pro-inflammatory macrophage programs and that alternative activation can be accompanied by increased mitochondrial activity and lipid metabolism. The framework is therefore moderately supported on a mechanistic level.The main limitation concerns simplification. Macrophages do not exist only in two fixed states, and their metabolism varies according to tissue, stimulus, duration of the response, and nutrient availability. In particular, the increase in fatty acid oxidation in M2 macrophages does not prove that this pathway is always essential for their phenotype. Further validation in humans and in different pathological contexts is required.

Aggiornato al 24/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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