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Targeting HIF-1 for cancer therapy - A review of the evidence

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1. ABSTRACT

The analyzed publication is a narrative review on the potential oncological applications of inhibiting HIF-1, the hypoxia-inducible factor 1. The objective was to describe how reduced oxygen availability and certain genetic alterations can increase HIF-1 activity in tumors, promoting the expression of genes involved in energy production, blood vessel formation, cell invasion, and survival. Since the available material contains only the abstract, no systematic study selection methods or original quantitative data are reported.In section 4.9 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the explanation that when oxygen is scarce, HIF-1a accumulates and activates genetic programs that help the cell adapt. Independent experimental evidence confirms the oxygen-dependent control of HIF stability, the link to glycolytic metabolism, and the activation of VEGF, a protein that promotes the formation of new blood vessels. An important limitation concerns red blood cells: in the body, the erythropoietin response in the liver depends primarily on HIF-2a. The narrative is therefore well-supported at a mechanistic level, but it should not be interpreted as a general clinical demonstration or as a therapeutic indication.

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 was whether HIF-1, a transcription factor—that is, a protein that regulates which genes are used by the cell—represents a useful target in cancer therapy. The hypothesis discussed is that the activation of HIF-1 under conditions of hypoxia, or reduced oxygen availability, promotes genetic programs that are useful for the growth and persistence of tumor cells.Its relevance to section 4.9 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns, above all, a specific segment of the narrative: oxygen deficiency increases the activity of HIF-1α, and this factor activates genes that make the cell more capable of adapting to the hypoxic condition. The publication lists, among the regulated areas, angiogenesis, cell survival, and glucose metabolism. However, based solely on the available abstract, it cannot demonstrate the entire sequence described in the book nor quantify the effect in healthy individuals or in specific diseases.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material is only the abstract of a narrative review published in 2003. Therefore, it is not a single clinical trial, an animal study, or an analysis of a patient cohort described in the abstract.The authors summarize preclinical evidence on the inhibition of HIF-1 and its relationship with tumor growth, glucose metabolism, angiogenesis, invasion, and cell survival. The bibliographic search strategy, study inclusion and exclusion criteria, the number of publications evaluated, the populations or experimental models, the endpoints, the statistical analyses, and the follow-up are not reported in the available material.

4. RESULTS

The core finding reported in the abstract is that HIF-1 activates the transcription of genes involved in key aspects of tumor biology. In simple terms, when a cell receives a signal of oxygen scarcity, it can modify its genetic instructions to produce proteins useful for managing that condition. The areas indicated include the formation of new blood vessels, cell survival, glucose metabolism, and invasion.The abstract further states that hypoxia within the tumor and genetic alterations can increase the expression of HIF-1a, and that this increased expression has been associated with higher mortality in various cancers. The prognostic association is not quantified: hazard ratios, confidence intervals, P-values, tumor types, number of patients, and duration of follow-up are not reported in the available material.For the purpose of the book passage, it is particularly relevant that HIF-1 is presented as an activator of genes involved in the adaptive response to hypoxia. However, the abstract does not list the individual genes nor does it provide direct experimental measurements on glycolysis, VEGF, erythropoietin, or survival. Such details therefore require confirmation from independent primary studies.

5. INTERPRETATION

The biological significance of the publication is clear: HIF-1 functions as part of a system that allows cells to modify their behavior when oxygen is insufficient. In a tumor, this adaptation can be unfavorable because it may help cells persist in poorly oxygenated areas. In the language of the book's paragraph, HIF-1a therefore represents the link that connects reduced oxygen levels to the activation of genes suited to that condition.The molecular detail is that the HIF-1a subunit is regulated by oxygen availability. When oxygen levels are normal, it is typically targeted for degradation; when oxygen decreases, its stability increases, and it can contribute to the transcription of target genes. This does not mean that every effect observed in tumor cells is present with equal intensity in all tissues, or that HIF-1a alone determines a clinical outcome.The publication subject to the Evidence Review therefore primarily supports the following segment: hypoxia or genetic alterations increased HIF-1 activity activation of genes involved in adaptation. It does not directly demonstrate, in the available material, that HIF-1a increases red blood cells in humans, nor that every cellular survival response is mediated exclusively by this isoform.

6. INDEPENDENT CONFIRMING EVIDENCE

An initial cellular study clarified the first step of the narrative. In cells with a VHL defect, a protein involved in the disposal of HIF, the HIF-α subunits were stabilized even under normal oxygen levels; the reintroduction of VHL restored oxygen-dependent

instability. This confirms that the rapid degradation of HIF in normoxia and its stabilization in hypoxia are fundamental components of the oxygen-sensing system [1]. The limitation is that these are experiments on cells and not a direct measurement of organ adaptation in humans.A second study explored the energetic significance of the adaptation. In hypoxic cell models, HIF-1 increased the expression of PDK1, a protein that reduces the entry of pyruvate into the mitochondria. In practical terms, this shifts part of the energy production toward glycolysis, which is the pathway that allows energy to be derived from glucose with less dependence on oxygen. Forced expression of PDK1 in cells lacking HIF-1α increased ATP, the main cellular energy currency, reduced reactive oxygen species, and limited apoptosis, which is the programmed cell death induced by hypoxia [2]. The result confirms the metabolism-adaptation-survival pathway, but it remains preclinical.Regarding the formation of new vessels, a study using Hep3B cells and genetic reporter systems showed that HIF-1 activates the transcription of VEGF, the vascular endothelial growth factor. Mutation of the HIF-1 binding site in the VEGF promoter eliminated hypoxia-induced activation, while a dominant-negative form of HIF-1α reduced it in a dose-dependent manner [3]. This directly supports the link between hypoxic signaling, HIF-1, and increased expression of a pro-angiogenic gene. However, it does not prove that every increase in VEGF produces effective new vessels or improves the oxygenation of a tissue in the organism.

7. CONFLICTING EVIDENCE

The part of the book's statement regarding the increase in red blood cells requires an important clarification. In mice with targeted genetic inactivations, the induction of erythropoietin in the liver during anemia or hypoxia depended primarily on HIF-2a and not on HIF-1a. In the same study, the glycolytic gene Pgk remained dependent on HIF-1a [4]. The direction of the evidence does not deny that the HIF system participates in the regulation of erythropoiesis, but it indicates that specifically attributing the increase in red blood cells to HIF-1a would be an oversimplification.This difference between isoforms is biologically relevant: HIF-1a and HIF-2a share some upstream signals, but they can control different genes depending on the tissue and context. No directly conflicting evidence sufficiently relevant to the general ability of HIF-1 to regulate genes for adaptation to hypoxia has been identified; 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 individual steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Preclinical and clinical literature not detailed in the available abstract	Describes HIF-1 as a regulator of angiogenesis, glucose metabolism, and cell survival in tumors	biologically consistent evidence	moderate
[1]	Cellular and molecular	Cell lines with VHL defect and VHL reintroduction	VHL promotes the degradation of HIF-a subunits in the presence of oxygen; hypoxia increases their stability	direct confirmation	moderate
[2]	Cellular and genetic	Hypoxic cells and cells lacking HIF-1a	HIF-1 induces PDK1, promoting glycolysis, higher ATP, lower reactive oxygen species, and less apoptosis	direct confirmation	moderate
[3]	Cellular and molecular	Hep3B cells and VEGF promoter reporter systems	HIF-1 is necessary for the hypoxic activation of VEGF transcription	direct confirmation	moderate
[4]	Animal and genetic	Mice with conditional inactivation of Hif-1a and/or Hif-2a in the liver	Hepatic induction of erythropoietin and polycythemia depend primarily on HIF-2a, while Pgk depends on HIF-1a	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication is consistent with its use in the section dedicated to HIF-1a. The most well-supported point is that oxygen deficiency reduces the degradation of HIF-1a and promotes the activation of genes that modify metabolism and vascular response. Independent evidence confirms, in particular, glycolytic adaptation and VEGF induction. The component related to cell survival is supported primarily by experimental models. The statement regarding red blood cells, however, requires a more specific formulation, because HIF-2a plays a predominant role in hepatic erythropoietin. Overall, the narrative is supported at a mechanistic level and requires caution when extended to clinical outcomes or all tissues.

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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