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Regulation and function of mTOR signaling in T cell fate decisions - Evidence review

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1. ABSTRACT

The analyzed publication is a narrative review on the mechanisms by which mTOR, a kinase that coordinates nutrient availability and immune signals, participates in the maintenance, activation, and differentiation of T cells. Only the abstract is available in the provided material; therefore, a structured literature search, study selection criteria, or original quantitative results are not reported.In section 6.3 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that AMPK, a sensor of low energy availability, can inhibit mTORC1 via TSC2 and promote conditions compatible with immune tolerance. Independent studies confirm the AMPK-TSC2-mTORC1 molecular pathway and show, in mouse models, that metabolic programs associated with AMPK can increase the generation of regulatory T cells. However, other experiments indicate that mTORC1 is necessary for the full function of already formed regulatory T cells. The chain is therefore well-supported at a mechanistic level, but requires caution when extended to immune tolerance 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 research question of the publication was to understand how mTOR, the mechanistic target of rapamycin, integrates signals received by T cells with the availability of energy and nutrients. T cells are white blood cells that can transform into subtypes with different tasks: some support the response against infections or other dangers, while others help limit it to prevent excessive reactions.The general hypothesis illustrated is that antigen recognition and metabolic signals activate mTOR, guiding T cells toward different functional fates. This makes the publication relevant to section 6.3 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi: the book describes mTOR and AMPK as metabolic regulators with opposite effects on the immune system.The contribution verifiable from the abstract alone is primarily conceptual: mTOR links metabolism, activation, and differentiation of T cells. The available abstract does not directly report experiments on the phosphorylation of TSC2 by AMPK. Therefore, the analyzed study cannot, based on the accessible material, quantitatively demonstrate that specific molecular step nor establish clinical effects in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a narrative scientific review, not an experimental study involving participants, animals, or proprietary cell cultures. The available material consists exclusively of the abstract. The literature search protocol, databases consulted, search timeframes, inclusion and exclusion criteria, number of selected articles, or a formal risk of bias assessment are not reported.The authors state that the review focuses on mTOR signaling mechanisms in homeostasis and the functional fates of T cells, also discussing the potential implications of pharmacological targeting of mTOR. This information does not equate to a systematic review: it indicates the topic covered, but does not allow for quantifying the completeness of the evidence selection.

4. RESULTS

The main biological message is that a T cell does not determine its function solely based on the immune signal received: it also assesses whether it has the necessary resources to grow and multiply. According to the abstract, mTOR plays this role of integrating immune and metabolic signals.Under equilibrium conditions, multiple inhibitory mechanisms control mTOR activity and contribute to the homeostasis of T cells, that is, the maintenance of an appropriate number and function of these cells. After the recognition of an antigen by naive CD4-positive or CD8-positive T cells, mTOR is activated and programs differentiation into functionally distinct cell lineages.The abstract does not report sample sizes, P-values, effect sizes, dosages, quantitative comparisons, or original experimental results. Furthermore, it does not explicitly report the phosphorylation of TSC2 by AMPK. Consequently, the passage in the book regarding AMPK, TSC2, and mTORC1 must be evaluated through independent experimental evidence that has directly studied that relationship.

5. INTERPRETATION

In simple terms, mTOR tends to promote high-energy-consuming cellular programs, which are useful when an immune response needs to expand rapidly. AMPK, a protein activated when available energy decreases, can instead help limit processes that consume a lot of energy. The model described in the book is therefore biologically plausible: AMPK can act as a metabolic brake on mTORC1, the mTOR complex most associated with growth and protein synthesis.The molecular detail consists of the activation of TSC2, a protein that can reduce signal transmission to mTORC1. This does not mean that AMPK always shuts down the immune system, but rather that under specific energy conditions, it can reduce some cell growth signals. The publication analyzed places this mechanism in the context of decisions regarding T-cell fate, but the abstract alone does not directly document TSC2.The narrative of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is therefore supported at different levels: the link between metabolism, mTOR, and T-cell fate is the general framework covered by

the review; the AMPK-TSC2-mTORC1 link is derived from independent experimental data; and the idea that this promotes immune tolerance is supported primarily by mouse models and does not constitute clinical proof in humans.

6. INDEPENDENT SUPPORTING EVIDENCE

The most direct molecular pathway was studied by Inoki and colleagues in cellular systems. When cellular energy was scarce, AMPK phosphorylated TSC2 and increased its activity. TSC2, in turn, reduced downstream mTOR signals that promote protein synthesis and growth. The authors further showed that this phosphorylation was necessary for the regulation of protein translation and cell size during energy deficiency. This study directly confirms the part of the book's statement regarding AMPK, TSC2, and the inhibition of the mTOR signal; however, it is not a study on T cells or immune tolerance in humans [1].A second line of confirmation concerns the possible immunological significance of the metabolic axis. In a study on mouse CD4-positive T cells, Michalek and colleagues observed that Th1, Th2, and Th17 effector cells relied more heavily on glycolysis, while regulatory T cells exhibited more activated AMPK and a greater dependence on lipid oxidation. In a murine model of asthma, metformin, used as an AMPK activator, reduced Glut1 expression in activated T cells and increased the percentage and number of regulatory T cells in the draining lymph nodes. The study therefore offers biologically consistent confirmation of the idea that AMPK activation can promote a regulatory program, but the model was animal-based and metformin can have effects that do not depend exclusively on AMPK [2].Together, the two studies build a convergent chain. The first shows the AMPK-TSC2-mTORC1 biochemical brake. The second links a metabolic profile with active AMPK to an increased generation of regulatory T cells in a murine inflammatory model. Neither, considered in isolation, proves that TSC2 phosphorylation is the sole cause of immune tolerance or that the same relationship produces identical effects in all human diseases.

7. CONFLICTING EVIDENCE

Important contextual evidence shows that it is incorrect to interpret mTORC1 as a signal that is always incompatible with tolerance. Zeng and colleagues selectively deleted Raptor, an essential component of mTORC1, in mouse regulatory T cells. Cells lacking Raptor lost much of their ability to suppress inflammation in vivo, and the animals developed a severe early-onset inflammatory disease. The study indicates that, in already formed regulatory T cells, a certain level of mTORC1 activity is necessary for their functional efficiency [3].This observation does not contradict the fact that AMPK can inhibit mTORC1 via TSC2. However, it scales back a linear interpretation where less mTORC1 would always mean more tolerance. The effect depends on the cell stage, the type of T cell, the intensity and duration of the signal, and the immunological context. No directly conflicting evidence sufficiently relevant to the AMPK-TSC2-mTORC1 biochemical pathway has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the conceptual framework of the analyzed publication from independent research that confirms or defines the individual steps of the book'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 T cells; full text not available	Describes mTOR as an integrator of immune and metabolic signals in T cell fate decisions.	biologically consistent evidence	moderate
[1]	Cellular and molecular	Cell lines and murine embryonic cells	AMPK phosphorylates and activates TSC2 during energy deficiency, reducing mTOR signaling related to protein synthesis and growth.	direct confirmation	moderate
[2]	Animal and cellular	CD4-positive T cells and murine model of asthma	Regulatory T cells have higher activated AMPK; pharmacological activation of AMPK increased regulatory T cells in the murine model.	indirect confirmation	moderate
[3]	Animal and cellular	Regulatory T cells with Raptor deletion in mice	Loss of mTORC1 in regulatory T cells reduced their suppressive function in vivo and promoted severe inflammation.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication is relevant to the narrative because it describes mTOR as a regulator of T-cell functional decisions in response to immune and metabolic signals. The passage stating that AMPK can inhibit mTORC1 via TSC2 is well-supported mechanistically by independent cellular studies. The link to increased immune tolerance is moderately supported in mouse models, but it should not be turned into a universal rule: mTORC1 may be necessary for the function of already present regulatory T cells. Clinical translation in humans therefore requires specific validation by disease, tissue, and phase of the immune response.

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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