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REVIEW

Role of Bach1 Transcription Factor in the Mechanisms of Cell Death

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Abstract—Involvement of the transcription factor Bach1 in various scenarios of cellular regulation is reviewed herein. To date, the most extensively studied role of Bach1 is that of a repressor of the antioxidant genetic program initiated by the Nrf2 factor. This program counteracts oxidative stress, which triggers both ferroptosis and the intrinsic apoptotic pathway. Bach1 functions unrelated to the suppression of the Nrf2 transcriptional activity have been studied only fragmentarily. Nevertheless, among these, one could distinguish functions that are specific to the particular forms of cell death. A major consequence of such Nrf2-independent effects is, in particular, direct induction of the expression of the glutathione-specific gamma-glutamylcyclotransferase 1 (*CHAC1*) by Bach1; this leads to glutathione degradation and inactivation of the glutathione peroxidase 4 – a central enzyme in the ferroptosis mechanism responsible for the reduction of lipid peroxides. Independently of Nrf2, Bach1 also represses expression of the mitochondrial electron transport chain genes and activates expression of the pyruvate dehydrogenase kinase 1 (*PDK1*) and hexokinase 2 (*HK2*), thereby shifting cells toward the glycolytic pathway and rendering them more resistant to apoptosis. Furthermore, Bach1 influences expression of the inflammasome genes and modulates pyroptosis. Bach1 also regulates expression of a number of metallothionein genes and influences control of cuproptosis via the regulation of the free intracellular copper levels. Finally, Bach1 could inhibit autophagy through multiple mechanisms. In essence, the role of Bach1 in many processes – with the exception of the Bach1/Nrf2 axis – remains far from fully elucidated, given that the number of identified target genes exceeds 12,000, and the majority of them are regulated indirectly through formation of the specific protein complexes, which often include epigenetic enzymes. Nevertheless, in the context of various diseases – ranging from neurodegeneration to cancer – inhibition of Bach1 is precisely what is required to achieve a therapeutic effect. The review concludes by discussing clinical significance of Bach1 and the prospects for its therapeutic targeting.

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INTRODUCTION

The past 15 years have been marked by heightened interest in the mechanisms of gene activation and repression mediated by the transcription factor Bach1 (BTB and CNC homology 1), as well as in the potential for pharmacologically manipulating its stability and activity. Research in this area received significant impetus from the 2011 discovery of the direct link between Bach1 and cancer metastasis [1]. Subsequently, following the detailed characterization of a novel form of cell death – ferroptosis – in 2012 [2] and further studies into its underlying mechanisms, interest in Bach1 regulation intensified due to identification of its role in the suppression of the antioxidant response [3].

Bach1 is widely expressed in many human tissue types [4] and regulates numerous cellular metabolic processes, including heme homeostasis, response to oxidative stress, immune responses, epithelial-mesenchymal transition, senescence, and cell cycle [5]. Elevated levels of *BACH1* expression serve as a marker of cancer aggressiveness, including the triple-negative breast cancer, prostate cancer, ovarian cancer, and other cancers [6-8].

According to the ENCODE database, the number of Bach1 targets identified via the chromatin immunoprecipitation sequencing (ChIP-seq) exceeds 12,000. It is, therefore, not surprising that Bach1 not only participates, but in many cases plays a pivotal role in the mechanisms underlying the development of various diseases. Indeed, evidence has accumulated regarding the involvement of Bach1 in the pathogenesis of cardiovascular diseases, pulmonary fibrosis, skin disorders, and a range of other pathological conditions [9]. Furthermore, its involvement in the development of diabetes and gastrointestinal diseases [10, 11], as well as in most neurodegenerative disorders – such as Down syndrome, Alzheimer's disease, and Parkinson's disease [12-14] – has been demonstrated. Accumulation of Bach1 is observed in both cellular aging and neurodegenerative diseases; this protein deactivates the antioxidant genetic program by inhibiting the transcriptional activator Nrf2 (nuclear factor erythroid 2-related factor 2).

Studies involving genetic and pharmacological silencing have shown that Bach1 directly influences processes of cell death. Inhibition of its activity could both reduce metastatic potential of the cancer cells [15] and, conversely, enhance cell viability in neurodegeneration [13]. Consequently, Bach1 is considered a promising therapeutic target for the treatment of a wide range of diseases [9].

Specific mechanistic role of Bach1 in the cell death depends on the type of the cell death involved. Cell death is a fundamental process essential for the normal development of an organism and elimination of the dysfunctional cells. At the same time, it could result from pathological conditions, making it a potential target for therapeutic intervention [16]. According to the modern classification, cell death is categorized into accidental cell death (ACD), which occurs in response to extreme insults and is not subject to regulation, and regulated cell death (RCD), which is executed via specific molecular mechanisms and is potentially controllable. Programmed cell death (PCD) is a specific form of RCD that occurs under physiological conditions, whereas other forms of RCD are triggered by cellular stress.

One of the most extensively studied forms of RCD is apoptosis, which is activated by extrinsic and intrinsic stimuli and does not involve cell lysis [17]. Metal-dependent mechanisms underlie the various forms of regulated cell death. Ferroptosis is an iron-dependent type of cell death characterized by free radical-mediated lipid peroxidation [2]. Metal-dependent mechanisms of cell death also include the recently described cuproptosis, which is induced by the intracellular copper accumulation [18]. In addition, pyroptosis is classified as a form of RCD. Pyroptosis is activated by the immune system and is accompanied by the membrane rupture and release of pro-inflammatory cytokines [19]. Regulated forms of cell death also include regulated necrosis (necroptosis) and other pathways [20]. Beyond the various forms of RCD, autophagy – a lysosomal mechanism for degrading damaged proteins and organelles that could interact with the regulated cell death signaling pathways – plays a significant role [21, 22].

To date, the role of Bach1 has been most thoroughly studied in the context of the ferroptosis mechanism [3]. At the same time, data on its participation in the regulation of other pathways of programmed cell death remain limited and scattered. This review aims to systematize and analyze current data on the role of Bach1 in the regulation of various pathways of programmed cell death. Main attention is paid to apoptosis, ferroptosis, cuproptosis, and pyroptosis, since it is for these processes that the data have been accumulated to date, directly or indirectly indicating participation of Bach1 in their regulation. Additionally, the review examines the role of Bach1 in autophagy, which interacts with various cell death signaling pathways.

BACH1 STRUCTURE AND MECHANISM OF REGULATION

The Bach1 and Bach2 proteins (BTB domain and CNC homology) belong to the Cap 'n' Collar and basic region leucine zipper (CNC-bZIP) family of

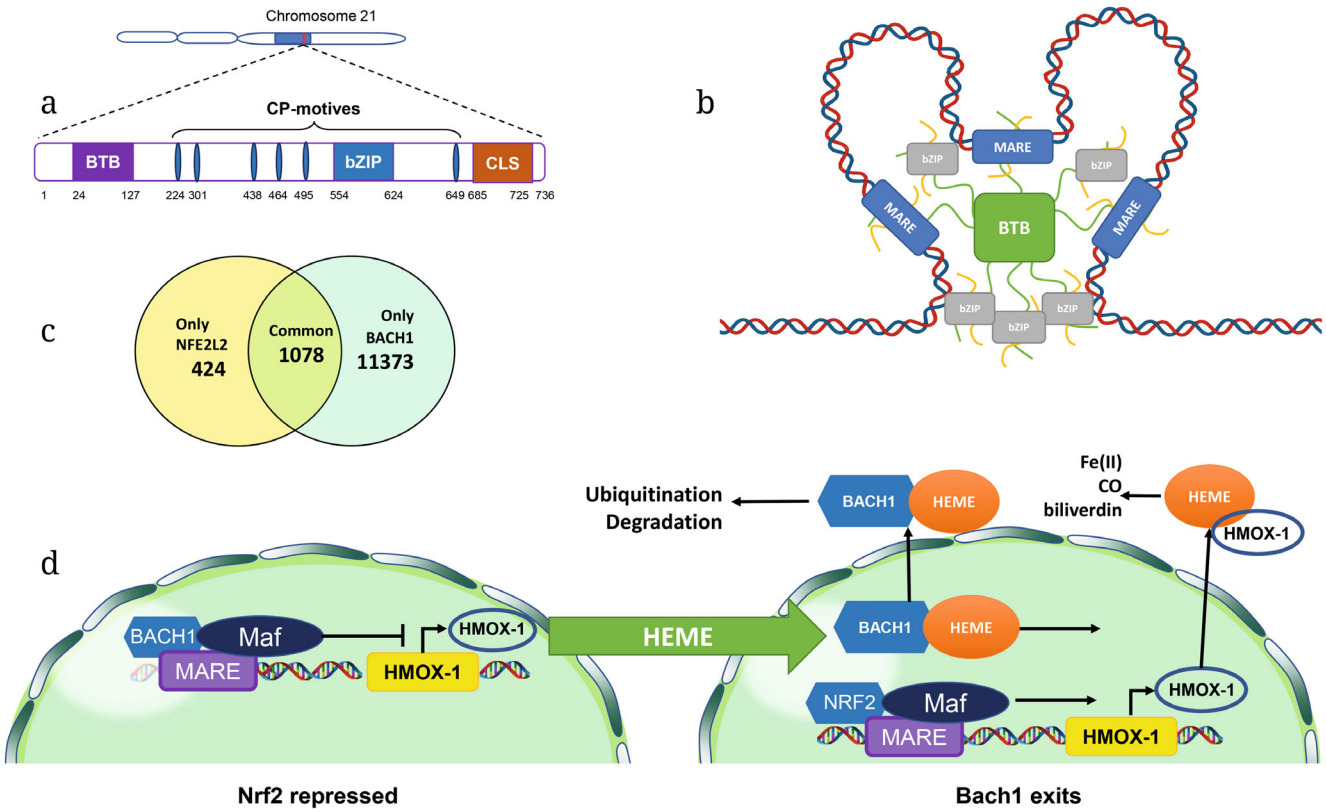

Fig. 1. Bach1 structural organization and regulation. a) Domain structure of Bach1. b) Formation of multimeric complexes. c) Venn diagram showing the number of genes shared by Nrf2 and Bach1 (ChIP-seq, ENCODE database). d) Competition between Bach1 and Nrf2 for binding to Maf proteins and MARE sequences in the *HMOX1* gene promoter.

transcription factors and share homologous sequences and domain organization [4, 7]. Bach1 is widely expressed in many cell types, whereas Bach2 is primarily found in immune system cells such as B and T lymphocytes, macrophages, and NK cells, as well as in neurons [23]. The *BACH1* gene is located on the chromosome 21 and encodes a protein consisting of 736 amino acids (Fig. 1). Consequently, in the cases of chromosome 21 trisomy (Down syndrome), increase in its expression is observed [24, 25], leading to oxidative stress and disruption of redox homeostasis. The effects of trisomy are multifactorial [26]; notably, the same chromosome harbors the cystathionine beta-synthase (*CBS*) gene. Its elevated enzymatic activity alters homocysteine metabolism and affects the folate cycle and methylation processes, thereby contributing to the cognitive decline and development of neurodegenerative changes (resembling Alzheimer's disease) in the individuals with Down syndrome [27]. The *CBS* gene is a target of the Bach1/Nrf2 pair; therefore, Bach1 inhibition is considered a potential approach to reducing oxidative stress in Down syndrome.

Bach1 has a multidomain structure (Fig. 1a). The N-terminus of the protein contains a BTB/POZ domain (Broad-complex, Tramtrack, and Bric-à-brac/pox virus and zinc finger), which is responsible for Bach1 dimerization and its interaction with chromatin [4].

In addition, Bach1 contains a basic region leucine zipper (b-ZIP) domain, which is required for the transcription factor to bind to DNA and interact with the small Maf family proteins (MafF, MafG, and MafK) [4]. In complex with Maf proteins, Bach1 regulates transcription of the target genes by binding to the specific regions known as MAREs (Maf recognition elements) within their enhancers or promoters. The human Bach1 protein also contains six so-called CP motifs (cysteine-proline motifs) [28]. Bach1 stability is regulated by several mechanisms. Oxidative modification of cysteine residues promotes export of Bach1 from the nucleus, followed by ubiquitination and proteasomal degradation. Ubiquitination of the dimeric and monomeric forms of Bach1 is mediated by the SKP-CUL1-F-box ubiquitin ligases FBXO22 and FBXL17, respectively [29]. Specific regulation occurs upon the heme binding to the CP motifs of the dimeric form of Bach1, which serves as a signal for its ubiquitination by the FEM1B-CRL2 complex and subsequent proteasomal degradation [30]. Bach1 stability is also regulated by oxygen levels: hydroxylation of proline residues by the HIF prolyl hydroxylase is followed by ubiquitination and proteasomal

degradation of Bach1 [31]. Thus, physiological regulation of the Bach1 protein stability is determined by the oxygen and heme levels, whereas oxidative modification of the protein renders the Bach1-dependent processes sensitive to the levels of reactive oxygen species (ROS). Bach1 deubiquitination is mediated by the enzyme USP47 [32]. A highly conserved CLS (cytoplasmic localization signal) domain is located at the C-terminus of Bach1; this domain is required for localization of the transcription factor in the cytoplasm [33], from where it is transported into the nucleus upon activation.

Crystal structures of the Bach1 BTB domain have been solved both for the free protein and protein in complex with ubiquitin ligases [34]. Unlike the BTB domain, the heme-binding domain (containing CP motifs) is unstructured; therefore, its crystal structure is currently unavailable. Dimerization of Bach1 and oligomerization with other bZIP-domain proteins lead to formation of both repressive and activating complexes that directly engage DNA (Fig. 1b). Fifty-three unique bZIP domains have been identified in humans; these have the potential to form up to 2809 different dimers through heterodimerization [35]. bZIP proteins are classified into 12 groups; Bach1 and Bach2 belong to the CNC group, alongside Nrf1 and Nrf2. Proteins in this group predominantly form heterodimers with members of other bZIP protein families [35]. Despite significant efforts to identify dimerization partners, the full spectrum of possible dimer combinations has not yet been established. In some instances, such complexes include epigenetic enzymes [5]; specifically, Bach1 could form complexes with the epigenetic regulators such as HDAC1, PRC2, G9a, and LSD2 [9]. Moreover, microRNAs and long-chain RNAs often participate in the repression mechanisms. Since the Bach1-mediated repression is indirect, the underlying mechanisms are specific to each individual case, and consequently, far from all of them have been characterized in detail.

THE BACH1/NRF2 AXIS IN OXIDATIVE STRESS

To date, the role of Bach1 has been most extensively studied in the context of oxidative stress regulation. Oxidative stress is a condition arising from an imbalance between the production of ROS and their elimination by the antioxidant defense system. A moderate increase in the ROS levels serves as a signaling function, participating in regulation of cell proliferation and differentiation. High levels of oxidative stress lead to chemical damage to lipids, proteins, and DNA. If the cell's antioxidant system fails to repair this damage, the outcome – depending on the intensity of the stress – may be either necrosis or activation of the regulated cell death mechanisms. Oxidative stress also plays a significant role in the pathogenesis of virtually all diseases, including neurodegenerative disorders, diabetes mellitus, and malignant neoplasms [36].

The transcription factor Bach1 is a key regulator of redox homeostasis, functioning primarily as a repressor of antioxidant defense genes [37]. The transcription factor Nrf2 acts as its functional antagonist (Fig. 1, c and d). Under physiological conditions, Bach1 competes with Nrf2 for binding to small Maf family proteins, thereby suppressing Nrf2's transactivation function and acting as a repressor of the antioxidant program. Concurrently, Nrf2 is sequestered in the cytoplasm by the redox-sensing adapter Kelch-like ECH-associated protein 1 (Keap1) – a component of the ubiquitin ligase complex – leading to the proteasomal degradation of Nrf2 [38]. Classic target of the Bach1/Nrf2 pair is the *HMOX1* gene, which encodes heme oxygenase-1 (HMOX-1) [39]. HMOX-1 catalyzes breakdown of heme into CO, biliverdin, and Fe^{2+} ions (Fig. 1), thereby reducing free heme levels but generating ferrous iron – a catalyst for ferroptosis. Upon accumulation, heme binds to Bach1, triggering its nuclear export, ubiquitination, and subsequent degradation [40].

Under conditions of oxidative stress, modification of the sensor thiol groups of the Keap1 protein leads to conformational changes and release of Nrf2, which next translocates to the nucleus and initiates the antioxidant program [38]. In the nucleus, Nrf2 competes with Bach1 for binding to MARE sequences, activating the *HMOX1* expression (Fig. 1d) and expression of other antioxidant response genes, thereby promoting heme degradation and reducing intracellular ROS levels [41]. The *BACH1* gene is a target of Nrf2 [42]; thus, a negative feedback loop is established between Bach1 and Nrf2 mediating fine-tuning of the cellular response to oxidative stress. Bach1 and Nrf2 also co-regulate expression of the genes involved in maintaining redox homeostasis, including those for glutathione biosynthesis (*GCLM*, *GCLC*), cysteine transport (*SLC7A11*), quinone detoxification (*NQO1*), and heme metabolism (*HMOX1*) [43, 44]. However, the number of commonly regulated genes is significantly lower than the number of genes specifically regulated by each of the transcription factors (Fig. 1c). In addition to the repression of the antioxidant genes, Bach1 can directly activate expression of the pro-oxidant enzymes – specifically NADPH oxidase 4 (NOX4) – leading to generation of ROS, lipid peroxidation, and ferroptosis in the spinal cord neurons [45].

Elevated ROS levels play a crucial role in initiating cell death pathways, contributing to both

activation of the mitochondrial (intrinsic) apoptosis pathway and depletion of the reduced glutathione, which leads to ferroptosis [46, 47]. In this context, Bach1 levels – stability of which is regulated by ROS levels and hypoxia – may act as one of the factors determining the choice between different types of cell death.

BACH1 ROLE IN FERROPTOSIS

Specific features of cell death in ferroptosis. Ferroptosis is a relatively recently described form of programmed cell death [2] that differs fundamentally from apoptosis and necrosis. It is driven by the iron-dependent peroxidation of the membrane phospholipids, leading to the loss of cell integrity and depletion of the antioxidant defense systems. Morphologically, ferroptotic cell death is characterized by the cell shrinkage in the absence of marked chromatin condensation or formation of apoptotic bodies. Mitochondria undergo specific changes: they decrease in size, their membranes exhibit increased electron density, cristae disappear, and the intermembrane space widens. Meanwhile, the plasma membrane retains its integrity until the terminal stage, and classic morphological signs of necrosis (swelling of cellular structures and early lysis) are typically absent [48].

The mechanism triggering ferroptosis involves both oxidative stress and kinase signaling pathways that lead to activation of lipoxygenase and the protein Beclin 1; however, the specific details remain to be fully elucidated [12]. The selenium-containing glutathione peroxidase 4 (GPX4) plays a central role in the execution of ferroptosis. This enzyme is localized within the phospholipid bilayer of membranes [49] and reduces cytotoxic lipid hydroperoxides to their corresponding alcohols, utilizing the reduced glutathione as a cofactor. In turn, glutathione reductase maintains the pool of reduced glutathione [50]. Direct inhibition of GPX4 (e.g., by the compound RSL3) leads to the uncontrolled accumulation of lipid peroxides and triggers a chain reaction involving formation of ROS and lipid peroxyl radicals, thereby inducing ferroptosis. Even before the term “ferroptosis” was introduced, the cell death caused by the blockade of the Xc^- system (a cystine/glutamate antiporter composed of SLC7A11 and SLC3A2 subunits) was referred to as oxytosis [51]. The Xc^- system facilitates uptake of cystine, which is required for glutathione synthesis, into the cell. Blocking this system leads to the cell death – a process recognized since 2012 as ferroptosis – though it occurs approximately four hours later than the cell death resulting from the direct GPX4 inhibition [12]. This pathway remains a subject of active study, as not only GPX4, but the entire cell responds to the gradual decline in the reduced glutathione levels. GPX4 inactivation leads to a runaway accumulation of lipid peroxides and peroxy radicals, ultimately disrupting the mechanisms controlling intracellular iron levels. This triggers ferritinophagy, the selective autophagy of ferritin, accompanied by the release of even greater amounts of ferrous iron. This stage renders the ferroptosis process irreversible. Inhibiting ferritinophagy (for example by blocking the interaction between ferritin and the NCOA4 protein) makes it possible to halt ferroptosis [52].

Bach1 as a ferroptosis stimulator. Bach1 is considered a key regulator of ferroptosis, controlling expression of several ferroptosis-related genes (Fig. 2). In the context of neurodegenerative diseases, Bach1 sensitizes cells to the cell death primarily by suppressing the genes that provide key protective mechanisms [3].

First, Bach1 affects iron metabolism by actively suppressing expression of the genes responsible for safe storage and export of iron ions: ferritin heavy and light chains (*FTH1* and *FTL*), which bind and isolate iron [37, 53]; ferroportin (*SLC40A1*), exporting labile iron from the cell [37, 54]; and heme oxygenase-1 (*HMOX1*) [39]. By suppressing expression of these genes, Bach1 renders the cell vulnerable to ferroptosis.

Furthermore, studies investigating pancreatic cancer cells have demonstrated that the genetic knockout or knockdown of the *BACH1* gene leads to the reduced levels of the protein IRP2 (iron-responsive protein 2) [54], as the *IREB2* gene, which encodes IRP2, is a target of Bach1. Thus, Bach1 is involved in regulating iron metabolism via IRP2; in the presence of excess heme, IRP2 undergoes ubiquitination and proteasomal degradation. Under normal conditions, the cytoplasmic proteins IRP1 and IRP2 exert post-transcriptional control over iron metabolism, including inhibition of ferritin mRNA translation when intracellular iron levels are low [54].

Secondly, Bach1 impairs functioning of the glutathione peroxidase 4 (GPX4) system by actively suppressing the genes required for glutathione biosynthesis, thereby promoting ferroptosis [50]. These genes include *SLC7A11* (encoding the xCT cystine transporter subunit) [55], *GCLC* and *GCLM* (encoding subunits of glutamate-cysteine ligase, a key enzyme in glutathione synthesis) [55], and the glutathione reductase gene *GSR*, a target of the Nrf2/Bach1 pair. Furthermore, the *GPX4* gene itself is a target of Bach1. The *BACH1* knockdown or knockout leads to a significant increase in the *GPX4* expression [55, 56], whereas Bach1 overexpression, conversely, suppresses GPX4 protein levels. For instance, in the gastric cancer

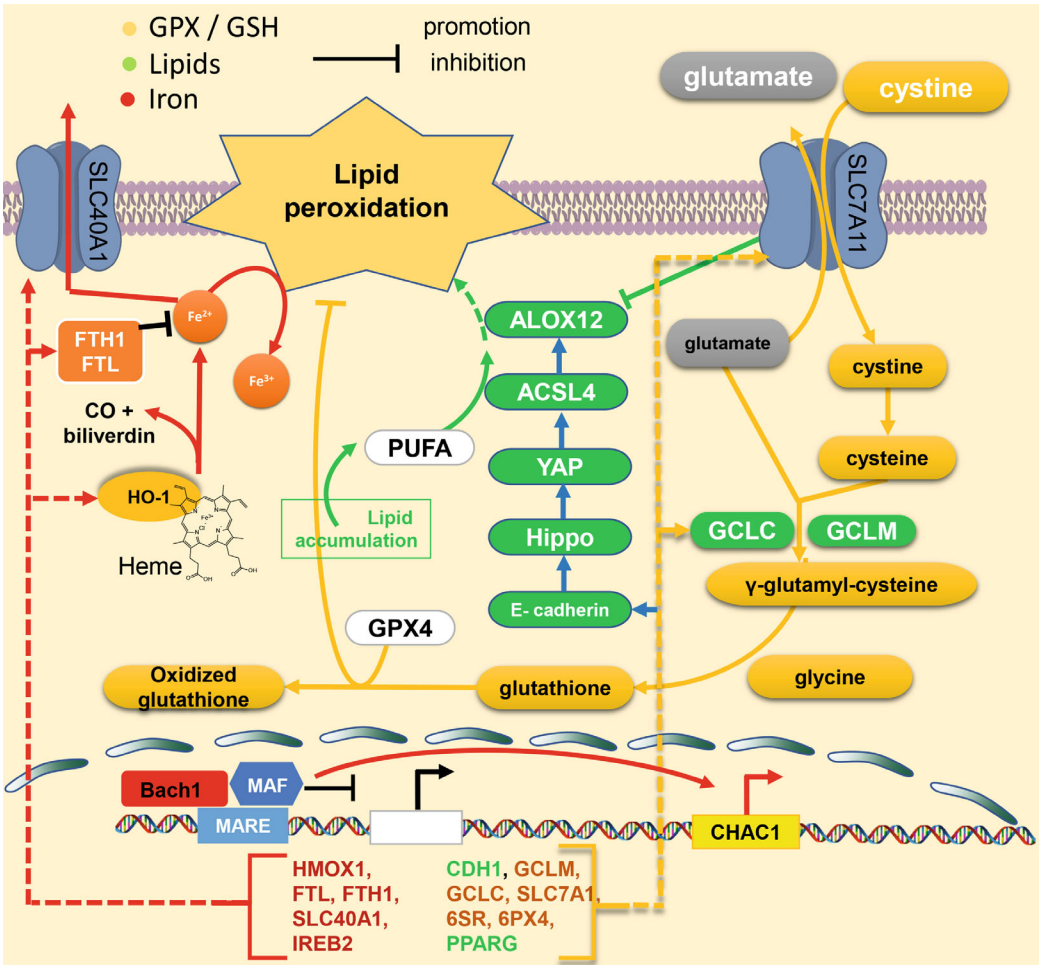

Fig. 2. Bach1 role in ferroptosis. Bach1 represses key protective genes and activates pro-oxidant pathways. Genes and metabolic pathways participating in iron metabolism are *FTH1*, *FTL*, *SLC40A1*, *HMOX1*, *IREB2*; in GPX4/glutathione system – *SLC7A11*, *GCLC*, *GCLM*, *GSR*, *GPX4*, *CHAC1*; in lipid metabolism *ACSL4*, *PPARG*, *ALOX12*, *SCD1*.

cells, Bach1 counteracted the protective upregulation of GPX4 [57].

It is also worth noting that Bach1 is capable of regulating glutathione levels not only by repressing genes involved in its biosynthesis but also by activating expression of the *CHAC1* gene, which encodes γ-glutamylcyclotransferase [58]. This enzyme is involved in glutathione degradation, and its activation by Bach1 contributes to the depletion of intracellular glutathione stores, further increasing cellular susceptibility to ferroptosis.

Third, Bach1 influences lipid metabolism, which plays a central role in the development of ferroptosis, since this type of cell death is driven by peroxidation of the membrane phospholipids containing polyunsaturated fatty acids (PUFAs) [3]. Key enzymes of PUFA synthesis – fatty acid elongase 5 (ELOVL5) and fatty acid desaturase 1 (FADS1) – have been identified as Bach1 targets via chromatin immunoprecipitation sequencing (ChIP-seq). At the same time, Bach1 represses transcription of the stearoyl-CoA desaturase 1 (SCD1), a key enzyme in the synthesis of monounsaturated fatty acids (MUFAs). Incorporation of MUFAs into membrane phospholipids reduces susceptibility to lipid peroxidation, thereby increasing cellular resistance to ferroptosis [59]. Inhibition of *SCD1* leads to the reduced MUFA content and increased sensitivity of the ovarian cancer cells to ferroptosis [60]. In the esophageal squamous cell carcinoma, Bach1 has been shown to bind to the regulatory regions within the second intron of the *SCD1* gene and suppress its transcription, thereby reducing oleic acid production and enhancing lipid peroxidation. Interestingly, in the esophageal squamous cell carcinoma, the Bach1–SCD1–oleic acid axis is linked not only to the regulation of ferroptosis but also to the lymphogenous tumor metastasis [61]. Bach1 also promotes the epithelial-mesenchymal transition in various cancer cells by suppressing the expression of E-cadherin, which mediates cell-cell contacts [8, 62]. Loss of such contacts could affect the NF2-Hippo pathway, leading to the increased expression of the gene encoding ACSL4

(Acyl-CoA Synthetase Long Chain Family Member 4), which converts free long-chain fatty acids into CoA esters [3, 63]. ACSL4 promotes incorporation of PUFAs into the membrane phospholipids, significantly increasing cellular sensitivity to ferroptosis [3]. Furthermore, the transporter SLC7A11 – whose gene expression is suppressed by Bach1 – is capable of directly inhibiting the lipoxygenase ALOX12 [64]. ALOX12 is an iron-dependent enzyme that drives lipid peroxidation [3]. Consequently, by repressing the *SLC7A11* gene, Bach1 could promote increased ALOX12 activity and accelerate generation of peroxylipids. Finally, Bach1 has been shown to limit lipid accumulation during adipocyte differentiation by suppressing PPARγ – a key regulator of lipid metabolism – whose gene (*PPARG*) is a direct target of the Bach1 repressor [65]. It is hypothesized that Bach1 could alter sensitivity of the cells to ferroptosis by influencing how cells handle PUFA accumulation, although this mechanism requires further investigation [3]. Thus, Bach1 plays a significant role in the cellular sensitivity to ferroptosis, including through its influence on lipid metabolism – specifically, by directly regulating the MUFA-to-PUFA ratio in the membranes.

Bach1/Nrf2 competition determines the cell fate in ferroptosis. Nrf2 and Bach1 compete with each other for binding to the same Maf proteins and identical DNA sites (Fig. 1d, example of heme oxygenase-1), thereby regulating ferroptosis in opposite directions [3]. Under normal conditions, Bach1 is stable and represses target genes, whereas Nrf2 is continuously degraded through the action of the Keap1 protein [66, 67]. Under conditions of oxidative stress or high heme levels, Bach1 loses its ability to bind to DNA and exits the nucleus [40, 41], whereas Nrf2 accumulates in the nucleus and triggers expression of the antioxidant genes. In addition to GPX4, a common target of Bach1 and Nrf2, negative regulators of ferroptosis include the coenzyme Q10 synthesis and regeneration systems, the ferroptosis suppressor protein FSP-1, and components involved in intracellular transport, lipid and fatty acid metabolism, and iron homeostasis, all of which are regulated by the Nrf2/Bach1 pair [3, 68]. Thus, the Bach1/Nrf2 balance determines the cell fate: a shift toward Nrf2 protects the cell against oxidative damage and ferroptosis, whereas predominance of Bach1 suppresses antioxidant defense and triggers cell death via ferroptosis. Ferroptosis is implicated in pathogenesis of a wide range of diseases, including ischemic injury, neurodegenerative disorders, and neoplastic processes [69]. It also functionally interacts with other forms of programmed cell death, particularly apoptosis and cuproptosis [70]. However, the role of Bach1 is not limited to counteracting Nrf2 (genes co-regulated by them account for only about 10% of all Bach1 targets) but also extends to the involvement in anti-inflammatory and other signaling pathways, where its function has been studied to a significantly lesser extent.

ROLE OF BACH1 IN APOPTOSIS

Apoptosis – key pathways and players. Morphologically, apoptosis is characterized by cell shrinkage and condensation, peripheral nuclear chromatin condensation forming characteristic hemispherical masses, and subsequent nuclear fragmentation. This results in the formation of compact apoptotic bodies that are phagocytosed without eliciting a significant inflammatory response. Typical features of apoptosis also include formation of the plasma membrane protrusions (blebs) – while membrane integrity is maintained until the late stages – cytoplasmic condensation, and orderly degradation of the intracellular structures. This constellation of features distinguishes apoptosis from necrotic and lytic forms of cell death [71].

From the molecular perspective, extrinsic and intrinsic (mitochondrial) pathways of apoptosis induction are distinguished. The extrinsic pathway is triggered by the interaction of death ligands (FasL, TNF-α, TRAIL) with their corresponding receptors (Fas/CD95, TNFR, TRAIL-R), leading to the recruitment and activation of caspase-8, followed by the cascade activation of the effector caspases-3 and -7 [72]. Activated caspase-8 cleaves the Bid protein, generating its truncated pro-apoptotic variant, tBid; this promotes displacement of the anti-apoptotic Bcl-2 family proteins from the complexes with the pro-apoptotic proteins Bax and Bak. The latter, in turn, oligomerize and form pores in the outer mitochondrial membrane, through which cytochrome *c* is released into the cytosol. In the cytosol, cytochrome c binds to Apaf-1 and procaspase-9 to form the apoptosome, leading to the activation of caspase-9. Caspase-9 next activates effector caspases (caspase-3 and -7), which carry out specific proteolysis of the structural and regulatory proteins [73].

Caspase-8 is a key regulatory node that acts as a molecular switch between apoptosis, necroptosis, and pyroptosis. Depending on the cellular context, caspase-8 could either activate caspases-3 and -7 or cleave Bid, thereby enhancing the mitochondrial pathway. Conversely, caspase-8 inactivation promotes caspase-1 activation and initiation of pyroptosis [73]. It is worth noting that the Bcl-2 family proteins can perform both pro-apoptotic functions (Bax, Bak, Bid, Bim, Puma, Noxa, Bad, Blk) and anti-apoptotic functions (Bcl-2, Bcl-xL, BAG), controlling mitochondrial membrane integrity and participating in the regulation of cytochrome c release [74].

Interplay between apoptosis and ferroptosis. Recent studies indicate an interplay between various cell death pathways, specifically apoptosis and ferroptosis. Interaction between these pathways largely occurs at the level of intracellular organelles, such as mitochondria, endoplasmic reticulum, and lysosomes [75]. For instance, apoptosis and ferroptosis share common features, including accumulation of the mitochondrial reactive oxygen species (ROS), increased mitochondrial membrane permeability, and development of the endoplasmic reticulum stress. The voltage-dependent anion channels (VDACs) of the mitochondria could serve as one of the points of intersection between the apoptosis and ferroptosis [12]. These proteins participate in control of permeability of the mitochondrial outer membrane and are involved in the regulation of apoptosis, including interactions with the Bcl-2 family proteins. At the same time, erastin – a classic inducer of ferroptosis – could target VDAC2 and VDAC3, promoting their degradation [12]. This process is accompanied by the disrupted mitochondrial metabolism and increased cellular sensitivity to ferroptosis. VDAC channels may play a crucial role in linking mitochondrial stress to ferroptosis.

Furthermore, disruption of the lysosomal membrane integrity leads to the release of cathepsin B and activation of caspases, thereby linking lysosomal damage to apoptotic cell death [76]. At the same time, lysosomes participate in the regulation of the intracellular iron pool – specifically through ferritinophagy – thereby contributing to the increased oxidative stress and development of ferroptosis [77].

In some cases, apoptosis and ferroptosis can occur simultaneously [78]. For example, p53, an important regulator of apoptosis, could also participate in the initiation of ferroptosis [79]. Induction of ferroptosis could also increase sensitivity to apoptosis [80]. Thus, exposure to the ferroptosis inducers (erastin or artesunate) leads to endoplasmic reticulum stress and activation of the PERK-eIF2α-ATF4-CHOP signaling pathway, accompanied by the increased expression of the pro-apoptotic protein Puma and subsequent activation of the TRAIL-mediated apoptosis [81]. Furthermore, inhibition of the pro-apoptotic protein Bid reduces the erastin-induced ferroptosis [82], whereas in the RSL3-induced ferroptosis, Bid is considered a downstream effector of GPX4 activity impairment [83]. Consequently, Bid could participate in the initiation of apoptosis upon exposure to the ferroptosis inducers. Activation of one cell death pathway could inhibit another. For example, induction of ferroptosis under conditions of cysteine deficiency is accompanied by the decrease in glutathione levels, which could limit caspase activation and, in turn, suppress apoptosis [84, 85]. Furthermore, during apoptosis, caspases could cleave the enzyme ACSL4, which is important for incorporation of polyunsaturated fatty acids into the membranes. Loss of ACSL4 functionality limits ability of the cell to initiate ferroptosis [86].

Experimental data indicate that the source of iron for ferroptosis could be not only transferrin but also mitochondrial hemoproteins, such as cytochrome c; this opens up the possibility of a switch from the mitochondrial apoptosis to ferroptotic cell death, depending on the peroxide levels and iron availability [87, 88].

Pro-apoptotic role of Bach1. The role of Bach1 in apoptosis is dual and depends on the cellular context. Acting as a pro-apoptotic factor, Bach1 sensitizes cells to apoptosis by altering redox homeostasis and increasing ROS levels. Bach1 represses genes involved in the cellular antioxidant response (such as *HMOX1*, *NQO1*, and *PRDX1*). Consequently, free radical metabolism is disrupted, leading to accumulation of the intracellular ROS. This process is accompanied by the mitochondrial dysfunction and an altered balance between the pro- and anti-apoptotic proteins of the Bcl-2 family and, thus, triggers apoptosis, as evidenced by the elevated levels of activated caspases. The mechanism has been confirmed in various studies; for instance, in endothelial cells, the *BACH1* overexpression led to accumulation of mitochondrial ROS, reduced levels of the anti-apoptotic proteins Bcl-2 and Bcl-xL, and activation of caspase-3 [89]. Similar effects are observed during the ischemia-reperfusion (I/R) injury in certain organs. In the context of I/R injury, increased *BACH1* expression is accompanied by the reduced expression of its antioxidant target genes – such as *HMOX1*, *NQO1*, and *PRDX1* – leading to the enhanced oxidative stress and activation of the mitochondrial apoptotic pathway [90-92]. It is noteworthy that all the identified genes are also regulated by the transcription factor Nrf2 [93]. Consequently, the Bach1/Nrf2 axis plays a key role in the regulation of redox homeostasis and could determine cellular sensitivity to apoptosis. In certain types of cancer, Bach1 could also promote apoptosis. For instance, in the breast cancer cells, activation of the CXCR3-B chemokine receptor by its ligand leads to the enhanced nuclear import of Bach1 and tumor cell apoptosis; this process is accompanied by inhibition of the *HMOX1* expression and, likely, increase in oxidative stress [94]. In another study, the *BACH1* knockdown attenuated apoptosis of the cells associated with the use of formononetin and chemotherapy, an effect linked to the reduction in overall oxidative stress levels [95]. Consequently, in the tumor cells of certain types of cancer, Bach1 could promote apoptosis by disrupting the antioxidant defense system of the cell.

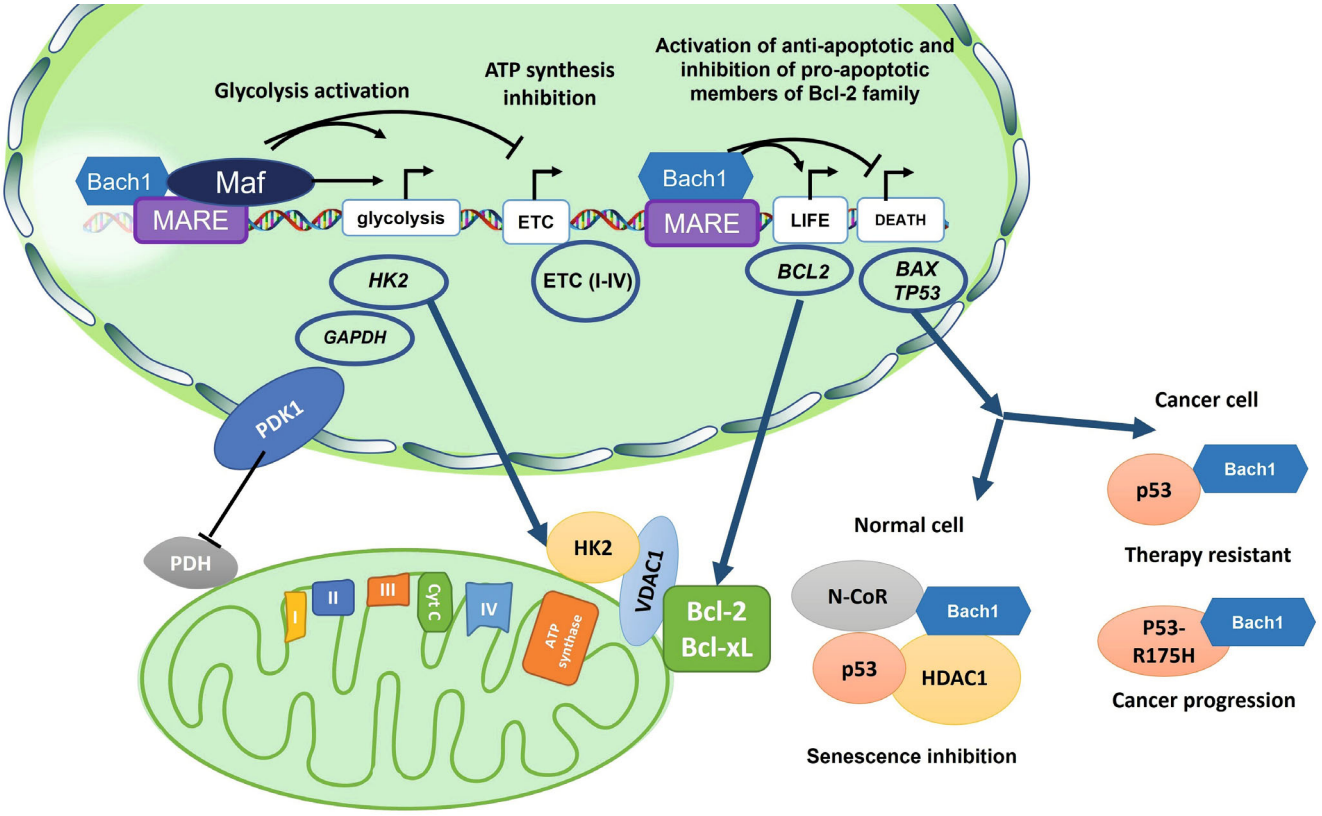

Fig. 3. Role of Bach1 in apoptosis. Activation of glycolytic genes (*HK2*, *GAPDH*) and repression of mitochondrial genes. Bach1 regulates expression of the apoptotic genes (*BCL2*, *BAX*, *TP53*). Interaction of apoptotic proteins with HK2 and VDAC1. Various scenarios of Bach1 interaction with p53 transcription factor.

Anti-apoptotic role of Bach1. The anti-apoptotic role of Bach1 is largely attributed to the repression of mitochondrial genes (Fig. 3). Furthermore, Bach1 activates expression of the pyruvate dehydrogenase kinase 1 (*PDK1*), leading to the inhibition of mitochondrial respiration [96]. Concurrently, Bach1 stimulates expression of hexokinase 2 (*HK2*), which directly interacts with the VDAC1 protein on the mitochondrial outer membrane. This interaction, firstly, stabilizes mitochondria by preventing opening of the mitochondrial pore and, consequently, inhibiting apoptosis. Secondly, HK2 utilizes ATP as a substrate, facilitating shift of the cell metabolism toward the glycolytic pathway and maintaining the so-called Warburg effect in the cancer cells. In this regard, development of the inhibitors targeting the VDAC1–HK2 interaction is of particular interest in oncology [97].

In addition to the general effect on mitochondria, namely switching the cell to the glycolytic pathway, Bach1 regulates expression of the genes involved in the initiation and progression of apoptosis, including *BIM* (*BCL2L11*) and *TNFRSF1A* [44]. Bach1 also regulates expression of the calcium signaling genes (*ITPR2*, *CALM1*), which is important for apoptosis initiation. It is noteworthy that these genes are not canonical Nrf2 targets, indicating existence of the Nrf2-independent pathways for the regulation of apoptosis involving Bach1 [98].

In tumor cells, Bach1 primarily exhibits anti-apoptotic properties, promoting tumor survival and progression. For instance, in the lung cancer stem cells, Bach1 activates the *CD44* expression and triggers the MAPK signaling pathway [99]. Furthermore, the *BACH1* knockdown induces apoptosis, reduces Bcl-2 levels, and increases expression of the pro-apoptotic proteins Bax and p53. Stabilization of the Bach1 protein through direct interaction with thioredoxin enhances the stem-like potential of cancer cells by activating the AKT/mTOR signaling pathway [100]. In the hepatocellular carcinoma, Bach1 also promotes suppression of apoptosis through activation of the PI3K/AKT/mTOR signaling pathway and inhibition of the mitochondrial death pathway [101]. Finally, in the mantle cell lymphoma and glioblastoma, Bach1 also acts as an anti-apoptotic factor, promoting tumor survival and progression [102, 103]. It should be noted that Bach1 also influences autophagy mechanisms by modulating cellular sensitivity to apoptosis. The role of Bach1 in the regulation of autophagy is discussed in greater detail in the Section “Bach1 and autophagy”.

Interaction between Bach1 and p53. Interaction between Bach1 and p53 is context-dependent and primarily serves to regulate the transcriptional activity of p53. p53 (*TP53*) is a key regulator of the cell cycle, DNA repair, and apoptosis; notably, mutations in the *TP53* gene are found in approximately half of all malignant tumors [104]. In normal cells (fibroblasts), Bach1 is capable of forming a protein complex with p53 that includes the nuclear corepressor N-CoR and the histone deacetylase HDAC1 [105]. This complex suppresses the p53-dependent cellular senescence, while no effect on apoptosis was observed in this model (Fig. 3). In the tumor cells, Bach1 typically functions as a p53 antagonist, inhibiting its activity and promoting cell survival. For instance, in glioblastoma, Bach1 interacts with p53, disrupting regulation of its transcriptional targets, and contributing to the chemotherapy (temozolomide) resistance [103]. Moreover, Bach1 exhibits specificity for certain hotspot mutant forms of p53 (p53R175H), forming stable complexes with them [106]. Such complexes recruit additional regulatory proteins, leading to the suppression of ferroptosis; notably, no effect on apoptosis was observed in this instance.

At the same time, under certain conditions, Bach1 could alter its influence on p53. For example, upon exposure to the specific therapeutic agents (such as formononetin), Bach1 could promote p53 activation and trigger apoptosis in the tumor cells [95]. Finally, Bach1 could directly regulate *TP53* expression, maintaining the level of this protein at low values in the lung or liver cancer stem cells [99, 101]. Thus, involvement of Bach1 in apoptosis depends on the specific conditions. The pro-apoptotic role of Bach1 manifests primarily under conditions of oxidative stress and is associated with the repression of antioxidant target genes and accumulation of ROS. The anti-apoptotic effect of Bach1 is characteristic mainly of tumor cells and is driven by the ability of Bach1 to shift cellular metabolism toward glycolysis, suppress expression of the pro-apoptotic genes, regulate survival signaling pathways, and inhibit the cellular stress response.

BACH1 IN OTHER TYPES OF REGULATED CELL DEATH AND AUTOPHAGY

Bach1 and cuproptosis. Cuproptosis is a copper-dependent form of regulated cell death associated with copper accumulation in mitochondria. Ferredoxin 1 (FDX1) plays a central role in this process; it facilitates reduction of Cu^{2+} to Cu^{+} and is essential for lipoylation of the tricarboxylic acid cycle proteins, including dihydrolipoyl acetyltransferase (DLAT) [107, 108]. The generated Cu^{+} binds to the lipoylated proteins, causing their aggregation, proteotoxic stress, and mitochondrial dysfunction, ultimately leading to cell death [109].

Bach1 could promote initiation of cuproptosis during tumor radiotherapy [110]. The reduced Bach1 levels are associated with the increased radioresistance in the tumor cells. This effect is thought to be mediated by the repression of the copper-binding metallothioneins *MT1E* and *MT1X*; under *BACH1* deficiency, the elevated expression of these proteins sequesters free copper and reduces its bioavailability, thereby inhibiting cuproptosis. Conversely, restoring *BACH1* expression or suppressing metallothionein expression increases cellular sensitivity to radiotherapy. Overall, the role of *BACH1* in the regulation of cuproptosis remains insufficiently understood and requires further investigation, including studies outside the context of radiotherapy.

Bach1 and pyroptosis. Pyroptosis is an inflammatory, lytic form of the regulated cell death. In the canonical pathway, it is triggered by the assembly of inflammasome – a multiprotein complex that activates caspase-1. Caspase-1 mediates maturation of the pro-inflammatory cytokines IL-1β and IL-18 and cleaves gasdermin D, the N-terminal fragment of which forms pores in the plasma membrane. Pore formation leads to the cell swelling and lysis, followed by the release of pro-inflammatory cytokines [111-114].

Bach1 could exert a protective effect against pyroptosis. For instance, the *BACH1*-deficient mouse macrophages exhibit increased sensitivity to inflammasome activation, accompanied by the enhanced secretion of the pro-inflammatory cytokines IL-1β and IL-18, a hallmark of pyroptosis [115]. This is thought to be associated with the reduced expression of the enzyme iNOS and decreased production of nitric oxide (NO), which normally inhibits pyroptosome formation.

Bach1 and autophagy. Autophagy is a lysosomal mechanism for degradation of the damaged proteins and organelles, which, depending on the cellular context, could maintain cell viability or participate in the development of regulated cell death [22]. Bach1 could participate in the regulation of autophagy by inhibiting it through various mechanisms. Specifically, Bach1 is capable of directly suppressing autophagy via transcriptional repression of the *ATG7* gene, a key component of the autophagy machinery. In the human bone marrow-derived mesenchymal stem cells, dexamethasone increased the level of *BACH1* expression and reduced autophagy activity, whereas the *BACH1* knockdown restored the *ATG7* expression and osteogenic differentiation. Binding of Bach1 to the *ATG7* promoter was confirmed using ChIP and reporter assays [116]. The inhibitory effect of Bach1

on autophagy has also been confirmed *in vivo*. In the models of age-related and surgically induced osteoarthritis, the Bach1-deficient mice exhibited an increased number of chondrocytes expressing the LC3 protein (a key autophagy marker), as well as reduced severity of the degenerative changes in the articular cartilage [117]. Similarly, in the hepatocellular carcinoma cells, downregulation of *BACH1* within the TET1-miR-34a-BACH1-p53 axis was accompanied by the enhanced autophagy and apoptosis and reduction in the pro-inflammatory factors [118].

An additional mechanism regulating autophagy is repression of the *SQSTM1* gene – a common transcriptional target of Bach1 and Nrf2 [119] – which encodes the so-called p62 "cargo" protein that recognizes damaged or ubiquitinated proteins and targets them for degradation via autophagy [120]. It is worth noting that the autophagy processes interact closely with the apoptotic signaling pathways and could either enhance or inhibit apoptotic cell death, depending on the cellular context. In particular, p62 is involved in the regulation of the mitochondrial (intrinsic) pathway of apoptosis [121]. Furthermore, stability of the p62 protein, like that of Nrf2, is regulated through its interaction with the redox sensor Keap1. Consequently, influence of the Bach1-p62 axis on apoptosis is dual in nature. On the one hand, p62 could promote activation of apoptosis by regulating autophagy and associated signaling pathways; on the other, it could suppress apoptosis by activating the antioxidant program – a result of Nrf2 stabilization occurring when p62 competes with Keap1 for binding.

CONCLUSION

The transcription factor Bach1 is a key regulator of redox homeostasis. It also participates in the cellular response to oxidative stress, largely determining cell sensitivity to various cell death pathways. By repressing antioxidant gene expression and regulating iron and glutathione metabolism, Bach1 promotes accumulation of ROS and increases cellular susceptibility to ferroptosis. Despite the progress in understanding Bach1 functions, its role in regulating cell death remains insufficiently characterized. This is due to both lack of the comprehensive picture regarding the Nrf2-independent functions of Bach1 and its unique target genes, and limited understanding of the mechanisms underlying novel forms of cell death – specifically ferroptosis, and particularly pyroptosis and cuproptosis. Furthermore, the dual role of Bach1 in apoptosis and the mechanisms governing the switch between its pro- and anti-apoptotic effects require further analysis, as do molecular mechanisms by which Bach1 regulates autophagy.

Beyond its fundamental significance, Bach1 is of considerable clinical interest as a potential prognostic marker. Elevated *BACH1* expression is associated with poor prognosis in a number of malignancies, including adenocarcinomas, glioblastoma, and triple-negative breast cancer [122-124]. Furthermore, increased expression of this gene in the malignant cells is associated with a number of processes that promote tumor progression, such as invasion and metastasis [5]. Thus, in the experimental models, the *BACH1* silencing inhibits invasion and migration of the prostate cancer cells [7]. It is noteworthy that the clinical significance of *BACH1* is not limited to its expression level. The rs372883C/T polymorphism in the 3′-untranslated region of this gene is also associated with sensitivity of the pancreatic adenocarcinoma to gemcitabine and patient survival [125]. Consequently, *BACH1* could be considered not only a prognostic but also a predictive biomarker for the efficacy of antitumor therapy.

It is important to note that the *Bach1*$^{-/-}$ knockout mice are fertile and exhibit no significant abnormalities in the body size or morphology, indicating that Bach1 is not critical for normal development and reproductive function [39]. These data provide further support for considering Bach1 as a promising therapeutic target.

Clinical significance of Bach1 extends to non-oncological diseases as well. Dysregulation of the Bach1/Nrf2 axis is considered a key mechanism in the development of neurodegenerative diseases, including Alzheimer's and Parkinson's diseases. For instance, in the preclinical models of Parkinson's disease, Bach1 inhibition exerts a neuroprotective effect [13]. Notably, Bach1 inhibition remained effective even after the disease induction, making this approach promising for further clinical study. Furthermore, accumulated data indicate involvement of Bach1 in the pathogenesis of cardiovascular diseases, pulmonary fibrosis, skin disorders, diabetes mellitus, and inflammatory gastrointestinal diseases [9]. For example, the level of *BACH1* expression is elevated in the heart tissue of the patients with pathological hypertrophy and heart failure, whereas the cardiomyocyte-specific deletion of *BACH1* in mice reduces hypertrophy and myocardial fibrosis and helps preserve cardiac function [126]. In this regard, *BACH1* silencing is considered a potential therapeutic approach, including for the patients intolerant to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers [9].

Selective Bach1 inhibitors capable of suppressing its activity without affecting other heme-binding proteins or heme-dependent enzymes are currently under development. Determination of the structure of Bach1 C-terminal domain in complex with heme via

cryo-electron microscopy [30] has made a significant contribution to this field, opening up possibilities for the rational design of the specific inhibitors. Development of such compounds shows promise for the treatment of both oncological diseases and neurodegenerative disorders.

Abbreviations

Bach1	BTB and CNC homology 1
GPX4	glutathione peroxidase 4
Keap1	Kelch-like ECH-associated protein 1
MARE	Maf recognition elements
Nrf2	nuclear factor erythroid 2-related factor 2
RCD	regulated cell death
ROS	reactive oxygen species

Contributions

K. V. Klycheva, M. O. Silkina, and A. V. Razumovskaya wrote the manuscript; D. M. Hushpulian and A. A. Zakharyants collected and analyzed literature data and discussed the results; B. Thomas and S. V. Kazakov provided critical review and scientific consultation; I. G. Gazaryan provided the concept and scientific supervision; S. V. Nikulin provided the concept and overall project supervision; all authors edited the manuscript and approved the final version.

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Ethics approval and consent to participate

This work does not contain any studies involving human and animal subjects.

Conflict of interest

The authors of this work declare that they have no conflicts of interest.

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