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Histone deacetylase inhibition overcomes rapamycin resistance in diffuse large B-cell lymphoma by inhibiting Akt signaling via mTORC2 - Evidence review

D.ssa M. Mondini[1]

1 Biologist, Italy

1. ABSTRACT

The analyzed study examined why rapamycin, a drug that inhibits the mTORC1 complex, has a limited cytotoxic effect in diffuse large B-cell lymphoma models. In cell lines and primary tumors, the drug inhibited mTORC1 targets but simultaneously increased the phosphorylation of AKT, a chemical modification that contributes to the full activity of this cell survival protein. Experiments linked this response to mTORC2 and its essential protein, Rictor.The research is relevant to section 4.11 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi because it documents an experimental example in which the selective blocking of mTORC1 can activate a compensatory response associated with cell survival. The histone deacetylase inhibitor LBH589 prevented the activation of AKT and overcame resistance to rapamycin in the studied model. Independent research confirms that mTORC1 inhibition can increase AKT through feedback loops and that blocking both complexes can be more effective in some lymphatic models. However, the mechanism depends on the cell type, the duration of exposure, and the drug; it does not demonstrate a clinical benefit in diffuse large B-cell lymphoma.

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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.

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2. ANALYZED STUDY

The research question was whether the limited effect of rapamycin in diffuse large B-cell lymphoma cells depended on the activation of alternative survival signals. The authors evaluated the hypothesis that blocking mTORC1, the mTOR complex that primarily supports protein synthesis and cell growth, could trigger the activation of AKT through mTORC2, the second mTOR complex that contributes to the regulation of AKT.The central point for the book's section is not that rapamycin is ineffective in every context, nor that every tumor responds in the same way. Instead, the study documents a specific segment of the chain: in the lymphoma cells examined, the inhibition of mTORC1 by rapamycin was accompanied by an increase in mTORC2-dependent AKT phosphorylation. When LBH589, a histone deacetylase inhibitor, was added, this adaptation was blocked and the antitumor effect was increased.This is preclinical research. It can therefore show causal relationships in experimentally treated cells and tumor samples, but it cannot establish that the drug combination improves survival, quality of life, or clinical response in people with diffuse large B-cell lymphoma.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

According to the available abstract, the authors used diffuse large B-cell lymphoma cell lines and primary tumors. The number of cell lines, the number of primary samples, the selection criteria, the collection period, and the clinical characteristics of the patients are not reported in the available material.Rapamycin was used to inhibit mTORC1. The authors evaluated cytotoxicity, i.e., the treatment's ability to damage or eliminate tumor cells, and the activity of the molecular pathway through phosphorylated proteins. Phosphorylation is the addition of a phosphate group to a protein; in this case, it was used as an indicator of the activity of mTORC1, mTORC2, and AKT. Rictor, a component of mTORC2, and Raptor, a component of mTORC1, were also experimentally reduced via genetic knockdown, i.e., targeted decrease of gene expression.To verify whether it was possible to prevent the compensatory response, LBH589 was added. The authors also studied the possible role of the phosphatase PP1, an enzyme that can remove phosphate groups from proteins, and HDAC3, a histone deacetylase. Doses, exposure times, details of laboratory techniques, endpoint criteria, and statistical methods are not reported in the available material.

4. RESULTS

The initial result was that rapamycin inhibited mTORC1 in both the cell lines and the primary tumors evaluated, but it produced only minimal cytotoxicity. In simple terms, the drug blocked a part of the network that promotes growth and protein synthesis, without, however, significantly eliminating lymphoma cells in the experimental model. Quantitative values, cell viability percentages, and P-values are not reported in the available abstract.In parallel with the blocking of mTORC1, rapamycin increased the activation of eIF4E and AKT. eIF4E is a protein involved in the initiation of protein synthesis; AKT is a kinase, which is a protein that regulates numerous cellular signals related to metabolism, growth, and survival. The most relevant finding for the book's narrative is that the phosphorylation of AKT induced by rapamycin was reduced by the knockdown of Rictor, but not by the knockdown of Raptor. This indicates that, in the cells studied, the AKT response required mTORC2 and was not a direct consequence of maintaining mTORC1.The addition of LBH589 overcame resistance to rapamycin by blocking the activation of AKT. The experiments also supported the involvement of PP1 in the reduction of AKT phosphorylation induced by LBH589; the knockdown of HDAC3 reproduced this effect. The abstract interprets these results as evidence of a mechanism in which the inhibition of histone deacetylases hinders the activation of mTORC2 and AKT. Complete numerical data on pharmacological synergy, apoptosis, or dose comparisons are not reported in the available abstract.

5. INTERPRETATION

For a cancer cell, blocking mTORC1 can mean reducing the programs that support protein production and growth. However, the cell can activate alternative pathways to maintain survival. In the study analyzed, the increase in AKT phosphorylation following rapamycin represents precisely this adaptive response: while one branch of mTOR was inhibited,

the mTORC2-AKT branch remained or became more active.The specifically documented segment is therefore: in diffuse large B-cell lymphoma cells, rapamycin mTORC1 inhibition increased Rictor/mTORC2-dependent AKT phosphorylation reduced cytotoxic efficacy. LBH589 interrupted this segment by reducing AKT phosphorylation and increasing the effect of rapamycin. This is the precise reason why the publication is consistent with the passage in paragraph 4.11 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi.The causal conclusion is solid within the studied cells because the dependence on mTORC2 was also verified by reducing Rictor. However, important limitations remain. The activation of AKT following mTORC1 inhibition can depend on various feedback circuits; the study does not prove that the same mechanism prevails in all lymphoma subtypes or in patients. Furthermore, LBH589 can influence numerous genes and proteins, so its effect cannot be attributed exclusively to PP1 or mTORC2.

6. INDEPENDENT CONFIRMATORY EVIDENCE

Initial independent confirmation concerns the general principle of the compensatory response. O'Reilly and colleagues studied human tumor cell lines and tumor samples from patients treated with the rapamycin analog RAD001. Inhibition of mTOR increased the expression of IRS1, a protein that transmits signals from growth factor receptors, and activated AKT. Inhibition of the IGF-1R receptor prevented this activation and increased cell sensitivity to mTOR blockade. The study therefore confirms that mTORC1 inhibition can remove a feedback brake and increase AKT; the upstream mechanism does not necessarily coincide with the one identified in lymphoma, but the direction of the adaptation is consistent [1].Wan and colleagues observed a similar result in rhabdomyosarcoma cell lines and xenografts. Rapamycin and experimental reduction of S6K1, a downstream target of mTORC1, increased AKT phosphorylation. Blocking the IGF-1R receptor prevented the increase in AKT induced by rapamycin; the combination of mTOR and IGF-1R inhibition produced a greater reduction in cell growth and survival compared to individual treatments. This confirms that an apparently selective blockade of mTORC1 can activate signals that counteract the antitumor effect, but it also shows that the compensatory node can be an upstream receptor and not just mTORC2 [2].A finding particularly relevant to the therapeutic part of the narrative comes from a subsequent study on lymphatic neoplasms. Gupta and colleagues compared rapamycin with OSI-027, an mTOR kinase inhibitor capable of blocking both mTORC1 and mTORC2. In cell lines and clinical samples of various lymphoid neoplasms, OSI-027 reduced proliferation and induced apoptosis, i.e., programmed cell death, more markedly than rapamycin. The drug reduced the phosphorylation of the targets of both complexes and induced regression of mantle cell lymphoma xenografts. The result supports the idea that the simultaneous blockade of the two complexes can avoid a portion of survival signaling; however, it does not directly concern diffuse large B-cell lymphoma and involves authors partially overlapping with the original study, albeit using different models and data [3].

7. CONFLICTING EVIDENCE

The response of mTORC2 to rapamycin is not uniform. Sarbassov and colleagues demonstrated that prolonged treatment with rapamycin can prevent the assembly of new mTORC2 complexes and reduce AKT phosphorylation in many cell types. In that context, rapamycin therefore reduced, rather than increased, signaling sustained by mTORC2-AKT [4].This evidence does not contradict the observation of the study analyzed in lymphoma cells, but it limits its generalizability. The direction of the effect depends at least on the cell type, the duration of exposure, and the balance between feedback circuits and the formation of new mTORC2 complexes. Consequently, it is incorrect to state that rapamycin always increases AKT or that it always inhibits mTORC2 after prolonged treatment.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study that is the subject of the review from the independent publications used to evaluate the narrative of the book's paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and primary tumor samples	Cell lines and primary tumors of diffuse large B-cell lymphoma; sample size not reported in available material	Rapamycin inhibited mTORC1 but increased Rictor/mTORC2-dependent AKT phosphorylation; LBH589 blocked this adaptation	direct confirmation	moderate
[1]	Cellular and human tumor samples	Tumor lines and biopsies of solid tumors treated with RAD001	mTOR inhibition increased IRS-1 and activated AKT; IGF-1R blockade prevented AKT activation	indirect confirmation	moderate
[2]	Cellular and animal	Human rhabdomyosarcoma lines, xenografts, and supplementary cell models	Rapamycin increased AKT phosphorylation via IGF-1R; dual blockade reduced growth and survival more effectively	indirect confirmation	moderate
[3]	Cellular, clinical samples, and animal	Lymphoid neoplasms, clinical samples, and mantle cell lymphoma xenografts	Combined inhibition of mTORC1 and mTORC2 reduced AKT, proliferation, and increased apoptosis compared to rapamycin	biologically consistent evidence	moderate
[4]	Cellular	Various cell types	Prolonged rapamycin prevented mTORC2 assembly and reduced AKT signaling in many contexts	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed directly supports the finding that, in the diffuse large B-cell lymphoma cells examined, blocking mTORC1 with rapamycin can be accompanied by increased AKT phosphorylation via mTORC2. Inhibiting histone deacetylases with LBH589 prevented this adaptation and increased the antitumor effect in the model.Independent literature confirms that feedback loops can limit the efficacy of mTORC1 inhibitors and that the combined blockade of mTORC1 and mTORC2 is biologically promising in certain tumor models. However, the strength of the conclusion is mechanistic: responses vary according to the cellular context and duration of treatment, and specific clinical validations are required before attributing proven therapeutic utility to this strategy in people with diffuse large B-cell lymphoma.

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.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **mTOR Inhibition Induces Upstream Receptor Tyrosine Kinase Signaling and Activates Akt**
O'Reilly et al., 2006
Cancer Research
DOI: https://doi.org/10.1158/0008-5472.CAN-05-2925

[2] **Rapamycin induces feedback activation of Akt signaling through an IGF-1R-dependent mechanism**
Wan et al., 2007
Oncogene
DOI: https://doi.org/10.1038/sj.onc.1209990

[3] **Dual mTORC1/mTORC2 inhibition diminishes Akt activation and induces Puma-dependent apoptosis in lymphoid malignancies**
Gupta et al., 2012
Blood
DOI: https://doi.org/10.1182/blood-2011-04-346601

[4] **Prolonged Rapamycin Treatment Inhibits mTORC2 Assembly and Akt/PKB**
Sarbassov et al., 2006
Molecular Cell
DOI: https://doi.org/10.1016/j.molcel.2006.03.029