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The PTEN/PI3K pathway governs normal vascular development and tumor angiogenesis - A review of the evidence

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ONLINE ARTICLE

ARTICLE INFORMATION

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1. ABSTRACT

The analyzed study genetically modified the *Pten* gene in mouse endothelial cells, which are the cells that line the inside of blood vessels. Partial loss of PTEN increased endothelial cell proliferation and migration and promoted tumor angiogenesis; complete loss caused severe vascular and embryonic defects. The work therefore describes PTEN as an important brake on the PI3K pathway in the growth and organization of vessels.In section 4.3 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the narrative that the PI3K-AKT signal regulates crucial cellular functions. However, the publication did not directly measure AKT activation, glucose transport, protein synthesis, or lipid metabolism. Independent studies confirm that AKT2 participates in glucose transport and that the PI3K-AKT signal can reduce apoptosis and contribute to lipid regulation. However, a human trial shows that insulin-induced AKT activation alone does not necessarily increase muscle protein synthesis: the nutritional context remains a determining factor.

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 was whether PTEN, a protein that inhibits certain intracellular growth signals, is necessary for endothelial cells to form normal vessels and to control tumor angiogenesis. The hypothesis was that reducing PTEN in endothelial cells would increase the activity of the PI3K (phosphoinositide 3-kinase) pathway, a network of signals that promotes cell growth, movement, and survival, with consequences for both vessel development and tumor vascularization.The relevance to section 4.3 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns the regulatory role of the PI3K network and its antagonist, PTEN. In simple terms, the work shows that removing a brake on PI3K signaling makes certain responses in vessel cells more active. However, it does not demonstrate that insulin produced these effects, it does not directly measure AKT, and it does not evaluate glucose transport, protein synthesis, apoptosis, or lipid metabolism as primary outcomes.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors used the Cre-loxP system, a genetic engineering technique that allows for the modification of a gene in selected cell types. They produced mice with the inactivation of one copy of *Pten* in endothelial cells and mice with the inactivation of both copies. The endothelial cells were also isolated and studied *in vitro*, that is, in cell culture.The only material available is the abstract. It indicates that embryonic development, tumor growth, angiogenesis, endothelial cell proliferation and migration, as well as the expression of several genes involved in vessel formation were examined. Genetic experiments relating to the p85a and p110γ subunits of PI3K are also reported. The number of animals, inclusion and exclusion criteria, tumor lines, detailed experimental protocols, observation times, statistical analyses, P-values, and confidence intervals are not reported in the available material.

4. RESULTS

In mice with the loss of a single copy of *Pten* in endothelial cells, the authors observed an increase in tumorigenesis accompanied by an increase in angiogenesis driven by vascular growth factors. In other words, the tumors had greater vessel formation, a condition that can promote their expansion. The effect depended in part on the p85a and p110γ subunits of PI3K.In culture, endothelial cells with partial loss of PTEN showed increased proliferation, i.e., an increased ability to multiply, and greater migration, i.e., the ability to move. The abstract does not report absolute values, percentages, concentrations, or statistical significance for these results.The complete loss of *Pten* in endothelial cells caused embryonic death before day 11.5 of development. The authors attribute this to bleeding and heart failure associated with reduced recruitment of pericytes—cells that stabilize small vessels—as well as vascular smooth muscle cells and cardiomyocytes toward the endocardium. This picture was associated with a reduction in the expression of Ang-1, VCAM-1, connexin 40, and ephrinB2, and an increase in Ang-2, VEGF-A, VEGFR1, and VEGFR2. The result indicates a disorganization of vascular maturation, not a direct demonstration of the metabolic functions of AKT.

5. INTERPRETATION

The primary biological significance is that PTEN helps maintain a proportionate response in the cells that build and stabilize blood vessels. When this brake is reduced, endothelial cells proliferate and migrate more; when it is eliminated entirely, vascular development becomes severely defective. This finding is consistent with a role for the PI3K pathway in the regulation of cell growth and survival.In the book's paragraph, the segment actually documented by the publication subject to the Evidence Review is narrower than the overall sentence: alterations in the PTEN-PI3K system modify cellular responses related to proliferation, migration, and vessel development. The link to AKT is biologically plausible because AKT is an important downstream effector of PI3K, but the available abstract does not report measurements of AKT phosphorylation, a chemical modification that indicates its functional activation. Therefore, the study alone cannot demonstrate that AKT stimulates all the functions listed in the paragraph, nor that such functions occur in the same way in every human tissue.

6. INDEPENDENT SUPPORTING EVIDENCE

The section regarding glucose transport is supported by an independent cellular study conducted on rat adipocytes and the 3T3-L1 cell line. Insulin promotes the arrival of the GLUT4 transporter at the cell surface, allowing glucose to enter the cell. Blocking AKT/PKBb, now primarily referred to as AKT2, reduced insulin-induced GLUT4 translocation by 56-66%. This result directly supports the role of AKT2 in glucose transport in adipocytes, but it does not prove that every AKT isoform performs the same function in all tissues [1].Regarding apoptosis, a set of molecular experiments on primary neurons showed that activation of the PI3K-AKT pathway phosphorylates BAD, a protein that can promote programmed cell death. This phosphorylation reduced the ability of BAD to induce cell death and promoted neuronal survival. Research therefore confirms a mechanism by which AKT can inhibit apoptosis, but the model was not a tissue metabolically regulated by insulin and does not allow for the automatic transfer of the result to all human cells [2].Regarding the regulation of lipid metabolism, a study on genetically modified mice evaluated AKT2 in the liver during obesity, leptin deficiency, or a high-fat diet. The absence of hepatic AKT2 reduced the accumulation of triglycerides in the liver; in leptin-deficient mice, it also prevented the increase in lipogenesis, i.e., the production of fats by the body. The data support the idea that AKT2 participates in the regulation of lipids in the liver under conditions of insulin resistance, but they describe a pathological animal model and not a direct measure of physiological lipid metabolism in humans [3].

7. CONFLICTING EVIDENCE

The claim that AKT promotes protein synthesis requires particular caution, as the response depends on the tissue and the availability of nutrients. In a randomized study of 18 healthy adults, seven hours of insulin infusion without amino acid supplementation increased AKT phosphorylation in the muscle, but did not increase the phosphorylation of mTOR, p70S6K, and 4EBP1, which are regulators of protein synthesis. The synthesis rates of mitochondrial, sarcoplasmic, and mixed proteins were lower during insulin infusion compared to saline between the second and seventh hour [4].This result does not deny that the AKT network can contribute to protein synthesis in other contexts. However, it shows that AKT activation, on its own, does not necessarily equate to an increase in protein production in human muscle when circulating amino acids decrease. No sufficiently relevant directly conflicting evidence has been identified regarding the role of AKT2 in glucose transport or BAD phosphorylation; this does not prove the absence of contrary findings.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from independent research that confirms or defines the individual steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal and cellular	Mice with endothelial Pten inactivation and endothelial cells	PTEN reduction increased tumor proliferation, migration, and angiogenesis; complete loss compromised embryonic vascular development.	biologically consistent evidence	moderate
[1]	Cellular	Rat adipocytes and 3T3-L1	Blocking AKT2/PKBb reduced insulin-induced GLUT4 translocation by 56-66%.	direct confirmation	moderate
[2]	Cellular and animal	Murine cells and primary neurons	AKT phosphorylated BAD and reduced its ability to induce apoptosis.	direct confirmation	moderate
[3]	Animal	Mice with Akt2 loss, leptin deficiency, or high-fat diet	Hepatic absence of AKT2 reduced triglyceride accumulation and, in one model, lipogenesis.	indirect confirmation	moderate
[4]	RCT	18 healthy adults undergoing insulin or saline infusion	Insulin increased AKT phosphorylation but not muscle protein synthesis without amino acid supplementation.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The original study convincingly shows that PTEN is essential for regulating PI3K signaling in endothelial cells and for proper vessel development. Its presence in the paragraph is consistent with the description of the PI3K-AKT network, but the publication does not directly demonstrate all the functions attributed to AKT.Independent evidence mechanistically supports the contribution of AKT2 to glucose transport, the anti-apoptotic role of the PI3K-AKT pathway, and the participation of AKT2 in lipid regulation in animal models. The statement regarding protein synthesis, however, requires a conditional formulation: it depends on amino acid availability, the tissue, and experimental conditions.

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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