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Metabolism controls the balance of Th17/regulatory T cells - Review of the evidence

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1. ABSTRACT

The publication analyzed is a narrative review examining how cellular metabolism contributes to steering the balance between regulatory T cells (Treg), which limit excessive immune responses, and Th17 cells, which participate in inflammation. The relevant passage from “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi primarily concerns AMPK, a protein that is activated when energy availability is reduced and which can promote the use of fatty acids as fuel.The review does not produce new experimental data, but synthesizes cellular and animal studies suggesting that Tregs tend to rely more on fatty acid oxidation, while effector cells, including Th17 cells, often show a greater dependence on glycolysis. Independent studies support this metabolic relationship and show that certain pharmacological activators of AMPK can increase Tregs and reduce Th17 cells in experimental models. However, genetic studies indicate that eliminating AMPK does not necessarily alter the choice between Tregs and Th17 cells. The narrative is therefore supported primarily at a mechanistic and preclinical level, not as an absolute rule demonstrated in humans.

ONLINE ARTICLE

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MISSION

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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 question addressed by the publication is whether the way a T cell produces and uses energy helps determine its immune function. The central hypothesis is that different metabolic programs favor different subtypes: Th17 cells, which are generally pro-inflammatory, are thought to be more dependent on glycolysis, while Tregs, which contribute to immune tolerance, are thought to make greater use of fatty acid oxidation.The specific reason why this research was cited in section 6.3 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is the segment of the chain according to which AMPK, a sensor of reduced energy availability, promotes a metabolism oriented toward lipid oxidation. The publication links this metabolic program to Tregs and contrasts this state with the increased glycolysis observed in Th17 cells.Since this is a narrative review, the study analyzed does not directly measure the effect of fasting, nor does it demonstrate that the activation of AMPK in a person automatically produces immune tolerance or turns off clinically relevant inflammation. Its contribution is to reconstruct a plausible biological relationship between energy availability, cellular metabolism, and the functions of specific T lymphocyte subtypes.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

This publication is a review of scientific literature, not an experimental study involving participants, animals, or samples recruited directly by the authors. The text integrates previous research conducted on laboratory-cultured T cells, murine cells, animal models of inflammation, and, to a more limited extent, human cells.The authors discuss glycolysis, the rapid process by which cells derive energy from glucose; mitochondrial oxidative phosphorylation, the production of energy within mitochondria; and fatty acid oxidation, the use of lipids as an energy source. They also describe mTOR, a kinase that integrates nutrient and growth signals, and AMPK, a kinase activated under conditions of lower energy availability.No systematic bibliographic research protocol is reported, no formal inclusion or exclusion criteria for studies are defined, the total number of evaluated publications is not indicated, and there is no quantitative meta-analysis. This information limits the ability to estimate how complete the selection of evidence was or whether it was free from subjective bias.

4. RESULTS

The central finding of the review is that T cells do not all use the same energy program. In simple terms, cells that need to grow and act rapidly tend to consume glucose quickly; cells dedicated to controlling the immune system response can instead make more intensive use of lipid fuels. The text attributes higher glycolytic activity to Th17 cells and a greater reliance on fatty acid oxidation to Treg cells.In the segment relevant to the book, the review reports that AMPK reduces energy-consuming cellular processes and promotes those that produce it. Among these is fatty acid oxidation. The authors also describe a functional antagonism between AMPK and mTOR: AMPK can reduce mTOR activity, while mTOR promotes programs associated with glycolysis and the differentiation of effector cells.The publication reports that the pharmacological activation of AMPK with metformin or other compounds has been associated, in some mouse models, with a reduction in the Th17:Treg ratio. However, it also reports an important limitation: the results obtained with pharmacological activators and those obtained by genetically deleting AMPK are not entirely consistent. It does not present new numerical values, samples, confidence intervals, or statistical analyses of its own, because it is not an original experimental study.

5. INTERPRETATION

In common parlance, AMPK can help a cell manage a phase of reduced energy availability. Instead of favoring rapid and costly programs, it can promote pathways capable of extracting energy from fats. In T cells, this configuration has been linked primarily to Tregs, cells that help limit excessive immune responses.The scientific detail is that AMPK can promote fatty acid oxidation and counteract signals regulated by mTOR. The publication that is the subject of the Evidence Review therefore links the transition "AMPK oxidative lipid metabolism Treg program" to the narrative in the book's paragraph. The opposite relationship, "mTOR glycolysis effector cells, including Th17," is described as part of the same

metabolic balance.This does not mean that AMPK is a simple switch that always transforms a Th17 cell into a Treg cell. Lymphocyte differentiation also depends on antigens, cytokines, tissue, duration of the stimulus, and nutrient availability. Furthermore, most of the evidence discussed comes from cells and rodents; the clinical significance in humans requires specific verification.

6. INDEPENDENT CONFIRMING EVIDENCE

Direct confirmation of the link between metabolism and T-cell subtype function comes from an experimental study on murine T cells. Th1, Th2, and Th17 effector cells showed higher levels of the glucose transporter Glut1 and increased glycolysis, while Tregs showed higher lipid oxidation and AMPK activity. In mice genetically modified to increase Glut1, effector cells selectively increased; Tregs, by contrast, were found to be dependent on lipid oxidation. The study supports the passage in the book that contrasts a glycolytic program in effector cells with a more lipid-oriented program in Tregs, but this remains preclinical evidence [1].A second study evaluated AICAR, an AMP analog that directly activates AMPK, in cell cultures and mice. AICAR increased Treg induction by enhancing their expansion and reduced the generation of Th17 cells. The authors also observed an increase in fatty acid uptake and mitochondrial biogenesis. When fatty acid oxidation was inhibited, the increase in Tregs induced by AICAR was reversible. This experiment mechanistically supports the sequence of AMPK activation increased lipid use increased Tregs; however, it does not prove that every drug that influences AMPK produces the same effect [2].A third study, in a mouse model of intestinal inflammation, found that treatment with metformin increased phosphorylated AMPK—the activated form of the enzyme—and Foxp3, the main factor that identifies Tregs. In the same model, phosphorylated mTOR, phosphorylated STAT3, and interleukin-17—signals associated with the Th17 response—decreased, along with indices of colitis severity. The result is biologically consistent with the book's paragraph, but metformin has multiple cellular targets, and the study cannot attribute every observed effect exclusively to AMPK [3].

7. CONFLICTING EVIDENCE

A significant element of caution comes from a genetic study in which AMPK was selectively deleted in the T cells of mice. In in vitro cultures, the absence of AMPK did not substantially alter differentiation into Th1, Th2, Th17, or Treg cells; nor was the suppressive capacity of Tregs compromised. In animals, however, T cells lacking AMPK showed lower overall expansion and reduced metabolic activity during the immune response [4].These results do not deny that AMPK participates in the energy management of lymphocytes, but they indicate that it is not necessarily the sole determinant of the choice between Treg and Th17 cells. The discrepancy with some pharmacological studies may depend on the model, the timing of stimulation, compensation by other metabolic pathways, and the additional effects of the molecules used. No sufficiently relevant directly conflicting evidence has been identified in humans; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent research used to confirm or define the metabolic pathway discussed in the paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature on T cells, murine models, and limited human data	Describes the link between AMPK, fatty acid oxidation, Tregs, glycolysis, and Th17.	biologically consistent evidence	moderate
[1]	Cellular and animal	Murine CD4+ T cells and Glut1 transgenic mice	Tregs show higher lipid oxidation and AMPK activity; effector cells are more glycolytic.	direct confirmation	moderate
[2]	Cellular and animal	T cells and mice subjected to immune stimulation	AICAR increases Treg induction, reduces Th17, and requires fatty acid oxidation.	direct confirmation	moderate
[3]	Animal and cellular	Murine model of colitis and cultured human intestinal cells	Metformin increases p-AMPK and Foxp3, reduces p-mTOR, p-STAT3, IL-17, and colitis severity.	indirect confirmation	moderate
[4]	Cellular and animal	Mice with selective deletion of AMPK in T cells	The absence of AMPK reduces cell expansion but does not stably alter the choice between Treg and Th17.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the section of the book regarding AMPK as a metabolic regulator associated with fatty acid oxidation and Tregs. Independent evidence confirms that Tregs and effector cells often possess different energy programs and that pharmacological activation of AMPK can shift the balance toward a more regulatory profile in experimental models.The most prudent conclusion is that this narrative is well-supported at the mechanistic and preclinical level. However, it is not proven that reducing nutrients, fasting, or taking AMPK-activating drugs automatically produces the same immune effect in people. The role of AMPK depends on the cell type, tissue, immune stimulus, and other active metabolic pathways.

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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