



Is Hypoxic/Altitude Training an Important Topic in the Field of Hypoxia?

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Abstract

Hypoxia is an essential topic in medical or biological sciences. The main aims of the present study were to examine the most important medical articles (i.e., the top 100 most cited) on hypoxia. We examine how the Nobel-prize awarded hypoxia inducible factor (HIF)-pathway discovery in the early 1990s has changed the thematic composition of this body of literature, with a special emphasis on the studies linking hypoxia and cancer. We searched Pubmed for articles with the terms #Hypox, #Altitude, or #Mountain in the title that have been published in biomedical journals and ranked the articles on their number of citations in Web of Science. A second search was performed in all journals for articles related to hypoxia and cancer. Strikingly, only 12 of the top-100 most-cited articles on hypoxia and only 3 articles of the top-100 articles related to cancer were published before 1995. Moreover, only 5 articles from prior 1995 reached 1000 citations, while 27 articles published in 1995 or later were cited more than 1000 times, most of them on the HIF-1 pathway. Eighty percent of the top-100 articles were related to the HIF pathway, while there were no articles on the application of hypoxia either for therapeutic use (i.e., hypoxic conditioning in patients) or for performance enhancement (i.e., altitude training in athletes). In conclusion, the early-1990s discovery of the HIF pathway and of its molecular regulation has shifted the focus of hypoxia research towards molecular mechanisms and consequences of tissue hypoxia, most notably in cancer. The importance of studies focusing on clinical and performance applications of systemic hypoxia is relatively lower.

Keywords Altitude training · Cancer · Hypoxia · HIF pathway · Mountain

Introduction

Between 1775 and 1777, Scheele [103] and Priestley [93] found a previously unknown gas in the air that was named “oxygen” by Lavoisier [64]. This fundamental finding paved the way for the understanding of the primary importance of the metabolic and physiological adaptations to oxygen availability and consequently to “The history of hypoxia” as elegantly reported by Richalet [98]. The Nobel prize in physiology or medicine for 2019 awarded to William Kaelin Jr, Sir Peter Ratcliffe, and Gregg Semenza for their work

on the molecular mechanisms underlying how cells adapt to different levels of oxygen supply is the most prestigious event of this long journey.

Since the 1950s, the term “hypoxia” (i.e., “abnormal condition resulting from a decrease in the oxygen supplied to or utilized by body tissue”; Webster’s New World College Dictionary, 4th ed 2010; from [98]) has been increasingly deployed in the medical or biological scientific literature:

1. In environmental physiology, to deepen the understanding of the physiological (i.e., cardiovascular and respiratory adaptations) and pathophysiological (i.e., acute mountain sickness) responses to severe hypoxia (e.g., in aviation physiology [34]) or to high altitude, as pioneered at the end of 19th–early twentieth century in Europe [97] and USA [134]).
2. With the development of cellular or molecular biology, to understand how variations in oxygen delivery lead to changes in gene transcription and to adaptive responses in cells and tissues. The importance of the isolation

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of the hypoxia inducible factor (HIF) has been unanimously recognized and celebrated by bestowal of the Nobel Prize [83]. The subsequent growing understanding of its role in cellular pathways and its molecular regulation, e.g., by the von Hippel–Lindau (VHL) protein, contributed to the recognition of various potential (clinical) applications, especially with regard to associated drug targets in various cancers [125]. Various HIF molecules and subunits (HIF-1 α , HIF-1 β , HIF-2 α , HIF-2 β , HIF-3 α , HIF-3 β) have been characterized and our understanding of their differential roles has increased substantially during the last decades. For example, the unique target genes of HIF-1 α and HIF-2 α and their different functions in glycolytic regulation, glucose consumption, or hypoxia responses are being continuously unraveled [50].

Numerous applications of hypoxia have also been investigated and published in the scientific literature:

3. In the clinical field, the continuous exposure to altitude or systemic intermittent hypoxic conditioning/training (not to be confused with pathology-associated "intermittent hypoxia" as in sleep apnea, for example) has been proposed to be an effective treatment strategy against different diseases, conferring various health benefits: e.g., cardioprotection [77]; neuroprotection [13]; and reduction of obesity [135]; cancer mortality [14], and cardiovascular diseases [28, 29].
4. Since the 1960s for enhancing performance in athletes, initially only in endurance sports due to the hematological benefit of prolonged exposure to altitude [23, 74] and more recently in intermittent (i.e., team or racket) sports [36, 82].

To our knowledge, there is no detailed analysis of the scientific contributions related to hypoxia. The main aims of the present study were to examine the most important (i.e., the most-cited) articles in this field and to examine how the HIF-pathway discovery may have changed the thematic composition of this body of literature, with a special emphasis on the studies linking hypoxia and cancer. Finally, the relative representation in hypoxia research of five different topics (pathophysiological responses to high altitude; physiological adaptive responses to hypoxia; molecular responses to hypoxia; clinical/therapeutic use of hypoxia; altitude training) was analyzed.

Methods

We first identified biomedical (biology, medicine, physiology, or "sport sciences") journals in PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) with potential articles on altitude or hypoxia. All journals with the terms #Med, #Physiol, #Biol, #Exerc, and #Cell in the journal name were first selected. For inclusion of the highest ranked general scientific and medical journals, we added journals with #Sci, #Lancet, #Jama, #Nature, #PNAS, and #BMJ in their names.

This yielded a list of 1726 journals or source titles. From this list, we removed those that were not closely related to human physiology or medicine (e.g., plants, veterinary, zoology, animals) reducing the list to 1668 journals.

Next we searched Pubmed for articles with the terms Hypox*, Altitude, or Mountain* in the title. This yielded 29,888 articles on the 15th march 2021.

The next step was to determine the number of citations for these articles. We performed a complete search for all the articles on Web of Science (<https://www.webofscience.com/>) on 16–17th march 2021. Basic information, including source journal, publication year, citations per year, and total number of citations, was extracted.

These publications were then ranked by the number of times cited and a list of the top-100 cited articles was created. Finally, we extracted from this list all articles related to cancer (i.e., titles containing the terms "tumour"/"tumor" or "cancer"), yielding a list of the top-100 articles on hypoxia but without a primary focus on cancer (Table 1).

Each of these 100 articles was then analyzed by two independent reviewers (GPM and JB) to classify them according to five distinct categories, regarding their main purpose:

1. Pathophysiological responses to high altitude—focus on adverse/maladaptive systemic physiological effects to hypoxia or high altitude.
2. Physiological responses to hypoxia—focus on adaptive systemic physiological and genetic effects to hypoxia.
3. Molecular responses to hypoxia—mechanistic studies with a focus on cell physiology and pathology.
4. Clinical/therapeutic use of hypoxia—therapeutic use of hypoxia in clinical populations, except cancer.
5. Altitude training—use of altitude/hypoxia for sport performance enhancement purpose.

A second search in Pubmed was performed in all journals for articles related to hypoxia and cancer, i.e., articles with #Hypox or #Altitude and #cancer in the title. This search yielded 3173 articles. As described for Table 1, we ranked

Table 1 Top-100 cited articles on “hypoxia”

Order number	References	Citations
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95	[140] Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. <i>JAMA.</i> 2011;306(6):613–619	533
96	[42] Hackett PH, Rennie D, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. <i>Lancet.</i> 1976;2(7996):1149–1155	529
97	[60] Krishnamurthy P, Ross DD, Nakanishi T, et al. The stem cell marker Bcrp/ABCG2 enhances hypoxic cell survival through interactions with heme. <i>J Biol Chem.</i> 2004;279(23):24218–24225	524
98	[80] Melillo G, Musso T, Sica A, Taylor LS, Cox GW, Varesio L. A hypoxia-responsive element mediates a novel pathway of activation of the inducible nitric oxide synthase promoter. <i>J Exp Med.</i> 1995;182(6):1683–1693	518
99	[121] Shweiki D, Neeman M, Itin A, Keshet E. Induction of vascular endothelial growth factor expression by hypoxia and by glucose deficiency in multicell spheroids: implications for tumor angiogenesis. <i>Proc Natl Acad Sci U S A.</i> 1995;92(3):768–772	516
100	[59] Koumenis C, Naczki C, Koritzinsky M, et al. Regulation of protein synthesis by hypoxia via activation of the endoplasmic reticulum kinase PERK and phosphorylation of the translation initiation factor eIF2alpha. <i>Mol Cell Biol.</i> 2002;22(21):7405–7416	506

The articles related to “cancer” are not displayed (see Table 2)

*Shows the review articles

these articles by citations. We added to this list the articles related to cancer extracted from Table 1 to create Table 2 with the top-25 articles related to hypoxia and cancer.

A third search was performed only in “sport sciences” journals, with “exercise,” “sport,” “applied physiology,” or “rehabilitation” in the journal title. This search yielded 3113 articles.

Results

The number of citations of the (bio)medical articles on hypoxia began to increase in the 1960s, while the rise in citations on “hypoxia and cancer” started later, in the end 90 s. The total number of citations is > 68,000 and > 18,000 in 2020, respectively (Fig. 1).

Table 2 Top-25 cited articles on “hypoxia and cancer”

Order number	References	Citations
1	[15] Carmeliet P, Dor Y, Herbert JM, et al. Role of HIF-1alpha in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. <i>Nature</i> . 1998;394(6692):485–490	2045
2	[38] Graeber TG, Osmanian C, Jacks T, et al. Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours. <i>Nature</i> . 1996;379(6560):88–91	2032
3*	[136] Wilson WR, Hay MP. Targeting hypoxia in cancer therapy. <i>Nature Reviews Cancer</i> . 2011;11(6):393–410	1809
4*	[10] Brown JM, Wilson WR. Exploiting tumour hypoxia in cancer treatment. <i>Nature reviews Cancer</i> . 2004;4(6):437–447	1745
5	[49] Hockel M, Schlenger K, Aral B, Mitze M, Schaffer U, Vaupel P. Association between tumor hypoxia and malignant progression in advanced cancer of the uterine cervix. <i>Cancer Res</i> . 1996;56(19):4509–4515	1508
6*	[128] Vaupel P, Mayer A. Hypoxia in cancer: significance and impact on clinical outcome. <i>Cancer Metastasis Rev</i> . 2007;26(2):225–239	1460
7	[145] Zhong H, Chiles K, Feldser D, et al. Modulation of hypoxia-inducible factor 1alpha expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: implications for tumor angiogenesis and therapeutics. <i>Cancer Res</i> . 2000;60(6):1541–1545	1280
8*	[92] Pouyssegur J, Dayan F, Mazure NM. Hypoxia signalling in cancer and approaches to enforce tumour regression. <i>Nature</i> . 2006;441(7092):437–443	1233
9*	[115] Semenza GL. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. <i>Oncogene</i> . 2010;29(5):625–634	1150
10	[91] Pennacchietti S, Michieli P, Galluzzo M, Mazzone M, Giordano S, Comoglio PM. Hypoxia promotes invasive growth by transcriptional activation of the met protooncogene. <i>Cancer Cell</i> . 2003;3(4):347–361	1008
11	[8] Brizel DM, Sibley GS, Prosnitz LR, Scher RL, Dewhirst MW. Tumor hypoxia adversely affects the prognosis of carcinoma of the head and neck. <i>Int J Radiat Oncol Biol Phys</i> . 1997;38(2):285–289	896
12*	[117] Semenza GL. Hypoxia-inducible factors: mediators of cancer progression and targets for cancer therapy. <i>Trends in Pharmacological Sciences</i> . 2012;33(4):207–214	894
13	[78] Maxwell PH, Dachs GU, Gleadle JM, et al. Hypoxia-inducible factor-1 modulates gene expression in solid tumors and influences both angiogenesis and tumor growth. <i>Proc Natl Acad Sci U S A</i> . 1997;94(15):8104–8109	889
14	[70] Li Z, Bao S, Wu Q, et al. Hypoxia-inducible factors regulate tumorigenic capacity of glioma stem cells. <i>Cancer Cell</i> . 2009;15(6):501–513	847
15*	[7] Brezis M, Rosen S. Hypoxia of the renal medulla—its implications for disease. <i>N Engl J Med</i> . 1995;332(10):647–655	842
16*	[57] Keith B, Simon MC. Hypoxia-inducible factors, stem cells, and cancer. <i>Cell</i> . 2007;129(3):465–472	799
17	[27] Erler JT, Bennewith KL, Cox TR, et al. Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the premetastatic niche. <i>Cancer Cell</i> . 2009;15(1):35–44	768
18	[96] Raval RR, Lau KW, Tran MG, et al. Contrasting properties of hypoxia-inducible factor 1 (HIF-1) and HIF-2 in von Hippel-Lindau-associated renal cell carcinoma. <i>Mol Cell Biol</i> . 2005;25(13):5675–5686	694
19	[32] Fukuda R, Hirota K, Fan F, Jung YD, Ellis LM, Semenza GL. Insulin-like growth factor 1 induces hypoxia-inducible factor 1-mediated vascular endothelial growth factor expression, which is dependent on MAP kinase and phosphatidylinositol 3-kinase signaling in colon cancer cells. <i>J Biol Chem</i> . 2002;277(41):38205–38211	672
20	[139] Xu RH, Pelicano H, Zhou Y, et al. Inhibition of glycolysis in cancer cells: a novel strategy to overcome drug resistance associated with mitochondrial respiratory defect and hypoxia. <i>Cancer Res</i> . 2005;65(2):613–621	638
21*	[138] Wouters BG, Koritzinsky M. Hypoxia signalling through mTOR and the unfolded protein response in cancer. <i>Nature Reviews Cancer</i> . 2008;8(11):851–864	623
22	[6] Birner P, Schindl M, Obermair A, Plank C, Breitenecker G, Oberhuber G. Overexpression of hypoxia-inducible factor 1alpha is a marker for an unfavorable prognosis in early-stage invasive cervical cancer. <i>Cancer Res</i> . 2000;60(17):4693–4696	611
23	[101] Sahlgren C, Gustafsson MV, Jin S, Poellinger L, Lendahl U. Notch signaling mediates hypoxia-induced tumor cell migration and invasion. <i>Proc Natl Acad Sci U S A</i> . 2008;105(17):6392–6397	588
24*	[95] Rankin EB, Giaccia AJ. The role of hypoxia-inducible factors in tumorigenesis. <i>Cell Death Differ</i> . 2008;15(4):678–85	586
25*	[9] Brown JM. The hypoxic cell: a target for selective cancer therapy—eighteenth Bruce F. Cain Memorial Award lecture. <i>Cancer Res</i> . 1999;59(23):5863–5870	579

*Shows the review articles

Fig. 1 **A** Total citations number per year (1950–2020) of articles on “hypoxia,” “hypoxia and cancer,” and “hypoxia in sport sciences”; **B** The respective contribution in the top-100 articles on hypoxia of the molecular, pathophysiology, and physiology approaches is shown. No articles related to clinical or sport (altitude training) applications reached the top-100

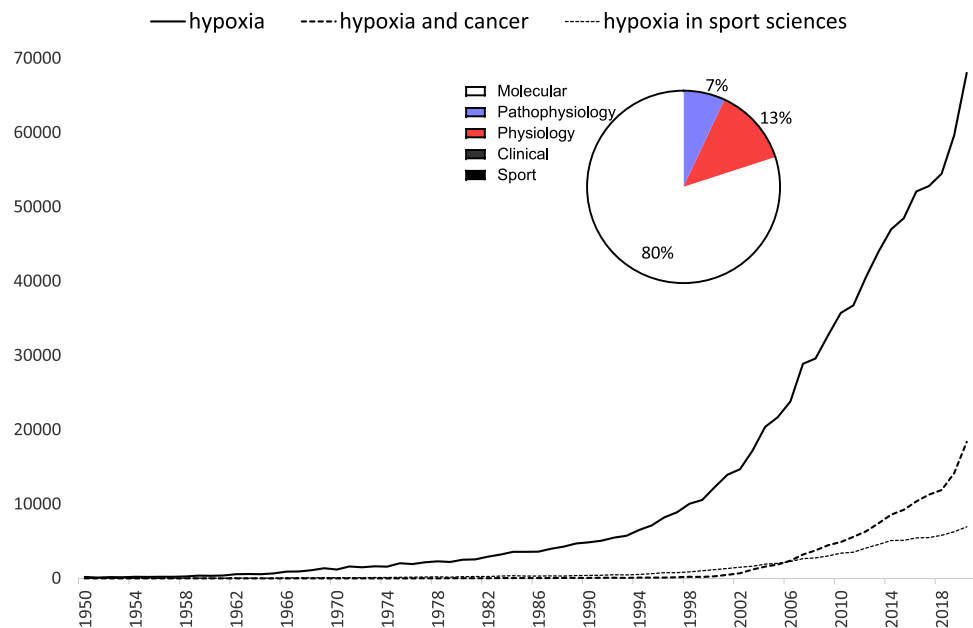


Table 1 displays the top-100 most-cited articles on hypoxia and Table 2 shows the top-25 articles on hypoxia related to cancer.

The mean number of citations of the top-100 articles on hypoxia (Table 1) is 973 (range: 506–4517) and 28 articles reached > 1000 citations. The publication years ranged between 1963 and 2014. Of the identified articles, 17 were reviews, of which 7 were (co-)authored by Gregg L. Semenza.

The mean number of citations of the top-100 articles related to cancer is 493 (range 213–2045). Only three articles were published prior 1995 (range: 1978–2018). Ten articles have > 1000 citations. Overall 31 articles related to cancer (Table 2 displays the top-25, all published since 1995; 11 are review articles) would be in the top-100 articles on hypoxia.

Of the top-100 articles on hypoxia, only 7 were on the pathophysiological responses and risks of hypoxia, 13 on the physiological responses to hypoxia, and most of them (80) on the molecular responses, mainly related to the HIF-1 pathway.

We did not identify any articles on the application of hypoxia either for therapeutic use (i.e., hypoxic conditioning in patients) or for performance enhancement (i.e., altitude training in athletes) in the top 100. However, there is a large increase in the number of citations in the “sport sciences” journals (Fig. 1), starting in the 1960s with an important rise in the last twenty years.

Wang et al. [130] published the most-cited article in 1995. Consequently, to display the impact of the discovery of the HIF pathway on the body of literature related to hypoxia, we arbitrarily chose to analyze two distinct periods

(until 1994 vs. since 1995): it is striking that only 12 of the top-100 most-cited articles on hypoxia and only 3 articles of the top-100 articles related to cancer were published prior 1995. Moreover, before 1995, only 5 articles reached 1000 citations. Since 1995, 27 articles reached 1000 citations, most of them on the HIF-1 pathway.

The three journals with the larger number of the top-100 articles published on hypoxia are *The Journal of Biological Chemistry* (26 articles), *PNAS* (11), and *Molecular and Cellular Biology* (8), while the preferred journals for the top-100 articles related to “cancer” were *Cancer Research* (17), *PNAS* (7), and *British Journal of Cancer* (6).

An outstanding point is that the Nobel laureate Gregg Semenza published 27 of these most-cited articles on hypoxia, including 10 with GL Wang as a co-author (including the most cited article in the list).

Discussion

The presented descriptive overview of the current biomedical literature provides some insights into the evolution of the research related to hypoxia:

1. The mechanistic investigation of how the body adapts to hypoxia is an important topic in biology and medicine since “the responses to oxygen in the cells and organisms is one of the most central physiological adaptation that animals have” (statement of the Nobel assembly).
2. The HIF pathway discovery in the 1990s, which was made possible with the increasing effectiveness of the molecular biology methods, opens the way to many

medical or pharmacological applications in many diseases, especially cancer. Since the literature on clinical applications of hypoxia is still relatively scarce, harnessing related strategies seems to be still at an early stage and requires future research.

3. Altitude training for sport performance enhancement is an important topic in sport sciences but attracts relatively limited attention compared to the overall hypoxia research field.

There is a long-term interest in medical sciences for hypoxia. This is shown by the increase in the total number of citations starting in the 1960s. Great studies have been published on pathophysiological and systemic physiological responses to acute hypoxia or to adaptations to prolonged exposure. One perfect example is the study by Shweiki et al. [120] on angiogenesis that is the most-cited article (3721 citations) prior 1995.

The scientific importance of the HIF pathway is confirmed by the large majority of publications based on molecular approaches related to HIF. Importantly, 97 of the top-100 articles on hypoxia have been published since 1995 with 27 having > 1000 citations. Thus, the early 1990s period—characterized by a switch from non-molecular to highly molecular-focused research—could be regarded as the period “when mountains moved.” This is further supported indirectly by the recent (end 1990s) increase in citations of the articles on hypoxia and cancer. Unsurprisingly, there is a large number of review articles (i.e., 17 in top-100 on “hypoxia”; 11 in the top-25 articles on “hypoxia and cancer”) in the most-cited ones. This has to be taken into account since the publication of original data is associated with different citation patterns than the publication of review articles.

Surprisingly, although several molecular articles on cancer suggested clinical potentialities and the fact that the Nobel committee awarded the prize also for the potential clinical applications, to date none of the clinical articles reached the top-100 position yet. While there is an increasing body of literature on the pros and cons of hypoxic conditioning, most of these papers have been published very recently. Similarly, the articles on the application of hypoxia in athletes exhibit a comparable minor impact, although the most-cited article of this field by Levine and Stray-Gundersen [66] reached 493 citations. Of interest is the discrepancy between the continuous increase of citations in “sport sciences” journals (Fig. 1) and the fact that the most-cited articles are almost exclusively in-vitro/in-cellulo molecular studies (Table 1). Our analysis shows that there is no decline in the (applied) physiology studies but the highly cited molecular studies “dilute” their numbers. Similar trends likely occur in many other “biomedical” fields.

One obvious limitation of this type of bibliometric analysis is the relevance of the citations number as metrics for assessing the research impact. Important articles for specific fields (e.g., mainly relevant for clinicians) may be cited more rarely than their (theoretical or practical) impact would suggest.

In conclusion, the discovery of the HIF pathway and of its molecular regulation in the early 1990s has revolutionized the research on hypoxia with the emergence of a considerably growing interest for its link to cancer. However, studies on clinical applications of hypoxia remain of comparatively lower interest yet but are promising.

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Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical Approval Not applicable.

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