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mTOR promotes an inflammatory response through the HIF1 signaling pathway in ulcerative colitis - Evidence review

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1. ABSTRACT

The original study evaluated whether mTOR, a cellular regulator sensitive to nutrients and growth signals, influences inflammation via HIF-1a in a co-culture model consisting of HT-29 intestinal epithelial cells and human CD4+ T lymphocytes exposed to TNF-a. Experimental increase of mTOR was associated with more HIF-1a, increased glycolysis, more Th17 cells, fewer Treg cells, and a more pro-inflammatory mediator profile. Silencing mTOR produced variations in the opposite direction.The research contributes to the narrative of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, according to which the mTOR-HIF-1a axis can reprogram immune cell metabolism and shift the balance between Th17 and Treg cells toward a more inflammatory response. Independent studies on T cells and mouse models support the mTOR-HIF-1a-glycolysis and HIF-1a-Th17/Treg segments. However, the original model does not demonstrate a causal relationship in humans with ulcerative colitis, and HIF-1a may have protective functions in the intestinal epithelium.

ONLINE ARTICLE

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2. ANALYZED STUDY

The research question was whether mTOR can regulate, through HIF-1a, the metabolism and fate of T lymphocytes in an experimental context that reproduces certain inflammatory signals in the gut. mTOR is a protein complex that integrates nutrient availability and growth signals; HIF-1a is a transcription factor, meaning a protein that modifies the activity of numerous genes. The authors hypothesized that an increase in mTOR promotes HIF-1a, glycolysis, and differentiation toward Th17 cells, while simultaneously reducing regulatory T cells, or Tregs.This is the point for which the publication is relevant to sections 6.2 and 10.6 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi: it experimentally documents the segment mTOR HIF-1a glycolysis Th17/Treg imbalance inflammatory signals. However, it does not demonstrate that the entire sequence occurs in the same way in the mucosa of patients with ulcerative colitis, nor that inhibiting mTOR is an effective or safe treatment for such patients.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors created a co-culture, a system in which different cell types are grown together, using HT-29 colon adenocarcinoma epithelial cells and human CD4+ T lymphocytes. The cultures were exposed to TNF-α, a cytokine—a signal produced by the immune system—that promotes inflammation.mTOR was manipulated in two directions: silencing, to reduce its expression, and overexpression, to increase it. HIF-1α, glycolysis, the proportion of Th17 and Treg cells, and the levels of pro-inflammatory and anti-inflammatory factors were evaluated. The number of cultures, the number of independent experiments, the technical methods for silencing and overexpression, the markers analyzed, the TNF-α concentrations, the statistical procedures, and the significance values are not reported in the available material. There is no clinical follow-up, as this is not a study on patients.

4. RESULTS

Under TNF-a stimulation, the co-culture showed an increase in HIF-1a in CD4+ T lymphocytes. This increase was accompanied by greater glycolysis, the process by which the cell rapidly derives energy from glucose, a higher proportion of Th17 cells, and a lower proportion of Treg cells. Pro-inflammatory factors also increased, while anti-inflammatory factors decreased.When mTOR was silenced, HIF-1a and glycolysis decreased. In the same vein, Th17 differentiation and pro-inflammatory components decreased, while anti-inflammatory components increased. mTOR overexpression produced opposite results: an increase in HIF-1a, glycolysis, Th17 levels, and pro-inflammatory factors, with a reduction in Treg cells and anti-inflammatory factors.The data most relevant to the book is therefore the coordinated variation observed in the cellular model: more mTOR was accompanied by more HIF-1a and glycolysis, a greater relative presence of Th17 cells, and a more intense inflammatory profile; less mTOR was accompanied by the opposite profile. The abstract does not report absolute values, percentages, confidence intervals, or P-values. It is therefore not possible to estimate the quantitative magnitude of the effects or their statistical precision from the available material.

5. INTERPRETATION

In simple terms, the results indicate that, in this model, mTOR can contribute to putting T cells into a rapid-response, high-glucose-demand mode. This mode is associated with an increase in Th17 cells, which are generally involved in defense but also in many inflammatory responses, and a reduction in Treg cells, which are cells that help limit excessive immune activation.The directly documented segment is mTOR HIF-1α glycolysis shift in the Th17/Treg balance and inflammatory mediators. The result is biologically consistent with the known role of HIF-1α in promoting glycolytic metabolic programs and with T cell specialization. However, the system uses HT-29 tumor cells and laboratory-cultured immune cells, not intestinal biopsies or people with ulcerative colitis. Therefore, it demonstrates an experimental in vitro relationship, but it does not establish the weight of this circuit in human disease nor the therapeutic efficacy of an mTOR inhibitor.

6. INDEPENDENT CONFIRMING EVIDENCE

Independent confirmation of the link between mTOR, HIF-1α, glycolysis, and T-cell fate determination comes from a study on murine T cells and mice. Under conditions favoring Th17 cells, glycolysis increased more than under conditions favoring Treg cells. Blocking glycolysis reduced Th17 development and increased Treg generation. HIF-1α was particularly expressed in Th17 cells, and its induction required mTOR signaling; its absence reduced Th17 cells, increased Treg cells, and protected mice from an experimental autoimmune disease [1]. This evidence directly confirms, in a mouse model, the mechanistic core of the sequence described in the book. The limitation is that it does not concern human ulcerative colitis.A second independent study further clarified the HIF-1α Th17/Treg pathway. In T cells and mice with a deletion of HIF-1α in CD4+ lymphocytes, the absence of the factor reduced the production of interleukin-17 and increased Treg cells expressing FOXP3, a protein essential for their regulatory function. The animals were also more resistant to a model of autoimmune neuroinflammation [2]. The work therefore supports the direction observed in the original study: lower HIF-1α activity can shift the balance away from Th17 cells and toward Treg cells. This remains a neurological autoimmune model, not an intestinal one.The part of the narrative regarding experimental colitis finds complementary confirmation in a study on mice with dextran sulfate sodium-induced colitis and on RAW264.7 macrophages. Dioscin improved signs of colitis in mice, reduced macrophage polarization toward the pro-inflammatory M1 phenotype, and increased the M2 phenotype. In cells, these changes were associated with a reduction in mTORC1/HIF-1α and glycolysis. Leucine, an activator of mTORC1, attenuated the inhibition of the M1 program and blocked the benefit observed in mice [3]. This research does not directly validate the Th17/Treg ratio, but it confirms in the same general pathological context that the reduction of the mTORC1-HIF-1α axis and glycolysis can be accompanied by reduced intestinal inflammation. The main limitation is the use of a mouse model and a compound with potential multiple targets.

7. CONFLICTING EVIDENCE

There is significant evidence of cell-type dependency. In a mouse model of TNBS-induced colitis, the deletion of HIF-1a in intestinal epithelial cells was associated with more severe symptoms, whereas persistent activation of HIF-1 in the epithelium reduced weight loss, colon shortening, and intestinal barrier permeability [4]. In other words, HIF-1 may promote inflammatory signals in immune cells but support barrier function in the cells lining the intestine.This evidence does not refute the result of the original study, which primarily evaluated T lymphocytes in co-culture, but it limits the notion that HIF-1a is uniformly harmful in colitis. The practical consequence for interpretation is that mTOR and HIF-1a should not be considered switches with a single effect: their function depends on the cell involved, the model of colitis, and the balance between immune inflammation and barrier repair.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the cellular model that is the subject of the Evidence Review from independent publications that confirm or define the biological chain.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental cellular	HT-29 co-culture and human CD4+ T cells exposed to TNF-a	mTOR overexpression associated with increased HIF-1a, glycolysis, Th17, and pro-inflammatory signals; silencing shows opposite direction	direct confirmation	moderate
[1]	Cellular and animal	Murine T cells and mice	mTOR supports HIF-1a and glycolysis; blocking glycolysis reduces Th17 and increases Treg	direct confirmation	moderate
[2]	Cellular and animal	CD4+ T cells and HIF-1a deficient mice	HIF-1a deficiency reduces Th17 and increases Treg	direct confirmation	moderate
[3]	Animal and cellular	Mice with DSS-induced colitis and RAW264.7 macrophages	Reduction of mTORC1/HIF-1a and glycolysis associated with lower M1 polarization and less severe colitis	biologically consistent evidence	moderate
[4]	Animal	Mice with TNBS-induced colitis and HIF-1a manipulation in the intestinal epithelium	Epithelial HIF-1 reduces barrier loss and is associated with less severe colitis	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed maintains, in a controlled cellular system, that an increase in mTOR can strengthen a metabolic and immune program associated with more HIF-1α, increased glycolysis, an increase in Th17 cells, a reduction in Treg cells, and higher inflammatory signals. This narrative is confirmed at a mechanistic level by independent research on T cells and murine models of inflammation and colitis. However, its translation to human ulcerative colitis requires validation in patient samples and clinical trials, not least because HIF-1α can have protective effects in the intestinal epithelium.

Aggiornato al 25/11/2026. 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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