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REVIEW ARTICLE **OPEN ACCESS**

Hypoxia-Inducible Factors-1 in Malignancies: Causative to Restorative

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ABSTRACT
Hypoxia is a condition where the cells are deprived of oxygen. This environment during the progression of the tumor masses will deprive the surrounding tissues and cells of available nutrients and oxygen which will in turn result in a molecular response leading to the transcription of Hypoxia-Inducible Factors (HIF-1). HIF-1 is involved in regulating several genes that are actively associated with angiogenesis, erythropoiesis regulation of pH along with various other metabolic pathways and these adaptations are crucial for the tumor cells for their clonal selection resulting in malignancy. To identify the mechanisms that enable the cells to adapt to the hypoxic conditions and recognize them as important targets for the treatment of cancer as well as to explore their significant role in restorative functions of the cell and to provide a link between the causative and restorative roles of HIF-1. Methods: Relevant published databases were searched and collected and the required data were included from the peer-reviewed, research articles from authentic sources as PubMed, Scopus, Web of Science, and Google Scholar. The systematic advancements in the area were noted for the review. Elevated levels of HIF have often been observed with increased metastasis and cell proliferation and for this reason, they can be recognized as important drug targets in cancer treatment. Thus, a clear understanding of the HIF pathways in carcinogenesis by identification and integration of the biomarkers involved is an advanced area for study, treatment, and for the development of drugs in the therapy of cancer.
Keywords: Hypoxia, HIF, HIF-1, HIF-1α, Cancer, Malignancies.

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INTRODUCTION

Hypoxia is characterized by diminished oxygen accessibility. The living organisms need a sufficient delivery of oxygen to the cells and tissues to perform their aerobic metabolism and energy generation. However, when cells and tissues fail to meet the sufficient amount of oxygen, it is known as hypoxia or oxygen deprivation. Since hypoxia may affect survival, cells and life forms have developed a few versatile systems, with many happening at the transcriptional level. O_2 concentration is markedly reduced in the core of tumors, where tumor cells are rapidly proliferated and form solid tumor masses. The poorly oxygenated tumor cells (pO2 <7 mmHg) begin to adapt to these low oxygen tension by a series of adaptive responses. During hypoxia, the proteome of the malignant cells undergo changes that can result in reduced cell growth, cell-cycle arrest, apoptosis ,and ultimately cell death. This phenomenon is common in tumor masses and leads to the dysfunctional blood supply and is characterized by epithelial-to-mesenchymal transition phenotype which facilitates metastasis.

Thus, when microenvironments surrounding these tumor cells are extremely hypoxic, the growth and proliferation of such masses is possible by the activation of the HIF pathway which brings about vasculature and thereby expanded the oxygen delivery to the region. [1,2]

The importance of HIF 1 in the cancer physiology has been a point of extensive discussion and concern. Here, the mechanisms associated with the cell adaptation in hypoxic conditions where it plays causative roles are considered ;after which the restorative or therapeutic potential as drug targets are discussed.

METHODOLOGY

A literature review of the published articles regarding the various mechanisms and pathways associated with hypoxia were collected including the therapeutic importance of HIF inhibition. A descriptive search and analysis was carried out using the popular Internet-based scientific databases such as Science Direct, PubMed, Springer, Elsevier etc. as well as in other sources such as research paper-based journals and scientific books that were available using the keywords HIF-1, cancer, malignancy, hypoxia etc. Other relevant sources of information were also reviewed thoroughly and the suitable articles were selected and finally put together to form the review article.

DESCRIPTION

The Normal Regulation Of Hypoxia Inducible Factors

The hypoxia inducible factor (HIF-1) serves as a crucial regulator of tumor cells to hypoxic environments by activation of 100 downstream genes that control the biological process required for survival and progression of tumor.It is a heterodimeric transcription factor consisting of subunits HIF-1α and HIF-1β.The α subunit has 3 isoforms called the HIF-1α, HIF-2α ,and HIF-3α.[3]The HIF-1α and HIF-2α functions similarly, and researches suggest that HIF-3α is relatively scarce since it is a negative regulator.

The functioning of HIF-1 essentially depends on the availability of HIF- 1α levels and its expression is governed by various translation process; wherein proteins are synthesized and proceeds via O_2 independent mechanism and protein degradation regulated primarily through O_2- dependent mechanisms. The molecular expression of HIF-1 is regulated by two complementary mechanisms , non-hypoxic and hypoxic factors .

Non Hypoxic factors

The cells respond to the diminished oxygen by expanding the degrees of HIF 1 through different post-transcriptional alterations. The decreased oxygen levels activate and causes the transcription of HIF-1α by various pathways like hydroxylation, phosphorylation, acetylation, sumoylation, ubiquitylation and S-nitrosation.[4] In hypoxia, the PHD (proline-hydroxylase domain-containing molecules) causes prolyl hydroxylation in HIF-1, which acts as a signal for pVHL(von Hippel-Lindau protein) ubiquitylation and ensuing stabilization of HIF-1a. [5] After hydroxylation, the pVHL, acts as a suppressor and causes the ubiquitination of HIF-1α. This ubiquitinated form will then facilitates the degradation of the proteasome. [6]When oxygen is present, the FIH(Factors Inhibiting HIF) hydroxylates HIF-1α resulting in a buildup of aspargine on the C-end, in this way inhibiting the role of coactivators p300/CBP and inactivates the transcription of HIF-1α .[7]

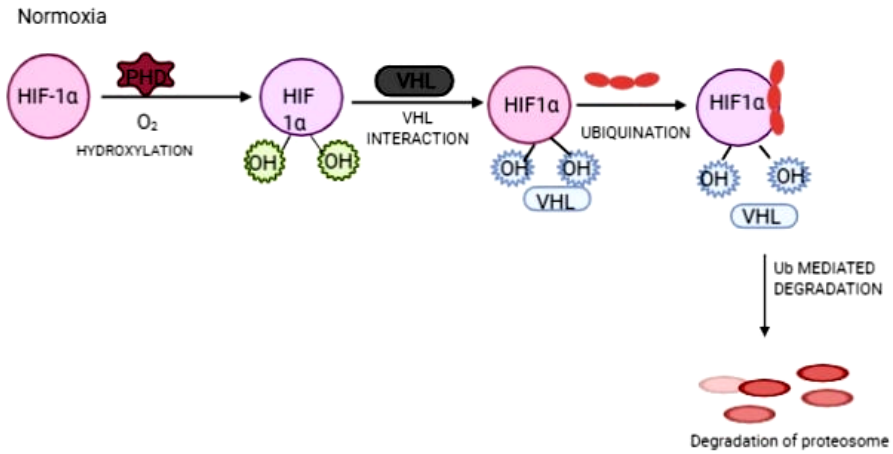

Figure 1.Regulation of HIF- α during normoxia

Hypoxic factors

During hypoxia, the activity of PHD and FIH are hindered and the enzymes lose their activity and inhibit the hydroxylation of HIF-α. In this way, the degradation HIF 1 α protein is halted and this facilitates the translocation of HIF-1α to the core and dimerizes with HIF-1β. The HIF-1α- HIF-1β heterodimer will then associate with HRE (Hypoxia Response Elements) in the nucleus within A/GCGTG sequence on the target genes.[8]This binding will lead to the transcription of several genes that are involved in the processes of angiogenesis, digestion, pH homeostasis, proliferation, metastasis and apoptosis.

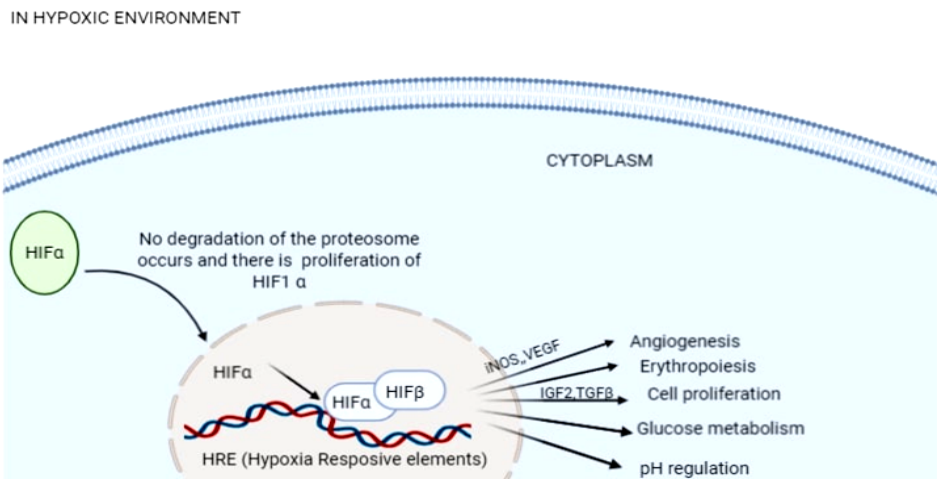

Figure 2 :Regulation of HIF -α during hypoxia.

The Role Of Hypoxia In Progression And Metastasis In Cancer

Overexpression of HIF-1α activates many crucial functions leading to cancer such as angiogenesis, cell proliferation,glycolysis,metastasis and resistance to treatment. Various proteomic alterations during hypoxia allow tumor masses to overcome their O_2 deprived state and survive through the following adaptations:

Hypoxia-induced angiogenesis, activation of the pathways of glycolysis and inhibition of apoptosis.

The blood vessels consist of a large network of tubes and capillaries which provide oxygen and nutrients to the entire body. In tumor cells, there is an extreme energy demand and in this case a reduced vessel formation creates a hypoxic environment. Moreover, the formation of new vessel is vital for hyperplasia to transform to neoplasia. So, abnormal angiogenesis is a pathological feature for tumor progression.

The shift in angiogenesis happens when HIF-1α facilitates the translation of various factors, for example, VEGF, stromal-derived factor 1,angiopoietin 2,cyclooxygenase 2 and other undifferentiated factors.[9-11] It was also demonstrated the levels of VEGF in glioma cells there is increased levels of HIF expression and by inhibiting HIF by transfection of predominant negative HIF-1α or siRNA decreased VEGF discharge and cell differentiation and proliferation.[12].In this way an elevation in the oxygen-carrying capacity of the hemoglobin through the activation and transcription of the genes coding for erythropoietin and transferrin happens thereby facilitating the increased delivery of oxygen to the tumor cells.

Facilitating the detachment of adhesion molecules by their downregulation when the oxygen level drops in the tumor cells.

An evident sign of a metastasizing cell is the transition from it's epithelial nature to a mesenchymal form which is often referred to as the epithelial-mesenchymal transition which is characterized by a loss in the cell-to-cell adhesion which is a character of the epithelial cells. Here, HIF-1 coordinates the connection of numerous EMT controllers thus playing a major role in the malignant proliferation of these cells. Numerous reports have depicted that activity of HIF-1α in disease favors malignancy by aiding in the loss of E-cadherin. [13]

Stimulating the signaling network in cancer cells by activating the various pathways such as HIF, MAPK(Mitogen activated protein kinase), PI3KB (Phosphoinositide 3 Kinase), NFκB(nuclear factor-κ-B) and diminishes or enhance its hypoxic effects by causing positive and negative feedback mechanisms and upregulation of specific growth factors like platelet-derived growth factor-B (PDGF-B), epidermal growth factors(EGF) and other elements that are involved in malignant proliferation.

When the number of cells increases in a tissue,the oxygen consumption also increases.So, after each cycle of cell division, the oxygen utilization will be more. And as cells proliferate in the case of the tumor the expression of VEGF is increased, which stimulates angiogenesis resulting in further perfusion that will meet the raised oxygenation demands of the expanded cell numbers.

The activity of a number of HIF-1 signals happen free of oxygen focus. They are principally proteins, which control the HIF -1 translation, differentiating efficiently in the presence of these hypoxic stimuli at this level, which causes the expression and stabilization of α-subunit. Proteins like the phosphatidylinositol 3- kinase (PI3K) pathway and protein kinase C (PKC) are involved in increased HIF-1α expression. In the case of PKC there is an elevated the expression of the ribosomal protein S6 and the phosphorylation of this protein in normoxic conditions, activates HIF-1α mRNA expression and in this

way reduces the degradation of the proteasome and increases the levels of HIF-1 complex in the cell. The PI3K pathway functions by activating HIF-1α through various lipopolysaccharides which mainly takes place in the macrophages and the vascular smooth muscles. [14,15]
Certain growth factors also stimulate the levels of during hypoxia ,particularly in two different manners. First, in the presence of hypoxia, the transcription of the HIF-1α is facilitated by the growth factors present in almost all cell types in a cell-dependent manner. Second, in hypoxia is the cytokines, growth factors and other molecules of the signaling pathways direct the synthesis of HIF-1α through the activation of the phosphatidylinositol 3-kinase (PI3K) or mitogen-activated protein kinase (MAPK) pathways.[16-20]
As mentioned, various adaptive pathways are initiated when the HIF-α dimerizes with the HIF-β subunit by the means of different gene transcriptions when the oxygen level falls.This process is also regulated in an oxygen-independent manner by induction of the IL-1β via cyclooxygenase 2 (COX-2) pathway.Here,the arachidonic acid is converted to mediators like prostanoids in the presence of cyclooxygenase 2 .The formed prostanoids increase the levels of HIF-1α even in the absence of hypoxia.[21] The Cyclin-Dependent Kinases (CDKs) can modulate the activity of HIF-1α by over-expression of CDK1 and promote lysosomal degradation.[22]
Under hypoxic conditions, the low-level non-coding, single-stranded regulatory MicroRNAs (miR-20b) bind with HIF-1α protein and activates it. The intracellular reactive oxygen species (ROS) activates HIF-1α protein in both hypoxic and normoxic conditions. This involves phosphorylation and finally stabilizes HIF-1α under normoxic conditions, that cause intracellular hypoxia.[23] For example, when fatty acids induce the mitochondrial uncoupling,it stabilizes HIF-1α in adipocytes in a high-fat diet.[24,25]

Cell growth

The transcriptional activation of HIF-1α and the FIH, on the basis of the dependence of oxygen for its function enables them a strong selection of different gene profiles that influences the cell growth. The hypoxic conditions often render the arrest of the phases of the cell cycle mostly in the G1/S phase.[26] This selectivity is also aided by the differential action of the three subunits of HIF-α and can facilitate cell proliferation or cause cell death .[27,28]

Metabolism

To begin with, HIF-1α invigorates glucose take-up important to make up for the general wastefulness of glycolysis, by upregulating glucose transporters like GLUT1 and GLUT3. [29,30]Secondly, it upregulates the glycolytic compounds like hexokinases and phosphoglycerate kinase 1. [31] Third, it hinders mitochondrial role by activating pyruvate dehydrogenase kinase (PDK), which phosphorylates and inactivates pyruvate dehydrogenase (PDH) and further catalyzes the change of pyruvate to acetyl-CoA, a rate-limiting part to step into the TCA cycle .[32,33]
Hypoxic cells can likewise switch among carbohydrates and aminoacids like glutamine precursors for the synthesis of unsaturated fat,through HIF-1α interceded proteolysis of ketoglutarate dehydrogenase.[34,35] This reductive carboxylation of the amino acid glutamine saves glucose in a hypoxic environment for malignant growth of cells furthermore, permits the production of macromolecules from the Kreb's cycle intermediates when mitochondrial transformations repress oxidation of glucose. Besides, HIF-1α initiates expression of unsaturated fat restricting proteins ;FABPs that are associated with unsaturated fat transport.

Clonal Changes

Certain clonal changes like gene mutations, gene amplification, alterations in the chromosome structure through rearrangements are induced by hypoxia that will promote the proliferation of the malignant masses by mechanisms that either activate the oncogenes or inactivate the tumor suppressor genes resulting in metasatsis. A classic example is the activation of genes encoding for increasing vasculature by angiogenesis. The general impact of mutations caused by hypoxia has profoundly increased the gene variants. It has likewise been proposed that hypoxia strongly favors the development of tumor masses. [36-39] Along these lines, any metastasized cell with such genomic or proteomic alterations that enables survival under hypoxic conditions which include poor regulation of the cell-cycle,cell division/death, or expanded angiogenic potential will exhibit a positive selection compared to the normal cells. Also,the progeny of these selected cells will divide at an accelerated rate over the non-adapted cells and in the long run will turn into the predominant cell subpopulation inside the tumor. Also, these cells have progressively great metastasis capacity and undergo extensive proliferation, which is a scope for the clinical discoveries of expanded locoregional spread, tumor metastasis, and resistance to treatment.

THERAPEUTIC TARGETS IN THE HIF-1 PATHWAY: CANCER

A clear picture of the mechanisms by which these factors are regulated has to be thoroughly understood to bring about an intervention that can rightly serve as therapeutic agents to treat these masses to bring about the proper diagnosis.Therefore,suppression of HIF-1 by downregulation is a promising field to terminate or suppress the progression of cancer because the ability of the cells to adapt to the anaerobic environment is halted.

One of the most significant approaches to achieving this downregulation is through the activation of hydroxylases which targets and leads to the degradation of the HIF-1 complex.These hydroxylases belong to the superfamily of 2-oxoglutarate (2OG)-dependent oxygenase and what is crucial is that a ferrous ion is present in their active site and important for the functioning.Therefore,the degradation is further aided by co-adminstering iron and ascorbate along with activating the hydroxylases. [40]The broad rundown of HIF activation gives a molecular environment to the numerous impacts of intratumoral hypoxia on the development of malignancy, and the detailed relationship between HIF-1α overexpression and unfavorable results in cancer patients.

A few medications are being created which will shut off HIF action with the objective of repressing tumor development and angiogenesis.

Direct inhibition of HIF-1 blocks transactivation, DNA binding, transcriptional action of HIF-1α,while indirect HIF-1 inhibition work by obstructing the HIF-1a translation. Hindering HIF-1 offers a novel method for balancing the tumor specialty and may have promising clinical results. Right now accessible HIF-1 inhibitors endure a colossal holding up of function because of their vague method of activity. When a share of HIF-1 inhibitors known so far shows antitumor activity by HIF-1a inhibitory system, which incorporates HIF-1 however isn't constrained to it. While on the other hand, some HIF-1 inhibitors have a more sophisticated HIF-1 inhibition which potentially includes hindering a few points in the HIF-1 pathway in a non-specific manner.

Just a couple of instances of HIF inhibitors that possibly target particular pathways related with HIF initiation have been depicted, among which echinomycin[41] and engineered polyamides [42] that repress HIF-1, and chetomin. [43] Furthermore, continuous efforts on focusing on dimerization of HIF-a with HIF-1β may prompt unforeseen outcomes,[44,45] given the ongoing evident accomplishment of inhibitors of the protein-protein complex. In any case, none of these has been up to this point proposed for clinical advancement. Interestingly, a developing rundown of nonselective HIF-1 inhibitors has been produced in the course of the most recent couple of years. [46,47]

The majority of the depicted HIF-1 inhibitors do as such by changing signal transduction pathways that are in an alternate way related with HIF or that are a piece of increasingly complex pathways applicable to human malignant growth, plainly restricting the particularity of their movement. Molecular inhibitors of HIF have been recognized that target chaperone proteins,[48,49]microtubules [50],topoisomerase I[51], solvent guanylate-cyclase,[52] and thioredoxin, [53] just as various signaling pathways that have been related with HIF-1a initiation including the mammalian target of rapamycin,[54,55] AKT,[56] Her2/Neu,[57] epidermal growth factor receptor, farnesyltransferase [18] Bcr-Abl,[58] and histone deacetylase[59].From a viewpoint, the association of HIF-1a in such an expansive scope of these pathways underlines its potential job as downstream ''effector'' agents on which various pathways may merge; then again, it brings up the cause of how to decide the HIF-1 inhibition to tumor development in every individual case.

Some other agents which are employed are inhibitors mRNA expression of H1F-1.Here the regulation is bought about in the translational level leading to the degradation of HIF-1 as the expression is halted. Aminoflavine which acts by inhibiting the HIF-1 mRNA expression is an example.[60]

Cardiac glycosides have also been identified as agents that affect the translation of HIF-1. Digoxin has particularly been recognized as a potent HIF-1 inhibitor. It acts by inhibiting the translation of H1F-1 using mTOR-independent mechanism and has shown anticancer effects.[61]

Far from to cytotoxic compounds that are given for short courses at the most extreme endured portion to exploit the destruction of malignant growth cells, HIF-focused on therapeutics ought to be focused on accomplishing continued HIF inhibition.

Following are some of the inhibitors employed in the cancer therapy by inhibition of HIF:

Table 1: HIF inhibitors.[62]

Mechanism of Inhibition	Agents
Inhibition of transcription of HIF-1a	
HIF-1a DNA binding inhibitors	Polyamides
HIF-1a/HIF-1b dimerization inhibitors	Acriflavine
HIF-1a transcriptional activity inhibitors	Chetomin
Inhibitors of HIF-1a protein translation	
mTOR inhibitors	Temsirolius
PI3K inhibitors	Wortmannin
Microtubule disrupting agents	2-Methoxyestradiol
Topoisomerase I and II inhibitors	Camptothecin
Inhibitors of HIF-1a protein degradation	
Hsp90 inhibitors	Galdanamycin
Histone deacetylase (HDAC) inhibitors	Trichostatin A
Protein and nucleic acid inhibitors	
HIF-1a stability inhibitors	Metallothioneins
Transcriptional activity inhibitors	Herceptin
mRNA and protein expression inhibitors	Small interfering RNA

Resistance To Radiation And Other Drugs:

Though, cells in these oxygen deprived hypoxic states are impervious to apoptosis, because of production of DNA radicals is greatly reduced and due to this there is decreased damage to the DNA,[63]and the stages of the cell cycle determine the sensitivity to radiations in the malignant masses. Studies have shown that the tumor masses in the S and the G1 phase were almost resistant towards the radiation.On the hand, the cells in the G2/M phase exhibited radiosensitivity as it is during this stage that the DNA repair shows most damage.[64]

An example of this is the in case of head-and-neck malignant growth tests with high resistance towards the chemotherapeutic agent carboplatin was observed along with increased levels of HIF-1α and HIF-2α which is supposed to aid this resistance.The conclusion was made because the biopsies of the chemosensitive tumors showed reduced expression of HIF-α.[65]

Another example is in the case of oropharyngeal tumors, the patients showed high expression of HIF-1α and therefore a lower probability to accomplish total reduction after irradiation.[66]Moreover, it has also resulted in the transcription of HIF-1, leading to angiogenesis. Therefore HIF-1 speaks to a substantial prescient marker and restorative objective for control, in a mix with chemotherapeutics and radiotherapy, as a treatment target.

Due to the above-mentioned reasons, the anticancer agents which include the radiation and drugs especially focus on the core part of quickly multiplying tumor cells.

CONCLUSION

Hypoxia manages tumor neovascularization, cell survival as well as death. Since hypoxia means expanded tumor proliferation and demeaning the ability and strength of the patients, immediate and backhanded techniques for estimating hypoxia joined with clinical perceptions may assist with foreseeing patient's result just as recognize patients who could profit by hypoxia/HIF-focused medications. Better comprehension of hypoxic models and in-depth understanding of the hypoxia-inducible reactions and signaling pathways will allow various novel focuses sooner. It has been featured that the role of HIF shifts in various settings. Different investigations have displayed that HIFs are upregulated in tumor cells. HIF-1 depicts a pleiotropic part by boosting different molecular and genetic strategies connected with tumorigenesis.

LIST OF ABBRIVATIONS:

HIF = Hypoxia Inducible Factors
PHD = Proline-Hydroxylase Domain-containing molecules
FIH = Factors Inhibiting HIF
pVHL = von Hippel-Lindau protein
HRE = Hypoxia Response Elements
VEGF = Vascular Endothelial Growth Factor
EMT- = Epithelial-Mesenchymal Transition

MAPK = Mitogen activated protein kinase
PI3K = Phosphoinositide 3 Kinase
NFκB = Nuclear Factor-κ-B
PDGF-B = Platelet-Derived Growth Factor-B
EGF = Epidermal Growth Factors
PKC = Protein Kinase C
COX-2 = Cyclooxygenase 2
CDKs = Cyclin-Dependent Kinases
GLUT = Glucose Transporters
PDK = Pyruvate Dehydrogenase Kinase
PDH = Pyruvate Dehydrogenase
FABPs = Fatty Acid-Binding Proteins
TCA = Tricarboxylic Acid Cycle
2OG = 2-Oxoglutarate
mTOR = mammalian Target of Rapamycin

ETHICAL ISSUE
Not applicable.

DECLARATION OF INTEREST
The authors declare that they have no relevant financial and non-financial competing interests with any organization. The authors alone are responsible for the content and writing of this article.

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