

Progression of the role of CRYAB in signaling pathways and cancers

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Abstract: CRYAB is a member of the small heat shock protein family, first discovered in the lens of the eye, and involved in various diseases, such as eye and heart diseases and even cancers, for example, breast cancer, lung cancer, prostate cancer, and ovarian cancer. In addition, CRYAB proteins are involved in a variety of signaling pathways including apoptosis, inflammation, and oxidative stress. This review summarizes the recent progress concerning the role of CRYAB in signaling pathways and diseases. Therefore, the role of CRYAB in signaling pathways and cancers is urgently needed. This article reviews the regulation of CRYAB in the apoptotic inflammatory signaling pathway and its role in cancers progression and as a key role in anti-cancer therapy targeting CRYAB in an effort to improve outcomes for patients with metastatic disease.

Keywords: CRYAB, signaling pathways, cancers

Introduction

Small heat shock proteins (sHsps or HspBs) form a large and evolutionary ancient family, whose members have been found in viruses, archaea, bacteria, plants, and animals.¹ The human genome contains 10 genes encoding sHsps.² Some sHsps (HspB1, HspB5, HspB6, and HspB8) are expressed ubiquitously, while others (HspB2, HspB3, HspB4, HspB7, HspB9, and HspB10) have been found only in certain tissues.³ sHsps are characterized by their complex oligomeric structures, allowing them to interact with each other to form homo- and hetero-oligomeric structures of dynamic size (up to 700 kDa).⁴ For instance, the heterooligomeric complex formed by HspB4 and HspB5 plays an important role in keeping the lens transparency.⁵ In heterooligomeric complexes, HspB6 and HspB1 mutually affect the structure of each other and the formation of heterooligomeric complexes might influence diverse processes depending on sHsps.⁶

HspB5, also known as CRYAB or α B-Crystallin, has an N-terminal domain, a central domain, and a C-terminal domain.⁷ Its structural and functional characteristics are shown in Figure 1:⁸ 1) low molecular weight of 22 kDa; 2) N-terminal domain of about 60 residues, a conserved α -crystallin structure of about 90 residues involved in the dimerization domain, and the 25-residue C-terminal domain containing the IXI motif; 3) the ability to form large oligomers; 4) dynamic quaternary structure; and 5) induction by stress conditions.

CRYAB was first discovered proteins in the lens of the eye⁹ and is also expressed in other parts of the body, such as the heart, skeletal muscle, ovaries, etc.^{10–12} However, CRYAB protein mutations associate with the different diseases. For instance, domain mutations (D109H, R120G, Q151X, G154S, P155Rfs9X, and R157H) are associated

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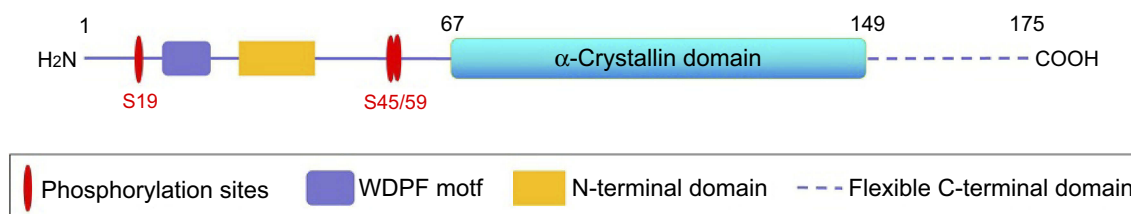


Figure 1 Schematic representation of the structure of the CRYAB protein (including the N-terminal domain, the flexible C-terminal domain, the WDPF domain, and the α -Crystallin protein domain, and the serine (S) phosphorylation site).

with myopathy.¹³ The dominant D109A mutation of CRYAB is pathogenic and associated with myofibrils myopathy.^{14,15} In addition to myopathy, mutations D109H, R120G, and X176Wfs19X are only associated with cardiomyopathy and cataract or discrete lens opacity.¹⁶ Other dominant mutations (R11H, P20R, P20S, R69C, D140N, K150Nfs34X, A171T) and recessive mutations (eg, R11C, R12C, R56W) are also described as associated with congenital cataracts, uniformly dispersed throughout the coding sequence.¹⁷ The autosomal dominant multisystem phenotype in the residual (D109H) mutation is not only associated with myopathy, but also with cardiomyopathy and lens cataract.¹⁸ Even point mutations or short deletions in CRYAB can lead to the development of different hereditary diseases.

CRYAB acts primarily as a chaperone, blocking the aggregation of denatured proteins and keeping aggregation-prone proteins in reservoirs of non-native, foldable intermediates within large, soluble, multimeric structures.¹⁹ The ectopic expression of CRYAB in diverse cell types has been demonstrated to confer protection against a broad range of apoptotic stimuli,²⁰ oxidative stress,²¹ and exposure to anticancer drugs.²² Simultaneously, silencing its expression by RNA interference sensitizes cells to apoptosis.²³ Similarly, a growing number of researchers have described the high expression of CRYAB in human cancers and the significant relationship between CRYAB and unfavorable survival of cancer patients.^{24–26}

So, what is the role of CRYAB in participating in the apoptotic and inflammatory pathways and what role does it play in the diseases? Here, we review recent advances implicating the importance of CRYAB in signaling pathways, its role in cancer progression, and as target molecules in anticancer therapy.

The role of CRYAB in the signaling pathway

CRYAB has multiple functions in cells, but how does it work? Based on the report, the apparent pleiotropic activity

of CRYAB may be due to its binding to chaperones and regulation of the activity and half-life involved in many protein targets involved in apoptotic cell death tumorigenesis and metastasis.^{27–29} And CRYAB contains several serine sites that can be phosphorylated by specific stress or mitogen-activated protein kinases.³⁰ Phosphorylation and oligomeric organization of these proteins are dynamic and are deeply modified due to changes in the cellular environment.³¹ In fact, these structural modifications are reversible and may be sensors in the cellular environment. Changes in the sHsps structure can lead to at least 300 different stoichiometries to allow them to interact with putative proteins.³²

Participation in apoptosis

Apoptosis is a programmed cell death that is negatively regulated by sHsps.^{33–35} In environmental damage such as heat shock, contrary to the increased expression of sHsps, the expression of these proteins is not up-regulated in apoptosis. In some cells, the expressed sHsps can counteract the apoptotic process mediated by the immune system or therapeutic drugs. CRYAB is now thought to interact with specific proteins and regulate their activity during the initiation and execution phases of apoptosis.^{36,37}

CRYAB is a recognized anti-apoptotic protein,³⁸ whose main property is to negative regulation of the proapoptotic members of the Bcl-2 family, Bax, and caspase-3.³⁹ CRYAB interacts directly with caspase-3, Bax, and Bcl-xS.^{39,40} In addition to interacting with these proteins, CRYAB inhibits their transfer from the cytoplasm to the mitochondria, thereby preventing stress-induced apoptosis.⁴⁰ Similarly, CRYAB interacts with p53 to sequester its translocation to the mitochondria, thus indirectly inhibiting its pro-apoptotic effect against the apoptotic Bcl-2 molecule.⁴¹ CRYAB protects cells from apoptosis by inhibiting caspase-3 and PARP (poly(ADP-ribose) polymerase) activation.⁴² CRYAB was also found to inhibit p53-dependent apoptosis mediated by the calcium-activated Raf/MEK/ERK signaling pathway by

inhibiting Ras activation.⁴³ CRYAB can also block UVA cell apoptosis by participating in the regulation of PKC α 1pha and Raf/MEK/ERK signaling pathway proteins.⁴⁴ In addition, CRYAB binds directly to the most potent endogenous inhibitor of apoptosis, X-linked inhibitor of apoptosis, to inhibit caspase.⁴⁵ CRYAB is involved in the regulation of intracellular apoptosis signaling, which inhibits apoptosis by activating the Akt signaling pathway and enhancing PI3K activity.⁴⁶ The above data indicates the anti-apoptotic effect of the CRYAB protein (Figure 2). Recently, results showed CRYAB protects cardiomyocytes against heat stress, likely by reducing F-actin aggregation (thus stabilizing the cytoskeleton), regulating the cell cycle, and preventing caspase-mediated apoptosis.⁴⁷

Involved in inflammation and redox

Intracellular CRYAB has been shown as one of the potent factors in controlling neuroinflammation in several occasions, for instance, multiple sclerosis (MS), an autoimmune demyelinating disease of the central nervous system (CNS). A surprising finding about CRYAB is that patients with MS have at least 70 different proinflammatory mediators (acute phase proteins, complement cascade members, and clotting factors). The interaction with CRYAB reduces the concentration of these peptides, leading to a decrease in inflammatory response.⁴⁸ In the CNS, microglia and astrocytes are the two main cellular components that participate in the inflammatory process. Recent research reports indicated the molecular and cellular basis of extracellular CRYAB-mediated suppression of neuroinflammation. In EAE mice, the expression of

CRYAB was significantly increased in astrocytes. CRYAB was preferentially expressed in astrocytes and can be secreted through exosomes. Expression levels of exosomal CRYAB secreted from astrocytes were markedly increased under stress. Furthermore, incubation of immortalized astrocytes or microglia cell lines with CRYAB remarkably inhibited astrocytes and microglia-mediated inflammatory responses in both autocrine and paracrine manners.⁴⁹

Another anti-inflammatory pathway associated with extracellular CRYAB involves activation of immunoregulatory responses in macrophages via endosomal/phagosome CD14 and Toll-like receptors 1 and 2 (two new CRYAB interacting proteins).⁵⁰ These reports clearly indicate that CRYAB has a different effect on inflammation.

Inflammation is also associated with oxidative stress, and, in this respect, CRYAB induces a reduced state in cells.^{51,52} In fact, CRYAB-expressing cells are accompanied by a decrease in mitochondrial membrane potential and reduced glutathione, a decrease in intracellular reactive oxygen species and nitric oxide levels, and iron uptake.^{53,54} Therefore, it can impair protein oxidation, lipid peroxidation, DNA damage, and cytoskeletal structure damage caused by oxidative stress.^{55–57}

CRYAB in diseases

CRYAB is a structural protein of the lens that helps maintain lens transparency.⁹ CRYAB is also expressed in non-tissue, including the heart, brain, skeletal muscle, skin, ovaries, and kidneys.^{10–12} Abnormal expression of CRYAB also occurs in many diseases, such as eye diseases^{58,59} and heart diseases.^{60,61}

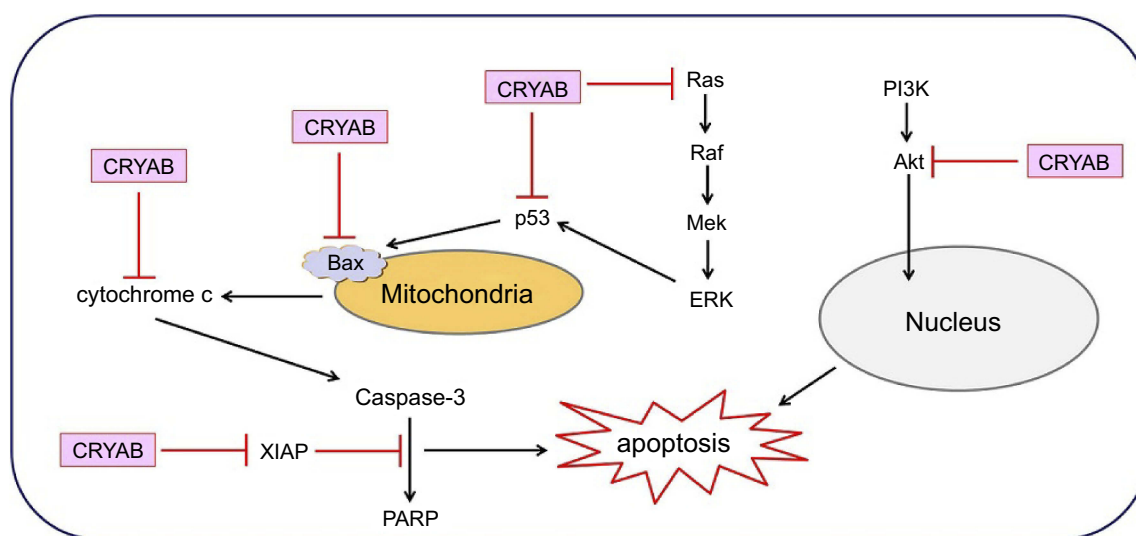


Figure 2 Schematic diagram of CRYAB protein involved in the regulation of apoptosis (inhibition: \perp , activation: \rightarrow).

There is increasing evidence that CRYAB is an important regulator of cardiac cytoprotection and is resistant to various forms of cellular stress. Over-expression of CRYAB in cultured cardiomyocytes and transgenic mouse hearts protects against ischemia or reperfusion injury⁵² and reduces cardiac hypertrophy caused by overload.⁵³ CRYAB-20 protein levels are reduced during ischemia, and reperfusion causes clinical damage to cardiac function. Administration of CRYAB-20 peptide reduced the infarct size of the mouse model of myocardial infarction and showed cardioprotective effects of CRYAB.⁶⁴ Most interesting is the recent discovery that abnormal expression of these chaperones often occurs in tumors.^{65–67} There is increasing evidence that CRYAB is diversified and significantly associated with cancer.^{68,69} Emerging strategies to therapeutically target CRYAB and/or interacting proteins to selectively activate apoptosis and/or derail the metastatic cascade in an effort to improve outcomes for patients with metastatic disease.²⁴

CRYAB in breast cancer

Breast cancer (BC) is one of the most common cancers for females and the leading cause of cancer-related death in females globally, with a high incidence rate and mortality.⁷⁰ BC may have evolved from a process of continuous progression of hyperplasia of mammary gland (HMG).^{71,72} According to reports, the expression of CRYAB was significantly up-regulated in HMG,⁷³ while it was also highly expressive in BC, such as basal-like, triple-negative breast cancer (TNBC), and mammary metaplastic carcinoma.^{74–76} Although Her2 has long been reported to be involved in the pathogenesis of brain metastases, it has recently been reported that CRYAB expression is associated with distant recurrence in TNBC patients and as the first distal site compared to early brain recurrence.^{77–80} Consistent with this pathogenic effect, CRYAB is closely associated with advanced tumor progression, lymphocytic infiltration, and death, and could be a novel oncoprotein biomarker of a poor prognosis in BC, especially in advanced patients.^{81,82} Paradoxically, the upregulation of CRYAB was not involved in the molecular chaperone in the progression of the disease,⁸³ and did not seem to have an independent impact on patient survival or to interfere with taxane-based therapy in two randomized clinical trials.⁸⁴

So how is the CRYAB protein regulated in BC? Upregulation of CRYAB may be associated with transcriptional activation. In fact, the CRYAB gene promoter contains the proto-oncogene Ets1, a member of the ETS

transcription factor family that bind to DNA at palindromic ETS-binding sites (EBS), which are activated by the oncogenic transcription factor Ets1. Ets1-mediated events appear to be associated with poor survival.⁸⁵ In addition, Bcl-2 is reported to be a positive prognostic marker for BC, and CRYAB is a marker of poor prognosis. In the correlation analysis, the two proteins demonstrated a weak negative correlation.⁸⁶ Simultaneously, CRYAB enhances tumorigenesis by regulating the vascular endothelial growth factor (VEGF) and confers anti-VEGF resistance to BC.^{87,88} It induces EGF and anchorage-independent growth of human mammary gland-like tumors through constitutive activation of the MEK/ERK pathway.⁸⁹ CRYAB can also be used as an oncoprotein because it transforms immortalized human mammary epithelial cells in invasive BC in nude mice, which have the same characteristics as mammary gland-like tumors.⁷⁵

CRYAB in lung cancer

Lung cancer (LC) is the most common malignancy worldwide, and also the leading cause of cancer-related mortality in the majority of developed countries.⁹⁰ The two major types of LC are small cell (SC) and non-small cell lung cancer (NSCLC), and the latter accounts for approximately 85% of all cases.⁹¹ Many studies are devoted to NSCLC, but there is still a lack of specific and valuable molecular markers to accurately indicate the prognostic status of NSCLC patients. Early studies have shown that CRYAB is up-regulated in NSCLC by analyzing gene expression profiles of Anip973R and its parental line.⁹² Is CRYAB an independent marker for prognosis in NSCLC? A study reported that CRYAB did not predict outcomes in patients treated for NSCLC. The reason is that larger studies are required to validate this finding.⁶⁶ Another study was the first to report on the differential expression of CRYAB with NSCLC, in both mRNA and protein level simultaneously. In addition, high CRYAB protein expression was correlated with certain clinic pathological attributes, including TNM stage and overall survival.⁹³ CRYAB, whose nuclear staining is an independent factor of poor survival, plays an essential role in NSCLC biology.⁹⁴ What's more, ERK-regulated CRYAB induction by matrix detachment inhibits anoikis and promotes lung metastasis in vivo.⁹⁵ Some studies have proved that CRYAB over-expression in idiopathic pulmonary fibrosis (IPF) disrupts Smad4 mono-ubiquitination by interacting with its E3-ubiquitin ligase, TIF1 γ , limiting its nuclear export, thus activating TGF- β 1-Smad4 pro-fibrotic activity, demonstrating that

CRYAB may also be a key target for the development of specific drugs in the treatment of IPF or other fibrotic diseases.⁹⁶ CRYAB may be distinguished as a novel prognostic biomarker in NSCLC patients, and targeting CRYAB may provide a promising strategy for NSCLC treatment.⁹³

CRYAB in hepatocellular carcinoma

Primary liver cancer is a cancer which occurs in liver and is the third most common cause of cancer-related deaths worldwide. Hepatocellular carcinoma (HCC) is the most prevalent subtype of primary liver cancer.⁹⁷ Much hope is focused on obtaining a better understanding of the mechanism relevant to this disease in order to develop new preventive, diagnostic, and therapeutic options. First, CRYAB promoted HCC progression in vivo and in vitro. Second, functional and genetic screens demonstrated that CRYAB overexpression fostered HCC progression by inducing EMT. Remarkably, CRYAB complexes with and elevates 14-3-3 ζ protein, leading to up-regulation of ERK1/2 activity. Clinically, CRYAB expression correlated with BCLC staging, patients' overall survival, and disease recurrence. Simultaneously, CRYAB overexpression activated the ERK1/2/Fra-1/slug signal to induce HCC cell EMT. The above results support the notion that CRYAB is a positive regulator of HCC growth and aggressiveness.⁶⁵ Moreover, upregulation of CRYAB is regulated by its upstream heat shock factor 1 (HSF1), the predominant regulator of heat shock response and whose phosphorylation is induced by glucose in HCC cell lines.⁹⁸ Therefore, expression of the CRYAB gene, which is related with the transferability and invasive capacity of hepatocellular carcinoma cells, can be used as a prognostic indicator in human hepatocellular carcinomas. It may also be involved in the malignant transformation of hepatocytes.⁹⁹

CRYAB in OS

Osteosarcoma (OS) is the most common primary malignant tumor in children and adolescents.¹⁰⁰ Early studies via detection of two-dimensional difference gel electrophoresis, the genomic analysis, and further studies in OS have indicated the amount of CRYAB was significantly increased, especially in advanced stages of the disease.¹⁰¹ CRYAB expression is high in OS tissues and is positively correlated with cell invasiveness and activity of ERK1/2 secreted by MMP-9 (Matrix Metalloprotein-9). Clinically, the high expression of CRYAB is associated with shortened survival and tumor recurrence in postoperative OS patients, and is a new adverse outcomes marker for OS

patients.¹⁰² A study showed krüppel-like factor 4 (KLF4), a zinc-finger transcription factor, and an essential regulator in many cellular processes, specifically bound the promoter of CRYAB and upregulated CRYAB expression in human osteosarcoma cells.¹⁰³ Another study revealed microRNAs-491 plays a role in osteosarcoma by directly targeting CRYAB.¹⁰⁴ Whether CRYAB protein is actively regulated or passively regulated, it is closely related to OS disease, and may be a new therapeutic target of OS.

CRYAB in colorectal cancer

Colorectal cancer (CRC) is the third most common cancer in both males, and the fourth leading cause of cancer-related deaths worldwide.¹⁰⁵ Research on early diagnosis of colorectal carcinogenesis biomarkers is still ongoing, and the selection of "personalized" treatment strategies provides a prognostic marker for colorectal cancer to improve the prognosis of the disease.¹⁰⁶ The study was the first to report the expression of CRYAB and splicing changes may mark the risk of cancer by CRC biopsy analysis.^{79,107} Its high expression, lymph node metastasis, distant metastasis, and tumor TNM stage were all significantly associated with the overall survival CRC patients. CRC patients with high CRYAB expression and positive distant metastasis encountered a significantly poorer overall survival.⁷⁹ Clinical data indicated that CRYAB expression upregulation had a positive association with TNM stage CRC patients.¹⁰⁸

CRYAB high expression could prompt tumor cell proliferation, invasion, and metastasis of CRC through EMT.^{108,109} Its expression level in CRC patients was closely correlated with MMP7 and E-cadherin, two core EMT gene products. In addition, three significant signaling pathways (PI3K, p38, and ERK) were involved in CRYAB-induced EMT.^{108,110,111} However, in certain cell types, the ERK, but not PI3K and p38 signaling pathways, may be crucially involved in the invasion, proliferation, and EMT induced by CRYAB over-expression. In summary, CRYAB may trigger the EMT in CRC by activating the ERK signaling pathway and is a potential tumor biomarker for CRC diagnosis and prognosis.¹⁰⁸ Also, CG/GG at CRYAB C-802G is correlated with CRC susceptibility, and this polymorphism may be a useful marker for the clinical outcome of CRC.¹¹²

CRYAB in head and neck cancer

Head and neck cancers comprise a heterogeneous group of tumors that arise in the paranasal sinus, oral and nasal

cavities, pharynx and larynx, and salivary glands. 90% of these tumors are squamous cell carcinomas and are newly diagnosed in 600,000 patients annually.¹⁰⁵ Only 40–50% will survive 5 years, making this the fifth-most frequent malignant cancer worldwide.¹¹³ Regarding brain cancer, high expression levels of CRYAB are evident in invasive gliomas.^{114,115} The higher expression of CRYAB may lead to prolonged survival of head and neck squamous cell carcinoma cells under hypoxic conditions, more likely by ROS formation.¹¹⁶ In laryngeal squamous cell carcinoma (LSCC), CRYAB is significantly overexpressed and correlated with malignant phenotypes. CRYAB had a poor prognosis in cancer patients²⁵ and may serve as a novel prognostic factor for LSCC.^{67,117} In oral squamous cell carcinoma, CRYAB is highly expressed and has a poor prognosis for cancer patients.¹¹⁸ It was first found that the single nucleotide polymorphisms at the promoter region of CRYAB, C-802G, is associated with patient oral cancer susceptibility, recurrence, and 5-year disease-free survival, but not metastasis.¹¹⁹

However, CRYAB staining with cutaneous squamous cell carcinoma of the head and neck (CSCCHN) with clinical Perineural invasion (PNI), a clinical indicator of poor prognosis, showed a decrease compared to non-PNI CSCCHN. Surprisingly, CRYAB is a key component in the machinery leading to degradation of cyclin D1, which is key to understanding how loss of CRYAB can lead to deregulated cellular growth in CSCCHN with PNI. It is possible that under-expression of CRYAB in tumors that exhibit neurotropism contributes to their more aggressive nature.¹²⁰

Moreover, in nasopharyngeal carcinoma (NPC), CRYAB is down-regulated.¹²¹ Activation of CRYAB suppressed NPC tumor formation in nude mice. Overexpression of CRYAB affected NPC progression-associated phenotypes such as loss of cell adhesion, invasion, interaction with the tumor microenvironment, invasive protrusion formation in three dimensional Matrigel culture, as well as expression of epithelial-mesenchymal transition-associated markers. CRYAB functions to suppress NPC progression by associating with the cadherin/catenin adherens junction and modulating the β -catenin function.¹²²

CRYAB expression is down-regulated in highly dedifferentiated malignant anaplastic thyroid carcinoma because of a tumor-specific transcription factor pattern.¹²¹ CRYAB gene silencing is present in rapidly growing dedifferentiated anaplastic thyroid carcinomas. The main underlying mechanism seems to be a tumor-specific transcription factor expression

pattern, which is most prominently characterized by down-regulation of the transcription factor, TFCEP2L1.¹²³

CRYAB in other cancers

CRYAB was highly expressed in gastric cancer tissues, contributed to gastric cancer cells migration and invasion via EMT, mediated via the NF- κ B signaling pathway, predicting a poor prognosis in patients with gastric cancer and, thus, possibly providing a novel therapeutic target for gastric cancer.¹²⁴

CRYAB was reported to be expressed in retinoblastomas, but it may not prevent apoptosis of neoplastic cells,¹²⁵ while in the same laboratory in the same year CRYAB was reported to be highly expressed in retinoblastoma after chemotherapy and may protect tumor cells from apoptotic signals produced by anticancer drugs.¹²⁶

Integrative analysis of transcriptomics and clinical data uncovered in the prostate a novel direct transcriptional regulation of CRYAB by Microphthalmia-associated transcription factor (MITF), a basic helix-loop-helix leucine zipper transcription factor that regulates the expression of lineage commitment programs that are essential for propagation of the melanocyte lineage.¹²⁷ Although there is no direct or mechanistic evidence of the MITF-CRYAB transcriptional axis in other cancer types, in melanoma both MITF and CRYAB expression are upregulated by BRAF/MEK-inhibitor treatments.^{128,129} In addition, the correlation between MITF and CRYAB is also present in colorectal cancer, but not in breast nor lung cancer.¹³⁰ These suggested that the MITF-CRYAB axis controls beyond prostate biology and CRYAB as a novel direct target of the transcription factor that is, at least in part, responsible for its tumor-suppressive activity in the prostate and could be considered as potentially protective against prostate cancer.^{127,131}

CRYAB, a proposed negative regulator of tumor necrosis factor-related apoptosis inducing ligand (TRAIL)- and cisplatin-induced mediated apoptosis, displayed low expression level significantly associated with adverse patient survival and acts as a molecular marker for the outcome of patients with ovarian cancer. The data showed molecular mechanisms underlying ovarian cancer cell apoptosis and resistance to TRAIL as an obstacle for its therapeutic efficacy.^{132,133}

Conclusions and prospects

As noted above, the expression and functional roles of CRYAB in cancers (Table 1), and further research needs to be done to reveal its underlying role in the progression and metastasis of diseases. Although the CRYAB protein has

Table I Expression and functional characterization of CRYAB in cancer

Name	Expression	Role	Upstream	Downstream	Reference
Breast cancer	Up-regulated	Oncogene	Ets1	Not mentioned	85
	Up-regulated	Oncogene	Not mentioned	VEGF	88
Osteosarcoma	Up-regulated	Oncogene	KLF4	Not mentioned	103
Hepatocellular carcinoma	Up-regulated	Oncogene	HSF1	Not mentioned	98
	Up-regulated	Oncogene	Not mentioned	I4-3-3ζ	65
Lung cancer	Up-regulated	Oncogene	Not mentioned	Not mentioned	93
Colorectal cancer	Up-regulated	Oncogene	Not mentioned	ERK	108
Laryngeal squamous cell carcinoma	Up-regulated	Not mentioned	Not mentioned	Not mentioned	67
Oral squamous cell carcinoma	Up-regulated	Not mentioned	Not mentioned	Not mentioned	118
Nasopharyngeal carcinoma	Down-regulated	Tumor suppressor	Not mentioned	E-cadherin and β-catenin	122
Gastric cancer	Up-regulated	Oncogene	Not mentioned	NF-κB	124
Retinoblastoma	Up-regulated	Chemoresistance	Not mentioned	Not mentioned	126
Prostate cancer	Down-regulated	Tumor suppressor	MITF	Not mentioned	127
Anaplastic thyroid carcinoma	Down-regulated	Tumor suppressor	Not mentioned	Not mentioned	121
Ovarian cancer	Down-regulated	Tumor suppressor	Not mentioned	Not mentioned	132

multiple functions, the most important function is to act as an anti-apoptotic polypeptide in various stress-induced apoptosis^{69,134} and as a molecular chaperone to block aggregation of denatured proteins by exposure to heat stress.^{134,136} Moreover, although the pre-clinical results of CRYAB-based anti-cancer drugs in vivo and in vitro are promising, there is still a long way to go from the laboratory to clinical trials. Another important issue is the off-target effect. Is the drug targeting CRYAB sufficient to control the ultimate anti-cancer effects when other HSPs are present? If the answer is yes, what is the underlying mechanism? Only if these events are fully explored can the treatment of CRYAB be used for clinical applications.

Therefore, according these data, we speculate that the plausible reasons for the ambiguous expression and function of CRYAB in cancers are listed as follows: i) CRYAB expression is developmentally related in some tissues; ii) CRYAB may be specific in certain tissues or populations; iii) cytoprotective and anti-apoptotic activities play a leading role in determining the role of CRYAB in promoting or inhibiting the development of certain types of cancer; and iv) the final functional role of CRYAB is affected by the synergistic or inhibitory effects of other HSPs regulatory molecules.

Disclosure

The authors report no conflicts of interest in this work.

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