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Tumor Discovery

REVIEW ARTICLE

Dysregulated heme metabolism in cancer progression: Pathways, biomarkers, and therapeutic challenges

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Abstract

Heme, a vital inorganic compound consisting of a tetrapyrrole protoporphyrin ring (protoporphyrin IX) with an iron ion at its core, is essential for several metabolic processes, including the electron transport chain, oxidative phosphorylation, glycolysis, and the tricarboxylic acid cycle. As a critical cofactor for enzymes such as hemoglobin, myoglobin, cytochrome P450, and peroxidase, heme is fundamental to normal cell function at physiological concentrations, and above these concentrations, it can also act as a driver of oncogenesis. Dysregulated heme metabolism profoundly impacts cancer biology, affecting tumor growth, progression, and resistance to currently available treatments. Disruptions in heme homeostasis alter redox balance, modulate immune responses, and increase metabolic flexibility within the tumor microenvironment (TME). Elevated levels of heme oxygenase, a key enzyme responsible for heme degradation, and other enzymes of the heme biosynthetic pathway—including transporter and trafficking proteins—are associated with enhanced cancer cell survival, therapeutic resistance, and immune evasion. Moreover, the buildup of porphyrins (porphyrin overdrive) within the TME has potential utility as a biomarker for early cancer detection and monitoring. This review synthesizes the literature on tumor-derived heme and its role in multiple cancers, emphasizing the significance of considering heme as a major factor in oncogenesis, including tumor initiation, progression, and resistance to current treatment options.

Keywords: Heme; Porphyrin overdrive; Tumor microenvironment; Metabolism; Therapy resistance

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Citation: Yadav AK, Singh P, Murali R, Venkatraman G, Gandhirajan RK. Dysregulated heme metabolism in cancer progression: Pathways, biomarkers, and therapeutic challenges. *Tumor Discov*. 2025;4(4):56-75. doi: 10.36922/TD025080015

Received: February 23, 2025

Revised: June 19, 2025

Accepted: July 3, 2025

Published online: August 29, 2025

1. Introduction

Heme, an organometallic compound, consists of a tetrapyrrole protoporphyrin (Pp) ring (PpIX) with an iron ion embedded at its center. This iron ion can exist in multiple oxidation states, primarily ferrous ion (Fe^{2+}) and ferric ion ($Fe3^{+}$).[1] Heme plays a pivotal role in regulating several metabolic processes, such as glycolysis, oxidative phosphorylation (OXPHOS),[2] and the electron transport chain (ETC).[3] It also acts as a coenzyme for many holoenzymes and essential proteins (e.g., hemoglobin, myoglobin,

cytochrome P450, and peroxidase) found in almost all living organisms, ranging from the simplest forms to more complex eukaryotes.[4] It is also central to many biological processes, including oxygen transport, drug and steroid metabolism, catalysis, and mitochondrial electron transport (Complex II–IV).[2,4] It is a cofactor for several enzymes directly involved in the antioxidant defense system.[5]

Beyond its role in cellular processes, heme also functions as a signaling molecule involved in diverse signal transduction pathways and protein complex assembly[6] (Figure 1). The physiological concentration of heme influences the transcription and translation of several genes, necessitating tight regulation of its synthesis and degradation.[7] Elevated heme levels are associated with various pathological conditions, including hemolytic anemia, sickle cell disease, porphyria, rhabdomyolysis, and several cancers.[8] Heme plays a dual role: on the positive side, it can suppress tumors by regulating ferroptosis; on the negative side, it can promote carcinogenesis by generating reactive oxygen species (ROS), modulating immune cell function, promoting dysbiosis, and inducing inflammation.[9]

This review summarizes recent findings on the role of heme in different cancers and highlights differentially regulated genes in the heme biosynthesis, homeostatic, and trafficking pathways across tumor types. In addition, this review explores the key role of heme within the tumor microenvironment (TME) and how it supports cancer cell growth and proliferation.

2. Physiological heme biosynthesis and trafficking

The term "heme metabolism" describes the metabolic reactions that result in heme synthesis, catabolism, and function. Heme biosynthesis is a highly conserved and regulated process that occurs in almost all living organisms. Nearly all multicellular eukaryotes biosynthesize heme at some point in their development or throughout their lives.[10] In humans, erythroid cells and hepatocytes are the primary sites of heme biosynthesis. While developing erythroid cells account for the majority of heme production, the liver contributes approximately 15% of the total heme synthesized in the body.[11] Bone marrow is the primary locus involved in synthesizing red blood cells, which require a large amount of hemoglobin for oxygen transport, followed by the liver, which is dedicated to the production of cytochrome P450, a marker enzyme of the endoplasmic reticulum critical for the metabolism of drugs, toxins, and other xenobiotics.[12]

In the first step of biosynthesis, succinyl co-A, a key precursor molecule, is condensed with glycine to form δ-aminolevulinic acid (ALA) by a mitochondrial enzyme, ALA synthetase, which also acts as a regulatory enzyme of the heme biosynthetic pathway. The formed ALA then translocates from mitochondria to the cytoplasm through passive diffusion, where the enzyme ALA dehydratase (ALAD) catalyzes the condensation in which two molecules of ALA form porphobilinogen (PBG)—a monopyrrole structure and the essential substrate for the porphyrin ring (a four-pyrrole subunit ring). The next step involves uroporphyrinogen (URO) synthetase, also called PBG deaminase, and URO III synthase (UROS), which convert PBG into URO III. The formed URO undergoes a decarboxylation reaction catalyzed by URO decarboxylase (UROD) to form 4-carboxyl coproporphyrinogen. Subsequently, porphyrinogen oxidase catalyzes oxidative decarboxylation, converting coproporphyrinogen into protoporphyrinogen. In the final step, ferrochelatase (FECH) catalyzes the insertion of Fe^{2+} into protoporphyrinogen to form heme[12] (Figure 2).

In addition to being synthesized *in vivo*, heme can also be obtained from the diet as myoglobin and hemoglobin, which are particularly prevalent in foods high in red meat (e.g., beef, veal, lamb, mutton, pork, and offal) and processed meat. The term "red meat" describes unprocessed muscular meat from mammals, while "processed meat" is meat that has been modified to enhance its flavor or extend its shelf life through processes such as salting, curing, fermenting, and smoking.[13] The availability of iron occurs through absorption either in the form of heme iron or non-heme iron.[14] Cytochrome B is present in the intestinal lumen and catalyzes the conversion of non-heme iron into Fe^{2+}, which is later absorbed through divalent metal transporter 1, also known as SLC11A2/DCT1/NRAMP2.[15]

Due to the complex porphyrin ring structure and charge, heme does not cross the plasma membrane directly. To compensate, two mechanisms are proposed to mediate its transport across the membrane: (i) receptor-mediated endocytosis in microvilli, which promotes heme binding and internalization and (ii) direct transport through the heme-specific transporter heme carrier protein 1.[16]

Heme trafficking is maintained by the feline leukemia virus subgroup C receptor (FLVCR) gene, a member of the SLC49 family, which encodes FLVCR1a and FLVCR1b, expressed as transporters on the surface of the plasma membrane and mitochondria, respectively. FLVCR1a is responsible for exporting heme synthesized in mitochondria into the cytosol, whereas FLVCR1b exports heme from the cell to the extracellular space to prevent cell toxicity. Together, these transporters help maintain heme homeostasis under a physiological state.[17-19]

Heme oxygenase (HO), an oxidoreductase residing in the endoplasmic reticulum, catalyzes intracellular

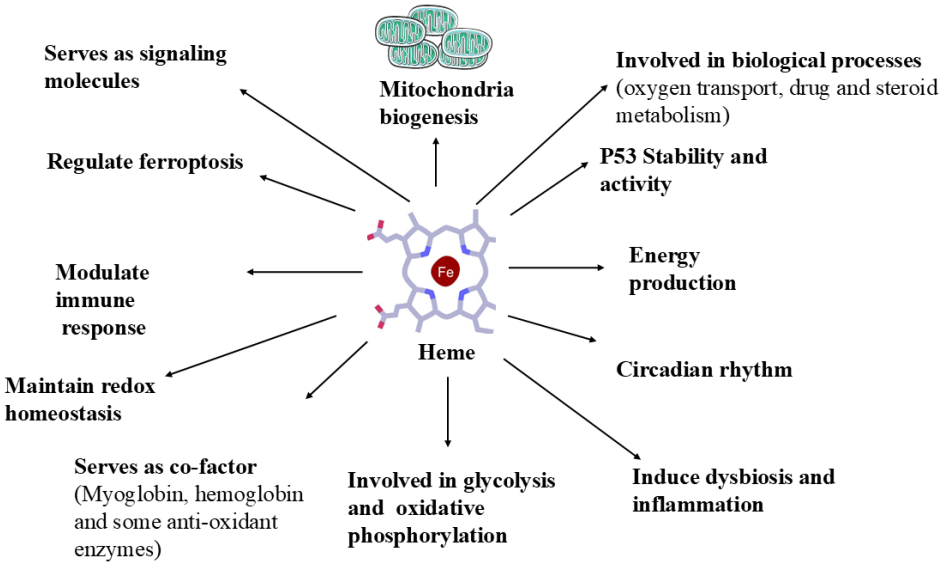

Figure 1. Multifaceted roles of heme in cellular processes. Heme is essential in numerous cellular functions, serving as a cofactor for various holoenzymes and facilitating critical biochemical reactions. Beyond its enzymatic roles, heme participates in processes such as immunomodulation, regulation of redox balance, gene expression, and signal transduction, highlighting its broad impact on cellular physiology. Image created using Servier Medical Art (https://smart.servier.com/).

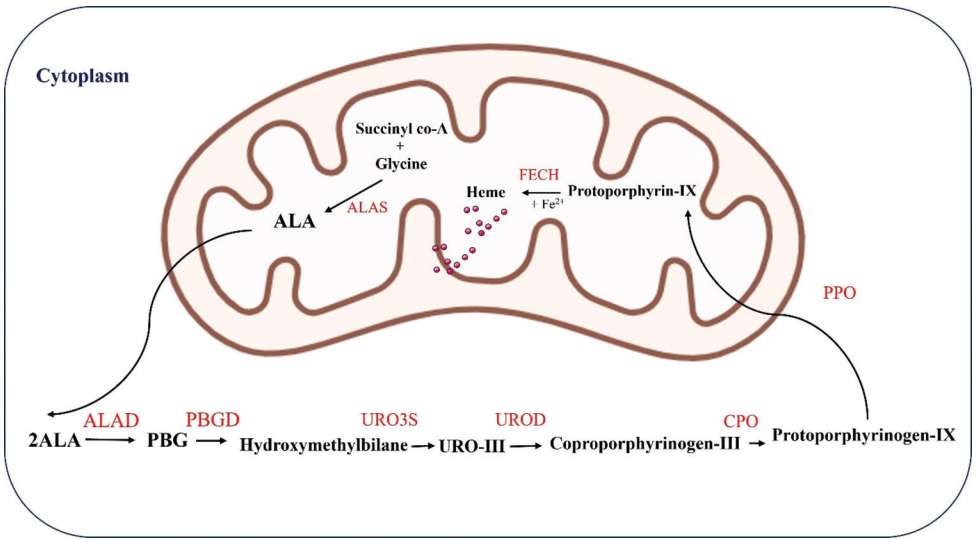

Figure 2. Heme biosynthetic pathway. The diagram illustrates the stepwise enzymatic pathway of cellular heme synthesis. Key enzymes include ALAS, ALA, ALAD, PBGD, URO3S, UROD, CPO, PPO, and FECH. The initial and final steps occur in the mitochondria, whereas the intermediate steps occur in the cytosol. Image created using Servier Medical Art (https://smart.servier.com/).
Abbreviations: ALA: Aminolevulinic acid; ALAD: Aminolevulinic acid dehydratase; ALAS: Aminolevulinic acid synthase; CPO: Coproporphyrinogen oxidase; FECH: Ferrochelatase; PBGD: Porphobilinogen deaminase; PPO: Protoporphyrinogen oxidase; URO3S: Uroporphyrinogen III synthase; UROD: Uroporphyrinogen decarboxylase.

heme degradation into biliverdin (BV), carbon monoxide (CO), and Fe^{2+}. BV is further converted into bilirubin by BV reductase, a potent antioxidant molecule that protects cells from oxidative damage.[20] CO is a well-recognized endogenous signaling molecule with diverse pathophysiological and pharmacological roles. It plays a crucial role in immunomodulation, organ protection, and circadian clock regulation.[21,22] In addition, CO is involved in several cellular processes, including anti-inflammatory responses, vasodilation, apoptosis modulation, and cell proliferation.[23] Free iron ions can function as Fenton reagents and catalyze ROS production, such as hydroxyl

radicals (OH^-) and lipid peroxides. These reactive species cause oxidative damage to lipids, proteins, and DNA, ultimately causing tissue injury and cell death.[24] Therefore, iron homeostasis is tightly regulated, with excess iron stored in the form of ferritin.[25]

Three isoforms of HO are present: HO-1, HO-2, and HO-3. HO-1, also known as stress or heat shock protein 32, is coded by the heme oxygenase 1 (*HMOX1*) gene located on chromosome 22q13.1. Most mammalian tissues exhibit low basal expression of HO-1, but several factors, including the presence of its substrate heme, heavy metals, inflammation, ultraviolet light, oxidative damage, and hyperthermia, lead to its upregulation.[26] HO-2 shows relatively stable expression compared with HO-1 and HO-3 and is also involved in protecting cells against oxidative stress. HO-3 is less studied, but some studies suggest that it functions similarly to HO-2, although with lower catalytic activity.[27] Under physiological conditions, - primarily catalyzes heme degradation; when heme levels become excessive, HO-2 facilitates its degradation.[28,29] The cytoprotective function of HO-1 shields cells from the adverse effects of radiotherapy, chemotherapy, photodynamic therapy (PDT), and other interventions targeting malignant diseases. Targeting HO-1 offers therapeutic advantages by enhancing the sensitivity of cancer cells to these treatment modalities.[30-33]

Ferroportin is a transporter protein of the SLC4 family, located on the membranes of duodenal enterocytes, facilitating the export of iron from cells into the bloodstream, particularly when extracellular iron levels are high. Under such circumstances, hepcidin, a pivotal regulator of iron absorption, binds to ferroportin, inducing its internalization and subsequent degradation, thereby reducing iron export from the cells.[34] Redox homeostasis is essential for numerous biological processes, as it governs signaling pathways involved in cell proliferation, apoptosis, DNA repair, cellular differentiation, and potential chemoresistance.[35] To maintain this balance, various detoxification mechanisms and antioxidant enzymes, including heme and HO, play a crucial role in its regulation.

Transcription factors regulating HO-1 expression include BTB domain and CNC homolog 1 (BACH1), hypoxia-inducible factor 1-alpha (HIF-1α), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and nuclear factor erythroid 2-related factors 1 and 2 (NRF1 and NRF2).[28,36] BACH1 is sensitive to cellular heme levels; hence, its transcriptional activity and protein levels are mediated by heme. Under normal conditions, low levels of NRF2 are primarily maintained through Kelch-like ECH-associated protein 1 (KEAP1)-mediated proteasomal degradation. Increased oxidative stress promotes NRF2 overexpression, which regulates the transcription of antioxidant genes and enzymes such as quinone oxidoreductase 1 (NQO1), HO-1, and nitric oxide synthase 3 (NOS3). Notably, costimulatory relationships exist between HO-1 and NOS3—nitric oxide induces HO activity, likely through NRF2 activation, and HO reciprocally stimulates NOS3 activity.[37]

3. Heme metabolism in cancer

Dysregulated heme metabolism and biosynthetic pathways in cancer cells promote metabolic reprogramming to enhance their aberrant growth and proliferation.[38] Metabolic reprogramming is commonly observed in almost all cancers, providing sufficient energy and supplying intermediates and precursor molecules for biosynthetic pathways, which are crucial for cell growth and survival in the TME.[39] Dysregulated heme metabolism and altered expression of heme enzymes involved in biosynthetic pathways lead to excessive heme accumulation within cells, which activates various transcription factors that induce HO-1. In the following sections, we highlight dysregulated heme pathways in multiple tumors that contribute to progression, survival, and immune suppression.

3.1. Lung cancer

Lung cancer, or bronchogenic carcinoma, is the leading cause of cancer-related deaths worldwide, with non-small cell lung carcinoma (NSCLC) representing approximately 85% of cases, making it the most prevalent and aggressive type of lung cancer.[39] Multiple risk factors and key metabolic molecules contribute to its development and progression, among which heme is particularly important.

Hooda *et al.*[40] reported that rate-limiting enzymes of the heme biosynthetic pathway, such as δ-aminolevulinate synthase 1 (ALAS1), along with the heme-trafficking proteins solute carrier family 48 member 1 (SLC48A1) and solute carrier family 46 member 1 (SLC46A1), are elevated in NSCLC. Increased mitochondrial heme levels are associated with enhanced mitochondrial OXPHOS, which elevates nicotinamide adenine dinucleotide phosphate and ATP production, ultimately supporting the rapid growth and proliferation of cancer cells.[41,42]

In addition, elevated heme concentrations activate adenosine 5'-monophosphate-activated protein kinase (AMPK) signaling, which in turn upregulates peroxisome proliferator-activated receptor γ coactivator 1-α expression in NSCLC, leading to activation of nuclear respiratory factors (NRF1 and NRF2) and mitochondrial transcription factor A. This cascade drives mitochondrial biogenesis and ultimately fulfils the energy demands of cancer

cells by providing sufficient ATP for rapid growth and proliferation.[43,44] Wiel *et al.*[43] demonstrated that BACH1, apart from regulating the activity of NRF2, plays a crucial role in mediating the transcription of hexokinase 2 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), thereby inducing glycolysis-mediated lung cancer metastasis. Targeting BACH1 or its downstream targets (hexokinase 2, GAPDH) prevents antioxidant-induced metastasis[43] (Figure 3).

Hooda *et al.*[40] demonstrated that heme degradation is elevated in NSCLCs, and inhibition of HO by tin Pp reduces colony formation. A recent study by Adapa *et al.*[9] showed that mid-heme biosynthetic genes, such as hydroxymethylbilane synthase (*HMBS*), *ALAD*, *UROS*, coproporphyrinogen oxidase (*CPOX*), and *FECH*, are highly dysregulated, and the transporter protein FLVCR is overexpressed. Higher expression of biosynthesis genes and transporter proteins is associated with poorer survival outcomes in lung cancer patients.

Cancer-associated fibroblasts (CAFs) significantly impact the TME and have been shown to contribute to porphyrin synthesis. Experimental evidence of porphyrin accumulation in CAFs isolated from primary lung adenocarcinoma highlights the role of stromal components in abnormal heme metabolism within the TME. This specialized microenvironment not only supports porphyrin production but also shapes the broader metabolic profile of cancer. However, the exact molecular pathways and transport mechanisms of porphyrins within the TME remain to be elucidated. CAFs drive porphyrin production, as evidenced by their accumulation near primary lung adenocarcinoma compared with areas distant from the cancerous tissue. This underscores the importance of the TME in facilitating cancerous cell growth, survival,

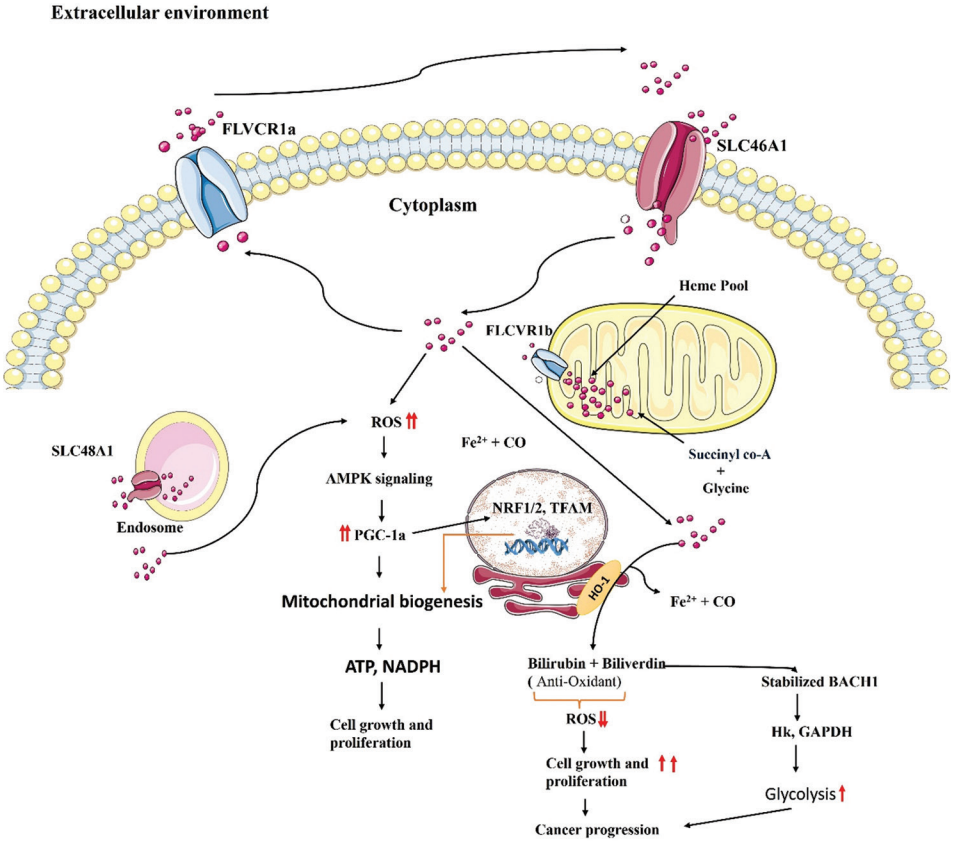

Figure 3. Overview of heme trafficking, degradation, and dysregulation pathways in lung cancer. The figure illustrates heme trafficking and degradation pathways, emphasizing the upregulated processes observed in lung cancer. Upward-pointing arrows indicate key alterations in heme transport, utilization, and catabolism that contribute to the carcinogenic landscape.
Abbreviations: AMPK: Adenosine 5'-monophosphate-activated protein kinase; BACH1: BTB and CNC homology 1; CO: Carbon monoxide; Fe^{2+}: Ferrous iron; FLVCR1a: Feline leukemia virus subgroup C cellular receptor 1a; FLVCR1b: Feline leukemia virus subgroup C cellular receptor 1b; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; Hk: Hexokinase; NADPH: Nicotinamide adenine dinucleotide phosphate; NRF: Nuclear factor erythroid 2-related factor; PGC-1α: Peroxisome proliferator-activated receptor γ coactivator 1-α; ROS: Reactive oxygen species; SLC46A1: Solute carrier family 46 member 1; SLC48A1: Solute carrier family 48 member 1; TFAM: Mitochondrial transcription factor A.

and proliferation. Furthermore, diverse stromal players converge to create a unique environment that fosters porphyrin synthesis and reshapes cancer metabolism. Nevertheless, the intricate molecular mechanisms and porphyrin trafficking routes within the TME remain to be fully understood.[41,44]

In a recent study, Wang *et al.*[45] demonstrated that heme-sequestering proteins (HeSPs), derived from bacterial hemophores, effectively disrupted tumor metabolism by depleting intracellular heme. *In vitro* studies using NSCLC cell lines (A549 and H1299) demonstrated that HeSPs selectively induced apoptosis in cancer cells while sparing normal cells, significantly reducing oxygen consumption, ATP production, and proliferation. In NSCLC xenograft mouse models, HeSPs impaired OXPHOS, suppressed tumor growth, and decreased glucose and glutamine uptake. HeSP2 treatment effectively suppressed lung cancer progression of both adenocarcinoma and squamous cell carcinoma subtypes, diminished OXPHOS, reduced angiogenesis, alleviated tumor hypoxia, and suppressed cell proliferation. In addition, HeSPs downregulated heme uptake proteins and angiogenic markers, leading to reduced vessel density in tumors.[46,47]

3.2. Colorectal cancer (CRC)

Cancer of the colon and rectum is collectively termed CRC, which is a leading cause of cancer death in affluent countries.[46,48] The 2024 Global Cancer Observatory data reported 152,810 new CRC cases with an estimated 24,310 deaths.[47] This increase is predominantly observed in affluent countries, indicating the role of environmental factors in the etiology of CRC. As affluent societies continue to exhibit low levels of physical activity, westernized lifestyles—such as diets rich in processed foods and red meat—contribute to obesity.[49] Approximately 90% of consumed dietary heme reaches the colon, favoring the activation of HO-1. Excessive heme leads to HO-1 overexpression, which saturates ferritin (the iron storage protein) and contributes to free Fe^{2+} accumulation and superoxide anion radical formation, a critical component in the initiation and progression of carcinogenesis.

CO, a product of HO-1 activity, exhibits anti-inflammatory properties by activating intracellular targets such as p38 mitogen-activated protein kinase (MAPK). This activation is linked to the suppression of pro-apoptotic factors (e.g., Bax, Bak, Bid, Bim), thereby stabilizing an anti-inflammatory cellular state and promoting the expression of protective cytokines to prevent inflammation-induced apoptosis[7,50] (Figure 4A). Although the HO-1/CO axis is viewed as a promising therapeutic target, studies indicate that CO exhibits a complex, dual role in tumor biology. Elevated CO levels serve as a diagnostic biomarker for CRC, indicative of increased HO-1 expression and its association with circulating CO levels. Interestingly, higher CO concentrations in CRC appear to paradoxically support tumor growth, potentially due to their anti-inflammatory properties, which, rather than protecting against the disease, may inadvertently sustain abnormal cell proliferation pathways that drive tumorigenesis.[51,52]

Hyperactivation of transcription factors, particularly NRF2, plays a significant role in CRC carcinogenesis. In addition, BACH1 may contribute to CRC carcinogenesis by repressing the transcription of *HMOX1* in low-heme environments. Low metabolic activity of HO-1 allows free heme iron to accumulate, and free heme iron is more cytotoxic than the inorganic iron produced by heme degradation.[26,53] HO interacts with intracellular cell adhesion molecule 1 (ICAM-1) and a subset of T cells, including effector T cells (Teff) and $CD8^+$ T cells, facilitated by a concentration gradient established by chemokine (C-C motif) ligand (CCL) 5 and C-X-C motif chemokine ligand 10, which allows Teff cell infiltration into the TME.[54] Reduced ICAM-1 expression in CRC cells renders them less detectable by the immune system, while the release of C-X-C motif chemokine ligand 10 further diminishes immune cell infiltration and cytotoxic action, enabling CRC cells to evade immunosurveillance.

In addition, HO-1 induction in the TME promotes a shift in macrophage polarization from the pro-inflammatory M1 type to the anti-inflammatory M2 type. This shift decreases oxidative stress, fosters immunotolerance, and supports cell proliferation, tumor growth, and angiogenesis[55] (Figure 4B). HO-1 induction in myeloid-derived suppressor cells impairs T cell cytotoxicity by activating the NF-κB/signal transducer and activator of transcription (STAT) 3 signaling pathway, facilitating cell immortalization, formation of pre-metastatic niches, and increased resistance to immunotherapy.[56] Growing evidence associates HO-1-driven immune modulation within CRC and the TME with lymph node metastasis and reduced survival in advanced stages, underscoring its role in facilitating tumor progression and chemoresistance.[57,58]

3.3. Prostate cancer (PC)

The prostate, a small gland located in the lower pelvis, just beneath the bladder and anterior to the rectum, functionally provides nutrients for sperm nourishment.[59] PC is a significant global health concern and a leading cause of mortality in men. It is characterized by metabolic changes that drive its transition from a non-cancerous to a more aggressive and malignant form. This dysregulated metabolic shift plays a major role in disease progression.[60]

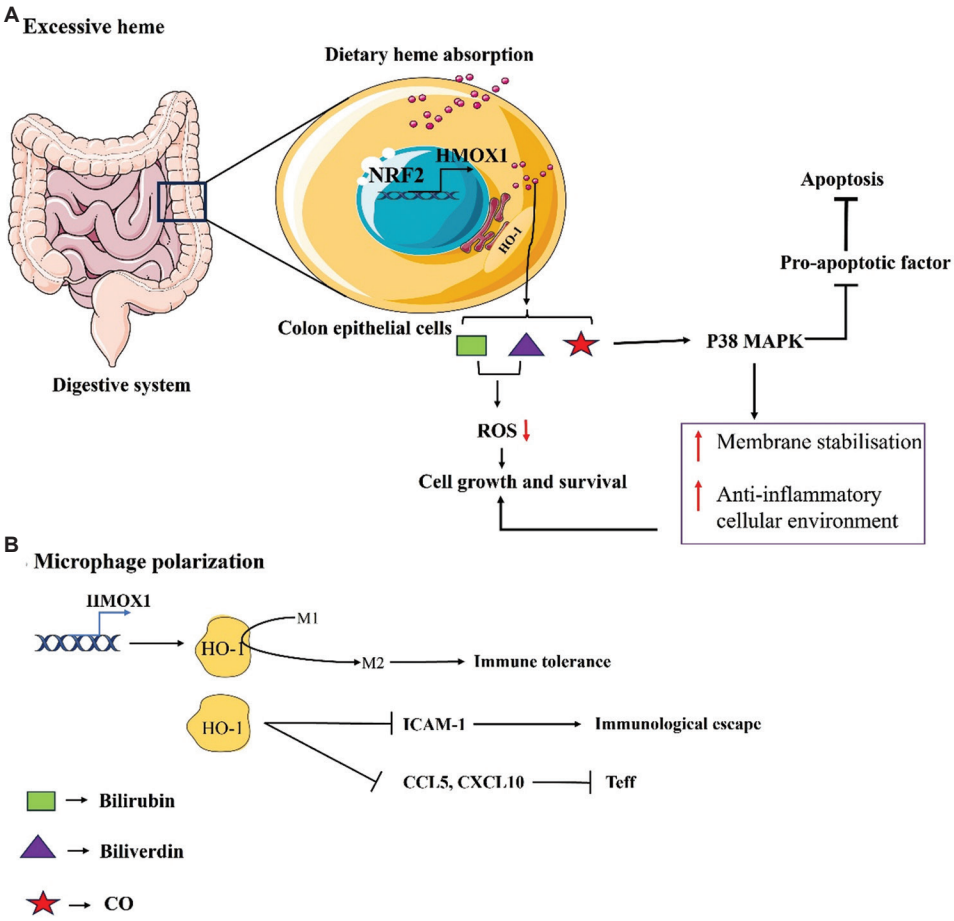

Figure 4. Overview of mechanisms of carcinogenesis in colorectal cancer. (A) Dietary heme is absorbed in the small intestine, enters the systemic circulation, and activates the NRF2 signaling pathway. This activation induces HO-1, which degrades heme into biliverdin, bilirubin, and CO. These metabolites contribute to cancer cell survival by activating the p38 MAPK pathway, reducing ROS levels, and promoting overall cell viability. (B) HO-1 exerts immunomodulatory effects by promoting a phenotypic shift from M1 to M2 macrophages and inhibiting Teff cells, thereby contributing to cancer progression.

Abbreviations: CCL5; Chemokine (C-C motif) ligand 5; CO: Carbon monoxide; CXCL10: C-X-C motif chemokine ligand 10; *HMOX1*: Heme oxygenase 1 gene; HO-1: Heme oxygenase 1; ICAM-1: Intracellular cell adhesion molecule 1; MAPK: Mitogen-activated protein kinase; NRF2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species; Teff: Effector T cell.

Heme is one such key metabolite whose homeostasis is dysregulated in PC, promoting cancer cell survival and proliferation.[61] Precise regulation of HO-1 is crucial for preserving cellular balance, as any increase beyond normal physiological levels is linked to various diseases, including PC.

In PC, oxidative stress facilitates the dissociation of NRF2 from KEAP1, a strong inhibitor of NRF2 with ubiquitin ligase activity that mediates NRF2 degradation through the ubiquitin ligase-mediated pathway. As a result, NRF2 translocates into the nucleus and binds to the antioxidant response element region in the HO-1 promoter region, leading to its transcriptional activation.[36,62,63] Elevated heme levels dissociate BACH1 (a heme sensor) from antioxidant response element sites, permitting HO-1 expression. NRF2 and BECH1 act in coordination under physiological conditions to maintain heme degradation homeostasis through HO-1.

Chronic inflammation activates the NF-κB signaling pathway, leading to NF-κB translocation into the nucleus, where it binds the HO-1 promoter and initiates transcription. In addition, activator protein-1 serves as another transcription factor promoting HO-1 expression.[64] Through these signaling pathways, HO-1 is upregulated as a coordinated response to oxidative stress, counteracting ROS-induced cellular damage and supporting cancer cell survival and proliferation. Furthermore, Salloom *et al.*[61] demonstrated that STAT1 is a potential inducer of HO-1, and inhibition of STAT1 with fludarabine, a STAT inhibitor, reduces HO-1 expression in various PC cell

lines[61] (Figure 5). Increased fecal porphyrins in patients indicate their potential as a tumor biomarker in PC.[65]

Hypoxic TME is a hallmark of solid tumors, including PC.[66] Under hypoxic conditions, HIF-1α is stabilized, which in turn promotes HO-1 overexpression. This suggests a bidirectional relationship between HIF-1α and HO-1.[67] CO inhibits propyl hydroxylases, enzymes that degrade HIF-1α under normoxic conditions; thus, HO-1 prevents the degradation of HIF-1α, leading to its accumulation. This promotes the transcription of hypoxia-related genes, inducing epithelial–mesenchymal transition (EMT), inhibiting apoptosis, and enhancing angiogenesis.[66] Under hypoxia, the induction of HO-1 supports cancer cell survival and adaptation to low oxygen levels by boosting antioxidative defense mechanisms and stimulating angiogenesis.[66,68]

Salloom *et al.*[61] demonstrated that increased HO-1 expression contributes to cancer cell resistance against standard treatments, such as chemotherapy and radiotherapy. By protecting cancer cells from the cytotoxic effects of these treatments, HO-1 contributes to both therapeutic resistance and disease progression. Gotardelo *et al.*[65] showed that PpIX (an autofluorescence molecule) could serve as a reliable biomarker for investigating PC progression and early detection using fluorescence and excitation techniques, potentially outperforming existing diagnostic methods such as prostate-specific antigen testing and digital rectal examination.[61,69]

Labile heme and hemopexin levels are inversely correlated in the plasma of patients with PC. Excess labile heme binds to G-quadruplex structures in the promoter region of the c-MYC gene, a key driver of many cancers, thereby promoting cancer progression. In contrast, sequestration of labile heme by hemopexin blocks heme-driven tumor growth and metastases, suggesting a potential strategy to prevent cancer dissemination.[70]

3.4. Glioma

"Glioma" is widely used to describe primary brain tumors and is further grouped into different types depending on the cell of origin. These include astrocytic tumors (e.g., glioblastoma, astrocytoma, and anaplastic astrocytoma), ependymomas, mixed gliomas, and oligodendrogliomas.[71] The World Health Organization (WHO) classifies gliomas into grades I to IV based on malignancy and histopathological features. Grade I gliomas

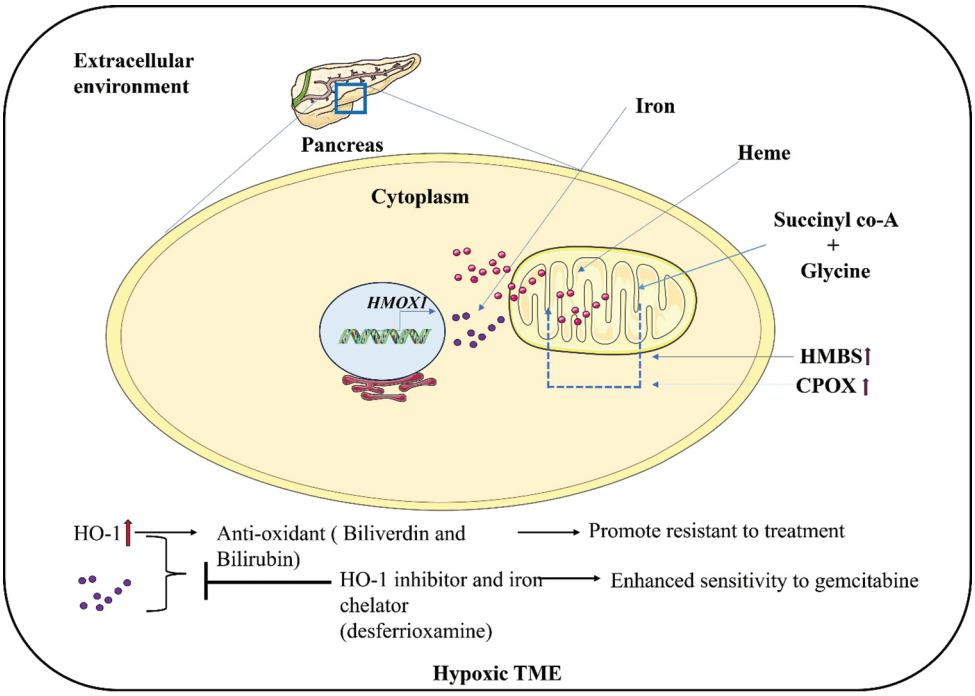

Figure 5. Mechanism of pancreatic cancer progression highlighting the role of HO-1 in promoting therapeutic resistance and cancer cell survival. Upregulation of heme biosynthetic enzymes, such as HMBS and CPOX, enhances heme synthesis, increasing the heme pool available for HO-1-mediated degradation. This process elevates antioxidant molecules such as biliverdin and bilirubin. The hypoxic TME further induces *HMOX1* expression, enhancing antioxidant production, supporting cancer cell survival, and promoting treatment resistance. Inhibition of HO-1, through HO-1 inhibitors or iron chelators such as desferrioxamine, improves sensitivity to gemcitabine.
Abbreviations: CPOX: Coproporphyrinogen oxidase; *HMOX1*: Heme oxygenase 1 gene; HO-1: Heme oxygenase 1; HMBS: Hydroxymethylbilane synthase; TME: Tumor microenvironment.

tend to have low malignancy and limited proliferative potential, while grade IV gliomas are highly aggressive and invasive. Glioblastoma multiforme (GBM), classified by the WHO as a grade IV tumor, represents the most malignant form.[72,73] GBM contributes to more than 60% of all primary brain tumors.[74] Growing evidence shows that heme plays a major role in cancer cell survival and progression, including glioma grades II to IV. Castruccio Castracani *et al.*[75] have shown that HO-1 upregulation is associated with increased proliferation and colony formation in glioma cell lines.[75] However, in highly malignant U87MG cells, the results were contradictory, indicating that HO-1 plays a permissive role in tumor growth. In addition, *HMOX1* expression in tumor cells was linked to a poorer prognosis in patients with grades II and III astrocytomas.[75]

Overall, these findings suggest that HO-1 plays a pro-tumoral role in the development of gliomas. CO levels further support tumor cell growth and survival. Dysregulation of the heme biosynthesis pathway is often associated with increased porphyrin levels in the blood, particularly in high-grade gliomas. A recent report highlights the potential of PpIX as a promising serum biomarker for high-grade gliomas, particularly for monitoring tumors.[76]

3.5. Ovarian cancer (OC)

OC is a lethal gynecological malignancy responsible for more deaths than any other gynecological cancer.[77] Most OC cases are often detected at the advanced malignant stage due to the absence of screening options during the early stage, as well as the cancer's tendency to spread. Furthermore, the emergence of chemotherapeutic resistance hinders effective treatment. Recent findings indicate that altered metabolism plays a critical role in cell transformation and tumor development. In OC cells, NRF2 activation leads to an increase in ubiquitin-specific protease 14 (USP14), a deubiquitinating enzyme, while elevated USP14 levels suppress HO-1 expression. Conversely, reducing USP1 produces the opposite effect, suggesting its involvement in regulating hememetabolism.[78]

In addition, depletion of BACH1 or inhibition of HO-1 significantly reduces USP14-driven invasion of OC cells, indicating that USP14 contributes to the homeostasis of heme metabolism.[78] Persistent overexpression of NRF2 leads to chemoresistance in OC.[74] HO-1 is highly elevated in OC cells. *In vitro* induction of HO-1 in ovarian cell lines (A2780 and Skov-3) promotes proliferation and metastasis by upregulating anti-apoptotic proteins (e.g., BCL2) and EMT factors (e.g., zinc finger E-box binding homeobox 1), while downregulating apoptotic proteins (e.g., Bax). Treatment with HO-1 inhibitors diminishes these effects.[79]

Li *et al.*[76] demonstrated that HO-1 expression correlates with patient survival in OC. HO-1 fosters the infiltration of immunosuppressive immune cells (e.g., regulatory T cells, macrophages, myeloid-derived suppressor cells, and T follicular helper cells) and modulates immune dynamics within the TME of OC. HO-1 also regulates inflammation by regulating the expression of chemokines (e.g., CCL3, CCL4, CCL2, CCL5) and chemokine receptors (e.g., C-C chemokine receptor types [CCR] 5, 1, 6, and 2) in OC. Conversely, HO-1 knockdown inhibits cell proliferation and invasion by enhancing apoptosis in OC cells.[76,79] Overall, HO-1 may serve as a biomarker for early-stage screening of OC and provides a potential avenue for therapeutic intervention.

3.6. Cervical cancer (CC)

In gynecological tumors, CC is the leading cause of death worldwide, with a higher incidence among 50–55-year-old women. In more than 95% of cases, infection with human papillomavirus (HPV) contributes to the development of CC.[80] Higher expression of NRF2 in CC activates the transcription of several genes, including *HO1*, promoting cancer cell survival and therapeutic resistance. Inhibition of either HO-1 or NRF2, directly or indirectly, can induce autophagy or apoptosis in CC cells. Studies have shown that silencing HO-1 enhances the thermosensitization of CC cells and synergistically promotes autophagic apoptosis and antiviral responses, offering a promising therapeutic strategy.[56,81]

3.7. Breast cancer (BC)

BC is the most common type of cancer affecting women globally. The 2024 Global Cancer Observatory statistics report indicates an estimated 313,510 new cases and 42,780 deaths in the United States.[48] Intra- and inter-tumor heterogeneity, as well as molecular subtypes, makes BC challenging to treat. Triple-negative BC is a highly aggressive form and is associated with multiple metabolic reprogramming events, including dysregulated heme metabolism.[82-85] Recent studies show that hemin exhibits anti-tumor activity, and its treatment promotes the overexpression of proteins related to iron, heme, adhesion, cytoskeleton, and lipid metabolism in LM3 cells.[86]

Administration of 5-ALA inhibits glycolysis, mitochondrial respiration, and cell growth in MDA-MB-231 cells. This is contrary to observations in other cancer types, where ALA treatment drives the heme biosynthesis pathway and promotes cancer cell survival and proliferation. The underlying mechanism of inhibition includes destabilization of BACH1, activation of AMPK, and stimulation of antioxidant response. As a photosensitizer, 5-ALA functions in PDT, particularly in

BC treatment. The mechanism of action involves activation of 5-ALA by light in the presence of oxygen, leading to ROS production, which induces apoptosis in cancer cells.[87,88] Furthermore, recent studies suggest that 5-ALA-PDT may sensitize BC cells to the anti-estrogen drug tamoxifen, thereby enhancing its therapeutic effectiveness. ATP-binding cassette subfamily G member 2 (ABCG2) inhibition by KO143, a potent and selective ABCG2 transporter inhibitor, increases PpIX accumulation in mitochondria, thereby making BC cells more susceptible to ALA-PDT.[89,90]

3.8. Pancreatic cancer (PaCa)

Pancreatic ductal adenocarcinoma is expected to become the second-leading cause of cancer-related deaths in the United States by 2030.[91] According to the 2024 cancer statistics, approximately 66,440 new cases and 51,750 deaths were attributed to pancreatic ductal adenocarcinoma in the United States.[48] Heme is a key metabolite that regulates numerous biological processes in living cells, and alterations in heme metabolism (e.g., synthesis, degradation, and trafficking) enzymes or proteins are associated with the progression of many cancers, including PaCa.

Heme synthesis is an essential metabolic process in PaCa and other cancer types. A recent study showed that HMBS has a modest effect on proliferation but significantly reduces tumor size. HO-1 is markedly upregulated in tumors, especially under hypoxic conditions, compared to normoxic tumors, suggesting that the TME drives the upregulation of HO-1 due to its hypoxic nature. Higher expression of heme biosynthetic genes (*HMBS* and *CPOX*) has been associated with poorer patient survival in PaCa, indicating that elevated gene expression is linked to more aggressive phenotypes and promotes cancer progression.[92] HO-1 and its products have anti-inflammatory and antioxidant effects, thereby making PaCa cells resistant to chemotherapy. Inhibiting HO-1 and chelating iron with chelators such as deferoxamine enhances sensitivity to the chemotherapeutic drug gemcitabine.[93,94]

3.9. Head-and-neck cancer (HNC)

Head-and-neck squamous cell carcinomas (HNSCCs) are the most frequently occurring cancers in the head-and-neck region. They arise from the mucosal lining of areas such as the oral cavity—including the lips, buccal mucosa, hard palate, front of the tongue, floor of the mouth, and retromolar trigone—as well as the pharynx and larynx.[95] In 2024, HNSCC accounted for 116,900 new cases and 24,460 deaths.[48] HPV infection and the consumption of tobacco or alcohol are the main risk factors for HNSCC development. *HMOX1* expression is significantly associated with worse overall survival at early stages; however, at later stages (cancer stage II-IV), the association between *HMOX1* expression and survival is lost. Furthermore, HNSCC–HPV-negative tumors show higher *HMOX1* expression than HNSCC–HPV-positive tumors, whereas tobacco and/or alcohol consumption does not correlate with *HMOX1* expression.[96]

Treatment of cells with hemin increases viability, proliferation, and cell cycle progression, and the underlying mechanism includes activation of cyclin D and a decreased level of p27 protein, which, in turn, promotes tumor progression. Inhibition of HO-1 with zinc Pp reduces cell viability and proliferation. Overall, these findings suggest that the combination of expression, activity, and subcellular location of HO-1 plays a significant role in HNSCC malignancy.[96]

UROD is upregulated in many diseases, including HNSCC, and functions as a pivotal regulator in the heme biosynthesis pathway. UROD was identified through RNA interference-based high-throughput screening as a tumor-selective target for radiosensitization in HNC. Gene knockdown of *UROD*, combined with radiation treatment, triggered caspase-mediated apoptosis and induced cell cycle arrest in HNC cells cultured *in vitro*, while combination therapy notably suppressed the tumor-forming capacity of HNC cells *in vivo* and delayed the growth of established tumor xenografts in murine models. Furthermore, lower levels of UROD before radiation are associated with improved disease-free survival rates, suggesting that UROD may serve as a valuable biomarker for predicting patient responses to radiation therapy.[97]

3.10. Liver cancer

The liver serves as a crucial organ, functioning as a fundamental hub for numerous metabolic processes, including carbohydrate, lipid, and protein metabolism, along with drug metabolism, detoxification, waste excretion, and bile synthesis.[11,98,99] The synthesis of heme, a critical process vital for key cellular functions such as energy generation and detoxification, is closely interconnected with hepatic functionality; consequently, any aberrations in heme metabolism are correlated with numerous hepatic pathologies—including porphyria, cirrhosis, Wilson's disease, and hemochromatosis.[100-103]

Hereditary hemochromatosis (HH), a common genetic disorder of iron overload linked to the *HFE C282Y* homozygous mutation, is increasingly recognized as a strong risk factor for hepatocellular carcinoma (HCC). Recent population-scale studies, including the United Kingdom Biobank, report that men with HH exhibit a >10-fold

increase in liver cancer risk, with over 7% developing HCC by the age of 75.[104] The oncogenic potential of HH is mediated by persistent *HAMP* suppression, leading to excessive intestinal iron absorption, hepatocellular iron accumulation, and subsequent oxidative stress, DNA damage, and chronic inflammation. These processes promote cirrhosis, a key pre-malignant state, and facilitate hepatocarcinogenesis through epigenetic remodeling and ferroptotic cell death.[105,106]

The 2024 Global Cancer Observatory statistics identify HCC as a leading cause of cancer-related deaths, particularly in men, with 28,000 new cases in males and 16,630 in females. In the United States, HCC is projected to result in approximately 29,840 deaths across both sexes.[48] Treatment options for HCC include surgical resection, which is of limited effectiveness and is often associated with chemotherapeutic resistance. Sun *et al.*[107] demonstrated that the p62–KEAP1–NRF2 antioxidative signaling pathway is a negative regulator of ferroptosis (i.e., a form of programmed cell death mediated by iron-dependent lipid ROS accumulation), and that activation of NRF2 inhibits ferroptosis in HCC cells.[107]

The inhibitory mechanism involves persistent expression of p62, which prevents the degradation of NRF2 and subsequently enhances its nuclear accumulation through KEAP1 inactivation. Activated NRF2 further regulates the expression of cytoprotective genes such as *NQO1*, *HO1*, and ferritin heavy chain 1, which are involved in detoxification, antioxidant production, and drug resistance.[108] NQO1 and HO-1 are antioxidants upregulated in response to erastin and sorafenib. Suppression of *NQO1* and *HO1* gene expression significantly enhances ferroptosis in HCC cells, indicating that the balance between ROS and antioxidant levels is critical for ferroptosis initiation.[107]

A study by Adapa *et al.*[109] demonstrated significant alterations in heme and related metabolic pathways in liver cancer. Their findings showed a marked downregulation of cytochrome P450 enzymes, such as CYP2A6 and CYP2C8, which are critical for detoxification and hormone metabolism, indicating reduced liver metabolic function in hepatoma cells. In addition, key enzymes in heme biosynthesis, including ALAS1 and ALAD, were downregulated, potentially leading to an accumulation of intermediates and disruption of the heme pathway. Furthermore, upregulation of dedifferentiation markers, such as cyclin-dependent kinase 6 and high mobility group AT-hook 1, suggests a shift toward stem-cell-like characteristics in cancer cells, enhancing their adaptability.[109]

Moreover, increased expression of ETC components, specifically cytochrome c1 and cytochrome c oxidase subunit 7B2, suggests that liver tumors may boost ETC activity to support cancer cell survival despite metabolic challenges. Porphyrin accumulation in liver cancer is an intriguing yet poorly understood phenomenon, as normal liver function typically prevents intermediate buildup while efficiently producing heme. The reasons behind this accumulation, which escalates with cancer progression despite having no known physiological role, remain unclear. Targeting this porphyrin surplus could offer therapeutic potential, highlighting the need for further research to elucidate the mechanisms and metabolic impacts of porphyrin buildup in liver cancer.[109,110]

3.11 Acute myeloid leukemia (AML)

AML is a type of hematological malignancy characterized by abnormal or poorly differentiated hematopoietic cells. Metabolic reprogramming, inter-/intra-tumor heterogeneity, and therapy-resistant leukemic stem cells present the greatest challenge to its treatment.[111,112] *MYCN*-driven AML depends on elevated heme biosynthesis to maintain mitochondrial activity and support leukemic cell self-renewal. High expression of heme biosynthetic genes, especially *UROD*, is linked to poor outcomes in AML patients. Disrupting heme production hampers leukemic cell growth, while interfering with porphyrin balance by inhibiting the ABCG2 transporter triggers cell death through p53 activation. Targeting heme metabolism could therefore be a promising therapeutic strategy in *MYCN*-driven AML.[113]

Overexpression of HO-1 is associated with drug resistance in solid tumors and AML. A study by Zhe *et al.*[114] demonstrated that HO-1 expression is elevated in drug-resistant AML cell lines (HL-60R), contributing to chemotherapy resistance. Cytarabine and daunorubicin treatment of HL-60R cells resulted in significantly higher viability than that of non-resistant HL-60 cells. When *HO1* gene expression was silenced, this resistance was diminished, and the cells regained sensitivity to chemotherapy.[113] Furthermore, HO-1 levels were markedly higher in patients with refractory and relapsed AML compared to those in complete remission and healthy individuals.[113] HO-1 is activated by several pathways, such as NRF2/c-Jun N-terminal kinase, phosphatidylinositol 3-kinase/protein kinase B, AMPK, and HIF-1α, but its contributions to AML chemoresistance remain clear.[114]

Inhibition of HO-1 enhances the sensitivity to chemotherapeutic molecules, and the downregulation of HO-1 mRNA or protein has been associated with increased patient survival in both chronic myeloid

Table 1. Summary of altered heme biosynthetic enzymes, transcription factors, and heme trafficking proteins and transporters in various cancers

Type of cancer/tissue	Enzymes/ transcription factors	Cellular status	Normal function	Consequences	References
Lung cancer (non-small cell lung carcinoma)	HMBS, ALAD, UROS, CPOX, and FECH	Highly dysregulated	Involved in the heme biosynthetic pathway	Increased heme production	40-44
	SLC48A1, SLC46A1, and FLVCR1	Increased	Heme trafficking protein	Excessive mitochondrial heme pool	
	PGC1A, NRF1, NRF2, and BACH1	Increased	Transcription factor (maintains redox balance)	Altered redox homeostasis, enhancing cancer cell survival	
Colorectal cancer	HO-1	Overexpressed	Heme degradation	Enhanced heme degradation, facilitating antioxidant production (e.g., BR, BV) and promoting cancer cell survival	53-56
	NRF2	Elevated	Plays a role in immunomodulation, organ protection, and the circadian clock		
	CO				
Prostate cancer	HO-1	Increased	Involved in heme degradation	Protection of cancer cells from oxidative damage through reduced ROS production and increased treatment resistance	64-66
	NRF2	Increased	Driver of HO-1 expression	Promote heme degradation	
Glioma	HO-1 and CO	Increased	Maintain redox balance	Promotion of cancer cell growth, survival, and proliferation	76,79
Ovarian cancer	HO-1	Increased	Heme degradation	Enhanced cell survival and resistance to chemotherapeutic treatment	82-84
	NRF2	Hyperactivated	Driver of HO-1 expression		
Cervical cancer	HO-1	Increased	Heme degradation	Enhanced cell survival and resistance to chemotherapeutic treatment	86
	NRF2	Hyperactivated	Driver of HO-1 expression		
Breast cancer	HO-1	Highly elevated	Heme degradation	Reduced intracellular ROS levels, promoting cancer cell survival	92-95
	Tfrc	Higher expression	Iron trafficking	Intracellular heme accumulation	
	SMAD 2/3, PTEN, and CTSB	Increased	Provide stability to the extracellular matrix and maintain immune homeostasis	Induction of EMT, facilitating migration and metastasis	
	Talin and vimentin	Decreased			
Pancreatic cancer	HMBS, CPOX	Highly increased	Involved in the heme biosynthetic pathway	Increased heme production	97-99
	HO-1	Increased	Heme degradation	Reduced intracellular ROS levels, promoting cancer cell survival	
Head-and-neck cancer	UROD	Increased	Involved in the heme biosynthetic pathway	Intracellular heme accumulation	101,102
	HO-1				
Liver cancer	ALAS1 and ALAD	Decreased	Involved in the heme biosynthetic pathway	Accumulation of heme intermediates	112-115
	CDK6 and HMGA1	Increased	Stem cell marker	Shift toward cancer stem cell-like properties	
	CYC1 and COX7B2	Increased	Component of ETC	Increased ETC activity, boosting ATP production	
Acute myeloid leukemia	HO-1	Increased	Heme degradation	Reduced intracellular ROS levels, promoting cancer cell survival	117,119-122
	ALAS1, ALAD, and FECH	Increased	Involved in the heme biosynthetic pathway	Increased heme production	

Abbreviations: ALAD: δ-aminolevulinate dehydratase; ALAS1: δ-aminolevulinate synthase 1; BACH1: BTB and CNC homology 1; BR: Bilirubin; BV: Biliverdin; CDK6: Cyclin-dependent kinase 6; CO: Carbon monoxide; COX7B2: Cytochrome c oxidase subunit 7B2; CPOX: Coproporphyrinogen oxidase; CTSB: Cathepsin B; CYC1: Cytochrome c1; EMT: Epithelial–mesenchymal transition; ETC: Electron transport chain; FECH: Ferrochelatase; FLVCR1: Feline leukemia virus subgroup C cellular receptor 1; HMBS: Hydroxymethylbilane synthase; HMGA1: High mobility group AT-hook 1; HO-1: Heme oxygenase 1; NRF1: Nuclear factor erythroid 2-related factor 1; NRF2: Nuclear factor erythroid 2-related factor 2; PGC1A: Peroxisome proliferator-activated receptor γ coactivator 1-α; PTEN: Phosphatase and tensin homolog; ROS: Reactive oxygen species; SLC46A1: Solute carrier family 46 member 1; SLC48A1: Solute carrier family 48 member 1; SMAD2/3: Mothers against decapentaplegic homolog 2/3; Tfrc: Transferrin receptor protein 1; UROD: Uroporphyrinogen decarboxylase; UROS: Uroporphyrinogen III synthase.

leukemia and AML.[115] A study by Lin and group showed that the downregulation of heme biosynthesis in AML is linked to increased sensitivity to apoptosis-inducing treatments, especially BCL-2 inhibitors such as ABT-199. In contrast, AML cells that do not downregulate heme biosynthesis display resistance to chemotherapies. Knockout experiments targeting crucial enzymes in the heme biosynthesis pathway (e.g., ALAS1, ALAD, FECH) and treatments that inhibit heme production amplify the apoptotic effect of the BCL2 inhibitor ABT-199. Overall, these findings indicate that suppressing heme biosynthesis can make AML cells more susceptible to apoptosis by impairing the ETC, particularly within heme-containing complexes III and IV, thereby enhancing the therapeutic outcome.[116] Huang *et al.*[117] demonstrated that silencing HO-1 in AML cells heightened apoptosis in response to Ara-C treatment while reducing the expression of chemoresistance-related proteins HIF-1α and GLUT1.[114,118]

In tumor cells, altered expression of certain enzymes and transcription factors associated with an enhanced capacity for PpIX synthesis, potentially reflecting increased heme production, is summarized in Table 1.

4. Conclusion and future perspectives

Dysregulated heme metabolism is associated with the pathogenesis, progression, and treatment resistance in many cancers. Metabolic reprogramming supports the uncontrolled proliferation and survival of cancer cells. Among these metabolic changes, heme metabolism is leveraged to maintain redox balance, support energy production, and provide resistance to cytotoxic therapies. This review has explored the role of dysregulated heme homeostasis across different cancers, highlighting key genes involved in these processes and their potential as therapeutic targets. One important avenue for future research is the development of targeted therapies that manipulate heme biosynthesis, trafficking, and degradation pathways. Inhibitors of HO-1 have shown potential in preclinical studies but require further validation to optimize their pharmacological properties and evaluate their safety and efficacy in clinical trials. Targeting transporter proteins could also improve clinical outcomes, as these are primarily involved in maintaining heme homeostasis within and between cells and promoting its degradation by HO-1, which generates antioxidant molecules (e.g., Bilirubin [BR], BV) that protect cells from ROS and oxidative damage, thereby enhancing survival.

The TME is highly dynamic and complex, comprising heterogenous populations of cells. Recent studies have shown that CAFs drive porphyrin production, which supports cancer growth and survival. Nevertheless, porphyrin overproduction appears to be confined to local CAFs, unlike those at a distance; however, the precise molecular pathways through which cancer cells modulate normal fibroblasts to secrete porphyrin remain elusive. This highlights the critical role of porphyrin in promoting tumor cell growth, survival, and proliferation within the TME. In addition, identifying specific biomarkers, such as porphyrin accumulation in the TME, could provide novel diagnostic tools for early detection and personalized treatment strategies. HO-1, a critical driver that is highly upregulated in most cancers, modulates the immune response by switching macrophages from the M1 to M2 phenotype, thereby rendering the TME immunosuppressive. HO-1 also interacts with several immune cell types and impairs their function.

Future studies are warranted to elucidate the precise mechanism by which HO-1 modulates immune cells. On the other hand, transforming growth factor β, which is highly elevated in almost all cancers, constitutes a major cause of immunosuppression within the TME.[117,119-126] Further research is required to determine whether HO-1 interacts with transforming growth factor β to promote TME immunosuppression, ultimately contributing to cancer cell growth, survival, proliferation, and resistance to available chemotherapeutic treatments.

Future research directions include the following:

(i) Therapeutic targeting of pathways: Investigating whether combining therapies that target heme biosynthesis and degradation (e.g., HO-1, BACH1, heme transporters) with immunotherapies can synergistically enhance anti-tumor efficacy remains a critical area for translational research.

(ii) Hypoxia-driven regulation of heme metabolism: Further studies are warranted to elucidate how hypoxic conditions within the TME influence porphyrin production by CAFs and whether this contributes to altered immune dynamics or therapeutic resistance. The non-canonical roles of hypoxia-inducible factors, particularly HIF-1α, in regulating heme metabolism and immune modulation through HO-1 also require detailed mechanistic exploration.

(iii) Heme metabolites as diagnostic tools: The potential of PpIX as an early-stage, non-invasive cancer biomarker, particularly through autofluorescence-based imaging or liquid biopsy, remains to be validated across multiple cancer types.

(iv) Trafficking and accumulation of heme intermediates: Understanding how porphyrin accumulation

and trafficking within the TME influence tumor progression could reveal novel intervention strategies, especially in tumors with altered ferroptotic or oxidative stress responses.

(v) Contextual roles of heme-responsive transcription factors. The downstream targets of BACH1, including *HK2* and *GAPDH*, are implicated in glycolytic reprogramming in lung cancer. Further research is needed to establish whether this metabolic axis is conserved in other malignancies, which may highlight wider therapeutic roles for BACH1 inhibition in metabolic oncology.

Acknowledgments

The authors express their gratitude to the Department of Human Genetics, Sri Ramachandra Institute of Higher Education and Research, Chennai, for their guidance and encouragement during the preparation of this review. Special thanks are extended to the members of the Redox Lab for their valuable insights and feedback.

Funding

Part of this work was funded by the Department of Biotechnology, India (Grant No: BT/PR44553/MED/30/2391/2021).

Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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