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The HIF-1a-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether T-cell metabolism contributes to determining which immune function the cell will adopt. Using experimental conditions that favored the differentiation of Th17 cells or regulatory T cells (Treg), the authors observed that conditions favoring Th17 increased glycolysis and HIF-1a expression. Blocking glycolysis reduced Th17 formation and increased Treg formation; HIF-1a deficiency reduced Th17, increased Treg, and protected mice from experimental autoimmune neuroinflammation.In section 6.2 and section 11.6 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that mTOR promotes HIF-1a, glycolysis, and an effector immune program. Independent evidence confirms, especially in cellular and murine models, the link between HIF-1a, the Th17 program, and experimental neuroinflammation. However, data on human cells indicate that some effects are context-dependent, so direct extension to human multiple sclerosis remains cautious.

ONLINE ARTICLE

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2. ANALYZED STUDY

The research question was whether the shift of activated T cells toward a more glycolytic metabolism—that is, a rapid use of glucose to produce energy and cellular materials—plays a role in the choice between two different immune fates: Th17 cells, generally associated with inflammatory responses, and Treg cells, which help limit excessive immune activation.The hypothesis was that HIF-1α (hypoxia-inducible factor, a protein that regulates the activity of many metabolic genes) acts downstream of mTOR, a protein complex that integrates signals from nutrients, growth, and cellular activation. The publication is relevant to the provided sections of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi because it documents the mTOR HIF-1α glycolysis segment increased Th17 differentiation and decreased Treg differentiation.The study can demonstrate a functional relationship in experimental T cell systems and in mice. However, it cannot prove that this sequence is the sole cause of multiple sclerosis in humans, nor can it establish that the inhibition of HIF-1α constitutes an effective or safe treatment for people with this disease.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

Only the abstract is available in the provided material. The study compared experimental conditions capable of promoting T-cell differentiation toward either the Th17 program or the Treg program. The authors evaluated glycolytic activity, the induction of glycolysis enzymes, and the expression of HIF-1α. They also blocked glycolysis and assessed the consequences on cell fate.To study the role of HIF-1α, cells lacking this factor were examined, as well as mice in which its absence was associated with protection against experimental autoimmune neuroinflammation. The abstract also reports that the induction of HIF-1α required mTOR signaling. Sample sizes, animal selection criteria, reagent concentrations, detailed analytical techniques, primary endpoints, the experimental period, and statistical methods are not reported in the available material.

4. RESULTS

The main finding is that conditions inducing Th17 cells, but not those inducing Treg cells, markedly increased glycolysis activity and the expression of glycolytic enzymes. In simple terms, cells directed toward an inflammatory function more intensely adopted a rapid metabolic mode, which is useful for supporting growth and effector activity. Absolute values, percentage variations, and P-values are not reported in the available material.Blocking glycolysis reduced the development of Th17 cells and increased the generation of Treg cells. HIF-1α was found to be selectively expressed in Th17 cells, and its induction required mTOR signaling. Furthermore, the absence of HIF-1α reduced Th17 differentiation, increased Treg differentiation, and protected mice from experimental autoimmune neuroinflammation.The data most relevant to the book is therefore directional and consistent: when the mTOR-HIF-1α-glycolysis program fails, the Th17 program decreases and the Treg program increases. The abstract does not report direct measurements of GLUT1, the glucose transporter mentioned in paragraph 6.2, nor quantitative data on the expression of individual glycolytic enzymes. However, it does report an overall increase in glycolytic activity and the induction of glycolysis enzymes under Th17 conditions.

5. INTERPRETATION

For a T cell, choosing glycolysis does not just mean obtaining energy quickly. It also means having materials available to grow, multiply, and produce molecules involved in the immune response. The study suggests that HIF-1α helps link this metabolic change with the choice to become a Th17 cell rather than a Treg cell.The segment directly documented by the publication subject to the Evidence Review is mTOR HIF-1α increased glycolysis greater Th17 differentiation and lower Treg differentiation. This supports the part of the narrative in “The Choice to Live Healthy or in Sickness” by Dr. A. Colonnese and R. Panzironi regarding the role of HIF-1α as a link between metabolic signals and effector immune function.The interpretation that this pathway constitutes a determining mechanism of central nervous system autoimmunity is plausible in the mouse model, because the loss of HIF-1α protected

against experimental neuroinflammation. However, it remains an interpretation that cannot be automatically transferred to human multiple sclerosis: the disease in humans is more heterogeneous and involves many cells, signals, and pathological stages.

6. INDEPENDENT SUPPORTING EVIDENCE

Independent confirmation of the link between HIF-1α and the Th17/Treg imbalance comes from Dang and colleagues. In murine T cells subjected to differentiation conditions, HIF-1α increased the Th17 program by activating the transcription of RORγt, the master regulator of Th17 specialization. The same study observed that HIF-1α can promote the degradation of FOXP3, a protein essential for Treg identity. The result confirms the HIF-1α increased Th17 program and decreased Treg program pathway, with cellular and animal mechanistic evidence. The limitation is that it does not prove the role of glycolysis on its own, nor does it describe multiple sclerosis in humans [1].Ikejiri and colleagues examined the role of oxygen availability in murine T cell differentiation. In a model involving an activation phase at 5% oxygen followed by reoxygenation, mTORC1 activation and Th17 differentiation increased. In the absence of HIF-1α, this increase in mTORC1 and Th17 differentiation was not observed. The study therefore supports the mTORC1 HIF-1α Th17 pathway and shows that the microenvironment can modify the intensity of the circuit. The limitation is that this is a murine cellular model with artificially controlled oxygen conditions [2].Further confirmation downstream in the chain comes from Shin and colleagues. The authors used a protein in mice designed to hinder the transcriptional activity of HIF-1α in the nucleus. In naive T cell cultures, the treatment dose-dependently reduced Th17 differentiation and the expression of IL-17A and RORγt. In mice with experimental autoimmune encephalomyelitis, a model of neuroinflammation, the treatment attenuated the disease. This result is consistent with the HIF-1α Th17 program experimental neuroinflammation link. However, it does not demonstrate clinical efficacy in humans, and the experimental molecule does not correspond to an established therapy [3].Overall, independent studies reconstruct a convergent chain: mTORC1 can promote HIF-1α under specific environmental conditions; HIF-1α can strengthen the Th17 molecular program and reduce the Treg program; its modulation can attenuate neuroinflammation in murine models. The confirmation is robust at the mechanistic level, but it does not equate to a clinical demonstration in multiple sclerosis.

7. CONFLICTING EVIDENCE

The direction of the effect of HIF-1α is not identical in every experimental model. Bollinger and colleagues studied primary human T cells and found that the pharmacological activation or inhibition of HIF-1α did not modify Th17 commitment as assessed by RORγt, unlike what is often observed in murine models. Under the same conditions, HIF-1α activation increased IL-17A secretion, and its inhibition reduced it in a dose-dependent manner. Furthermore, hypoxia reduced the suppressive capacity of human natural Tregs [4].These data do not negate the role of HIF-1α in the Th17 program, but they indicate that the effects may differ between species, T-cell subtypes, oxygen conditions, and methods of factor manipulation. The distinction is important: an increase in IL-17A does not necessarily coincide with an increase in Th17 differentiation, and results obtained in mice cannot be automatically considered applicable to human cells. No directly conflicting evidence sufficiently relevant to the specific result of the original study regarding protection against experimental autoimmune encephalomyelitis has been identified; this does not prove the absence of contrary findings.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from the independent research used to confirm or define the book's narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and animal	T cells and mice	mTOR promoted HIF-1α and glycolysis; loss of HIF-1α reduced Th17, increased Treg, and protected against experimental neuroinflammation	direct confirmation	moderate
[1]	Cellular and animal	Murine T cells and mouse models	HIF-1α increased RORγt and the Th17 program, also promoting FOXP3 degradation	direct confirmation	moderate
[2]	Cellular and animal	Murine CD4+ T cells under controlled oxygen conditions	mTORC1 activation and increased Th17 differentiation were dependent on HIF-1α	direct confirmation	moderate
[3]	Cellular and animal	Murine T cells and mice with experimental autoimmune encephalomyelitis	Functional inhibition of HIF-1α reduced Th17 and attenuated experimental neuroinflammation	indirect confirmation	moderate
[4]	Cellular	Human primary T cells	HIF-1α modulation altered IL-17A but not Th17 commitment as assessed by RORγt; hypoxia reduced Treg-mediated suppression	discordant evidence	preliminary

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study clearly supports, within the available experimental systems, that HIF-1α links the metabolic regulation of T cells to their differentiation toward a Th17 profile rather than a Treg one. The relationship with mTOR and glycolysis is confirmed by independent evidence, primarily from cellular and murine models. The link to neuroinflammation is supported in experimental autoimmune encephalomyelitis models. However, extending these findings to human multiple sclerosis requires clinical validation and studies that distinguish between cell subtypes, tissue microenvironments, and disease stages.

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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