


REVIEW ARTICLE

The Role of Cytoglobin in Cancer

Peran Sitoglobin pada Kanker

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ABSTRACT

Cytoglobin (Cygb) is a new member of the globin protein family, following the discovery of other globin proteins such as hemoglobin (Hb), myoglobin (Mb), and neuroglobin (Ngb). In 2001, Kawada et al. identified Cygb in hepatic stellate cells (HSCs) that play an important role in the repair of damaged liver cell tissue, hence the name stellate cell activation-associated protein (STAP). Cygb has a more universal role than Hb, Mb, and Ngb, and is expressed throughout mammalian tissues. Cygb is a globin with 6 coordination bonds (hexacoordinate globin). Cygb has been shown to play an important role in the normal cell respiratory chain, including oxygen storage, destruction of reactive oxygen species (ROS), terminal oxidase activity, regulation of fibrogenesis, and regulation of apoptosis. The role of Cygb in the respiratory process has been studied because it is associated with the globin family, and because of the upregulation of Cygb during hypoxia, but its specific role has not been elaborated. Recent research reports that Cygb has several implications for cancer. In most cancer cells, Cygb expression is upregulated by hypermethylation, suggesting epigenetic control. In cancer cells, downregulation of Cygb occurs which indicates a possible role as a tumor suppressor gene. In some malignancies, on the contrary, Cygb upregulation may be associated with resistance to hypoxia which indicates Cygb has two sides or Janus faces related to its role in cancer cells.

Keywords: cancer; cytoglobin; fibrosis, ROS

ABSTRAK

Sitoglobulin (Cygb) merupakan anggota baru keluarga protein globin, setelah ditemukannya protein globin yang lain seperti hemoglobin (Hb), mioglobin (Mb) dan neuroglobin (Ngb). Pada tahun 2001, Kawada et al. mengidentifikasi Cygb dalam *hepatic stellate cells* (HSC) yang berperan penting dalam perbaikan jaringan sel hati yang rusak, oleh karena itu disebut sebagai *stellate cell activation-associated protein* (STAP). Cygb mempunyai peran lebih universal dari Hb, Mb, dan Ngb, dan diekspresikan di seluruh jaringan mamalia. Cygb merupakan globin dengan 6 ikatan koordinasi (*hexacoordinate globin*). Cygb telah terbukti berperan penting pada pernapasan sel normal, diantaranya untuk penyimpanan oksigen, pemusnahan *reactive oxygen species* (ROS), aktivitas oksidase terminal, regulasi fibrogenesis, dan regulasi apoptosis. Peran Cygb pada proses pernafasan yang telah dipelajari karena dikaitkan hubungannya dengan keluarga globin, serta dikarenakan terjadinya upregulasi Cygb saat terjadi hipoksia, namun perannya secara spesifik belum bisa dijabarkan. Penelitian terbaru melaporkan Cygb memiliki beberapa implikasi pada kanker. Pada sebagian besar sel kanker, ekspresi Cygb diregulasi oleh hipermetilasi, menunjukkan kontrol epigenetik. Pada sel kanker terjadi *down regulation* Cygb yang menunjukkan kemungkinan peran sebagai gen penekan tumor. Pada beberapa keganasan terjadi sebaliknya, upregulasi Cygb terjadi kemungkinan dikaitkan dengan adanya resistensi terhadap hipoksia yang menunjukkan Cygb mempunyai dua sisi atau *Janus faces* terkait perannya terhadap sel kanker.

Kata kunci: kanker; sitoglobulin; fibrosis; ROS

INTRODUCTION

Cytoglobin (Cygb) is a new member of the globin protein family, after the discovery of other globin proteins such as hemoglobin (Hb), myoglobin (Mb), and neuroglobin (Ngb).¹ In 2001, Kawada et al. identified Cygb in hepatic stellate cells (HSC) which plays an important role in the repair of damaged liver cell tissue, hence it is called stellate cell activation-associated protein (STAP).² Since its discovery, many studies have been conducted to understand the functional role of Cygb but so far remains.³ Cygb is expressed in mammalian cells.^{4,5} Cygb has a more universal role than Hb, Mb, and Ngb, and is found in red blood cells, muscle cells, central nervous system cells⁵, brain, lungs, retina, liver, intestines, and esophagus.⁶

Cygb has been shown to play an important role in normal cell respiration, including oxygen storage, scavenging reactive oxygen species (ROS), terminal oxidase activity, and antifibrotic activity.⁷⁻⁹ Recent research reports that Cygb has several implications for cancer. In most cancer cells, Cygb expression is regulated by hypermethylation which results in a decreased expression demonstrates epigenetic control¹⁰, and indicates its possible role as a tumor-suppressing gene (TSG).¹¹ But, in some malignancies the opposite occurs, Cygb upregulation is related to resistance to hypoxia. Based on current research in this area, this review is being conducted to answer the putative role of Cygb in cancer.

STRUCTURE OF CYGB

Cygb is a globin with 6 coordination bonds (hexacoordinate globin), in contrast to Hb and Mb which are pentacoordinate globins.^{1,5,6,12} Cygb is a homodimer connected by two disulfide bridges. The Cys38 residue of one monomer binds covalently to the Cys83 residue of the other monomer, and vice versa. Mammalian Cygb has the longest amino acid arrangement compared to other globins, consisting of 190 amino acids, while other globins are only about 140-150 amino

acids. The amino acid arrangement in Cygb is conserved, the human and mouse Cygb amino acids differ only by 4%.^{6,13}

The molecular weight of Cygb is 20.9 kDa^{6,14,15} Cygb shows a high intrinsic affinity for O₂. The substitution or reduction of the two cysteines in Cygb leads to a reduction of Cygb affinity to O₂. This explains that the cellular redox state affects the structure of Cygb proteins with the formation of S-S bonds or cleavage, thereby affecting the binding of O₂.⁶

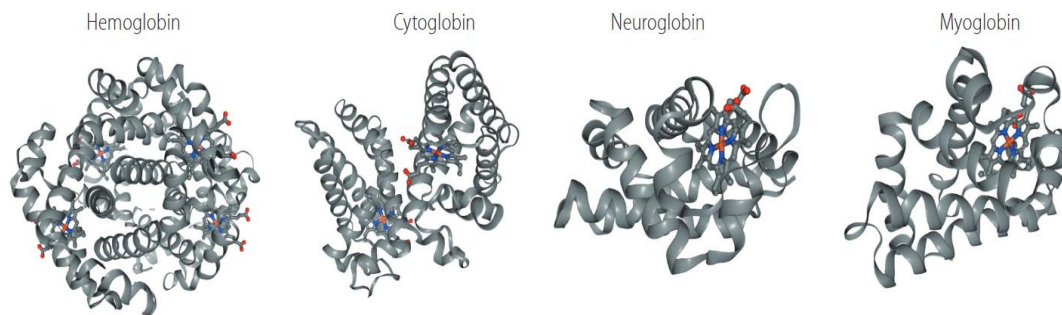


Figure 1. 3D structure of the four members of the globin. Human hemoglobin (RCSB Protein Data Bank accession number: 2HHB, tetramer158), cytoglobin (1V5H, dimer40), neuroglobin (1OJ6, monomer159), and myoglobin (3RGK, monomer160) were shown with alpha-helices group and heme group. The color scheme for the elements: is gray for carbon, red for oxygen, nitrogen blue, and yellow for sulfur.¹⁶

CYGB DISTRIBUTION

The gene encoding Cygb is located on chromosomes 17q25.3 in humans and 11qE2 in mice.¹³ Cygb is expressed throughout mammalian tissue⁴ and is present in cells.^{4,5} Cygb has a more universal role than Hb, Mb, and Ngb, and is found in red blood cells, muscle cells, central nervous system cells⁵, brain, lungs¹⁷, retina, liver, intestines, and esophagus.⁶ Cygb expression in some mouse organs is shown in Figure 2.

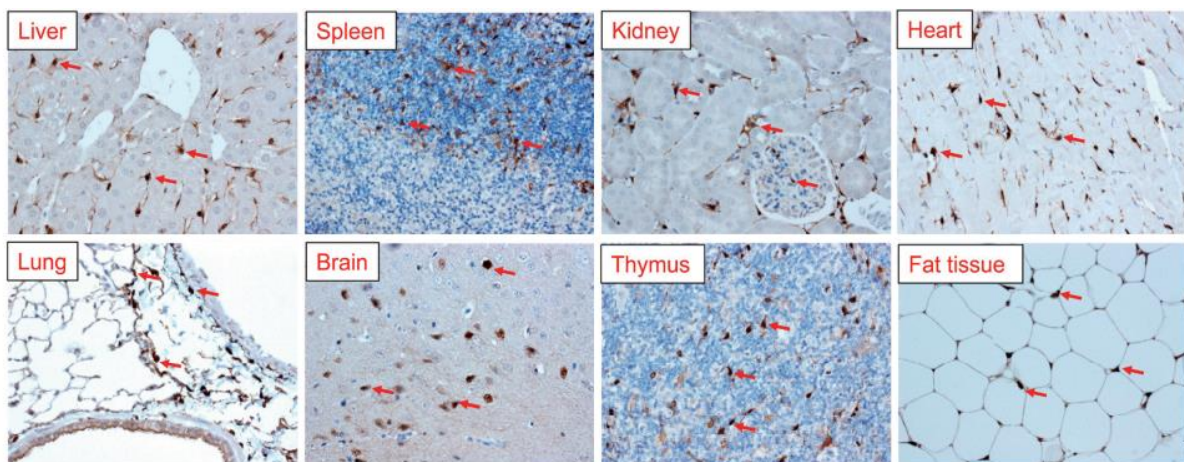


Figure 2. Cygb's expression in some organs of the mouse. Immunohistochemistry staining of Cygb antibodies shows positive Cygb density in all organs. The red arrow in the image shows Cygb's positive cell.⁶

Cygb in the liver was detected in hepatic stellate cells (HSCs),¹⁰ but not in hepatocytes, Kupffer cells (KCs), endothelial cells, or myofibroblasts.¹⁸ Cygb expression was also found in stromal cells in the spleen, kidneys, thymus, lungs, and in adipose tissue (Figure 2). In the heart, Cygb expression is found in fibroblasts, but not in cardiomyocytes. Recent studies showed that Cygb was also found in melanocytes, and the absence of Cygb was associated with a change from melanocytes to melanomas.¹²

At the cellular level,^{1,16} Cygb shows increased expression in fibroblast cell lines, for example, osteoblasts and chondroblasts, which are actively involved in the production of extracellular matrix.¹⁰ In addition, its expression has also been found in neurons, with localization mainly in the cytoplasmic and nuclear. Cygb expression specific to neuron cells shows Cygb has a different role compared to mesenchymal cells.³

REGULATION OF CYGB

Cygb promoter does not have a TATA box, contains a 1.4 kb long CpG island and several possible sites start transcription. Cygb non-encoding sequences are composed of several genes associated with cellular responses to hypoxia, namely hypoxia-responsive elements (HRE), hypoxia-inducible protein binding sites (HIPBS), and some recognition sites with hypoxia-related transcription factors. HREs are composed of a core motif of 50 -RCGTG-30, which is needed to bind hypoxia-inducible factor 1 (HIF1).³

HIF (HIF1, HIF2) is considered the primary regulator of cellular response to O₂ which regulates the transcription of a large number of genes involved in various metabolic pathways including apoptosis, angiogenesis, proliferation, pH regulation, glycolysis, and O₂ homeostasis and genetic instability. Hypoxia-inducible protein binding site contains protein sites involved in stabilization against hypoxia. Several transcription factor binding sites have been identified in Cygb promoters including HIF1, stimulatory protein 1 (SP1), activator proteins (AP1, AP2), nuclear factors (NF1, NF-kB, NFAT), CCAAT/enhancer binding protein (C/EBP), and cellular erythroblastosis of homologous E26 oncogene virus 1 (cETS-1). The binding sites of SP1 and NF-kB are arranged inside the CpG island in the CYGB promoter, playing a role in the epigenetic control of Cygb expression.

NF-kB, AP1 and C/EBP factors play a role in signal transduction associated with hypoxia, oxidative stress, and inflammation. ETS is a proto-oncogene involved in the development of stem cells and senescence pathways. Five transcription factors have been shown to bind and transactivate Cygb promoters. In hypoxic states, it was shown that there was an interaction between HIF 1 and the Cygb promoter but the mutagenesis of HIF1 and the EPO binding motif also proved to be very important in Cygb regulation. Recent studies have shown that NFAT and AP1 induce Cygb expression, mediated by calcineurin signaling.¹³ Calcineurin is a calcium-calmodulin-activated phosphatase that is important in engaging several heart-related gene signaling pathways for developmental regulation, hypertrophic processes, apoptosis, and metabolism. Calcium and calmodulin complexes will activate calcineurin in response to stress conditions such as hypoxia, ischemia, and pressure overload, and then activate several transcription factors such as NFAT and AP-1 so that Cygb expression activation occurs.²

In addition, *Cygb* is a downstream target of tumor growth factor b (TGF- β), platelet-derived growth factor, protein kinase C, and EPO signaling. *Cygb* signaling pathways are illustrated in Figure 3.¹³

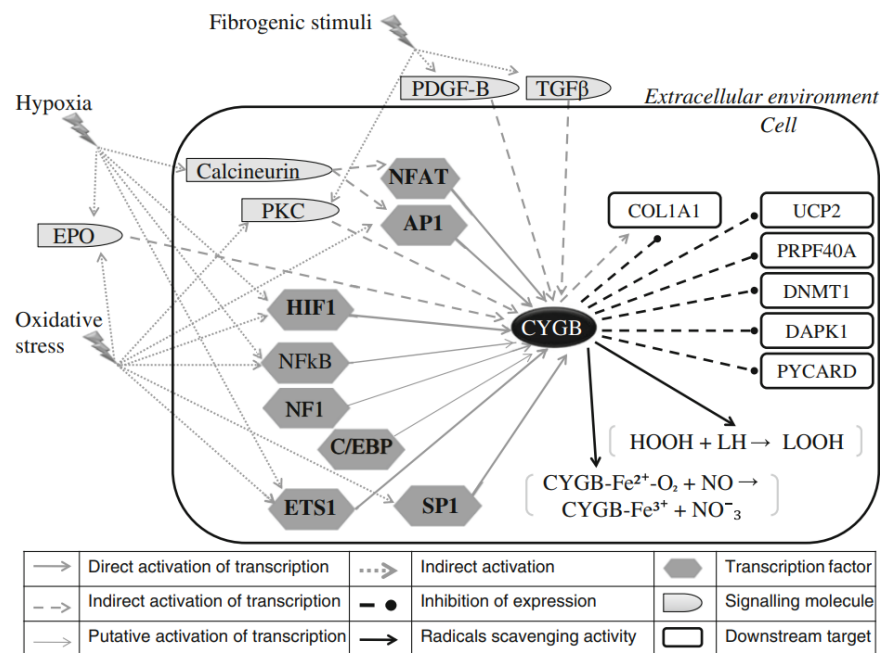


Figure 3. Upstream regulation and downstream targets from *Cygb*¹¹

Upstream regulation of *Cygb* is HIF, AP1, nuclear factors (NF1, NFkB, NFAT), C/EBP, and ETS-1 as responses to hypoxic conditions, oxidative stress, and fibrogenic stimulus.²⁴ *Cygb* expression as a downstream target is TGF- β , PDGF- β , protein kinase C, and EPO signaling.¹¹ AP1: activator proteins, C/EBP α : CCAAT/enhancer binding protein, COL1A1: collagen 1 α 1, DAPK1: death-associated protein kinase 1, DNMT1: DNA-methyltransferase 1, EPO: erythropoietin, ETS1: erythroblastosis virus E26 oncogene homolog 1, H_2O_2 : hydrogen peroxide, HIF1 α : hypoxia-inducible factor α , NF1: nuclear factor 1, NFAT: nuclear factor of activated T-cells, NFkB: nuclear factor-kB, NO: nitric oxide, PDGF- β : platelet-derived growth factor, PKC: protein kinase C, PRPF40A: RNA-binding and pre-mRNA processing factor, PICARD: PYD and CARD domain-containing protein, SP1: stimulatory protein 1, TGF- β : transforming growth factor β , UCP2: uncoupling protein 2.

Cygb expression regulation through upstream signals include oxidants (hydrogen peroxide, H_2O_2), oxygen pressure (pO_2), growth and inflammatory factors (IL-1 β , FGF2), and cell-to-cell interactions (NOTCH 2 and 3). NOTCH is a membrane-bound transcription factor that is activated in response to ligand binding through cell interactions and is shown to promote *Cygb* expression in smooth muscle. The effects of O_2 , FGF2, and phosphatase calcineurin (PP2B) were experimentally associated with the regulation of transcription factors specifically including HIF1, AP-1, and NFAT. This transcription factor binds to the response element (RE) located within the 1400 base translation initial site (TSS) of the *CYGB* gene. Although binding motives for ETS1, SP1, and LEF1 have been identified, direct evidence of this transcription factor binding to the promoter element has not been indicated. In contrast, p63 has been shown to interact with response elements but upstream regulators are unknown.³

ROLE OF CYGB IN CANCER

Advances in molecular research into another function of Cygb continue to evolve, namely, its ability to suppress tumor growth. The relationship and role of Cygb in cancer were first proposed based on a study of promoter methylation of tissue samples of patients with oral squamous cell carcinoma in 2006. The study explained that the methylation of promoters at the CpG site increased compared to the control of non-tumor samples. The same was found in studies on non-small lung neck and head cancer. These studies have shown that a combination of hypermethylation of promoters, loss of heterozygosity, and decreased expression is common in various types of cancer.^{13,18}

Research related to Cygb with tumor suppressive activity has been reported since 2006, showing that most cancer cells experience a dramatic decrease in Cygb expression in esophageal cancer.^{1,10} In addition, studies have reported a reduction in tumor growth by excessive expression of Cygb by cDNA cytoglobin transfection in non-small lung cancer cells and breast cancer cells. In another study, knockdown Cygb in glioma cells showed an increase in cell growth rate^{6,13} In various types of cancer e.g. ovarian, esophageal, pulmonary there was a decrease in expression/downregulation of Cygb. The occurrence of gene silencing mechanisms from Cygb is thought to be due to hypermethylation of Cygb promoters. However, inconsistent results occurred in lung cancer line cells that showed an increase in Cygb expression despite hypermethylation of the promoter, which indicated an alternative mechanism of Cygb gene downregulation.¹¹

Cygb overexpression will reduce the expression of several genes such as pre-mRNA processing factor (PRPF40A), uncoupling protein-2 (UCP2), collagen, type I, alpha 1 (COL1A1), and DNA methyl transferase 1 (DNMT1). UCP-2 (mitochondrial uncoupling protein) is involved in suppressing ROS and is also involved in the occurrence of chemoresistance in cancer. Regulatory disorders of PRPF-40 AND COL1A1 have also been reported to occur in various types of cancer. DNMT1 plays a role in the development of malignancy. Research shows that miR29b and miR133 cause a decrease in the expression of COL1A1 and UCP2. This is also supported because miRNA is involved in a wide variety of cancers, so research related to the exploration of miRNA's involvement in Cygb regulatory networks still needs to be developed.² Possible mechanisms of Cygb in tumor development and oncogenic progression are described in Figure 4.

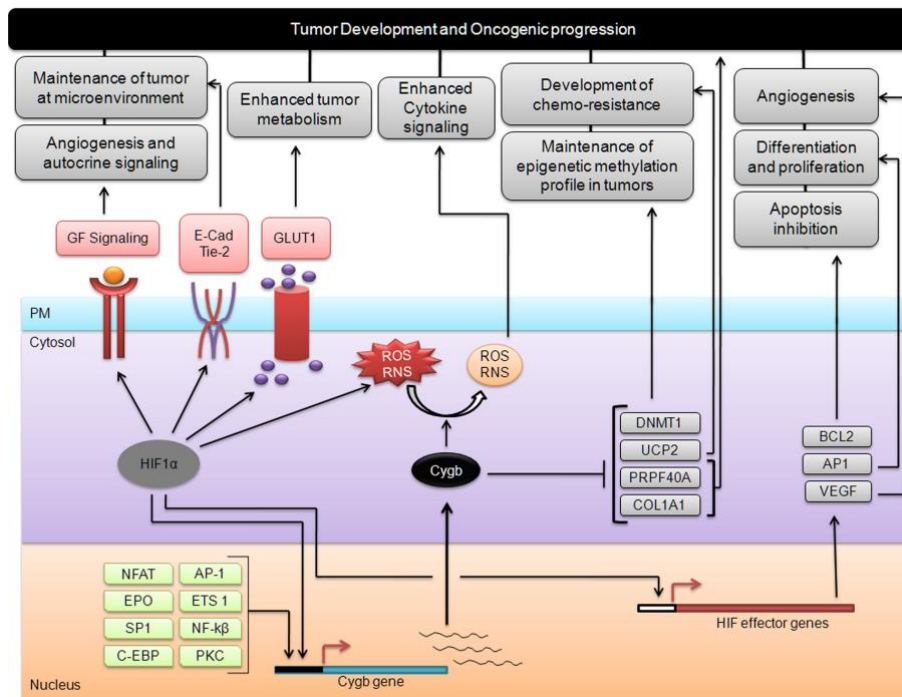


Figure 4. Possible mechanism of action of Cygb as a tumor suppressant.⁴

HIF1 α serves as a cellular response to hypoxia. It demonstrates the mechanism of tumor development by inducing the expression of genes involved in abnormal growth, angiogenesis, metastasis, apoptotic resistance, tumor cell metabolism, and the maintenance of stable deviant cells in the tumor microenvironment. It also inhibits other oncogenic factors such as DNMT1, UCP2, PRPF40A, and COL1A1.

JANUS FACES FROM CYGB

Several *in vitro* studies have shown dysregulation of Cygb expression in some cancer line cells and the presence of an inverse effect from before, namely the occurrence of excessive expression of Cygb. Cygb expression is upregulated in several types of cancers such as alveolar soft part sarcoma, lung carcinoma, and head-neck cancer,^{8,9} convinced researchers to speculate Cygb's function is highly contrasting and complex. Recently, the role of Cygb bimodal has been proposed in which Cygb is said to exhibit tumor suppressive function in normoxia but behaves like an oncogene under stressful conditions. The cytoprotective role of Cygb can lead to carcinogenesis or aggressiveness by protecting tumor cells from oxidative injury. Brantley et al. showed that partial agonists of aryl hydrocarbon receptor (AhR) 5F 203 may promote Cygb expression in triple-negative cancer cells and silencing of Cygb can partially inhibit the pro-apoptosis effects of 5F 203.¹³

The consensus concerning Cygb levels in cancer-line cells and their underlying molecular mechanisms is very difficult to explain. This is more confusing when considering the bimodal response associated with Cygb expression. Upregulation of Cygb after hypoxia can trigger the adaptation of cancer cells to grow in a hypoxic state.^{17,18} Pongsuchart et al. showed that Cygb expression in osteosarcoma cancer line cells can increase cell extravasation and a knockdown was subsequently found to be the opposite effect that showed that Cygb played a role in promoting metastases.¹⁸

Research shows Cygb's involvement in the down-regulation of caspase 2 and 3 to inhibit the occurrence of apoptosis in the brains of neonatal rats induced by hypoxia.¹⁴ Cygb's oncogenic function is thought to be due to the protective effect of Cygb in the mechanism against ROS annihilation shown in Figure 5. Understanding the regulation of ROS in normal and cancerous cells is very important because cancer cells require a moderate level of ROS for oncogenic development, a modified form of Cygb (mutant or post-translational modified variant) can be hypothesized to function as a "regulated ROS scavenger".

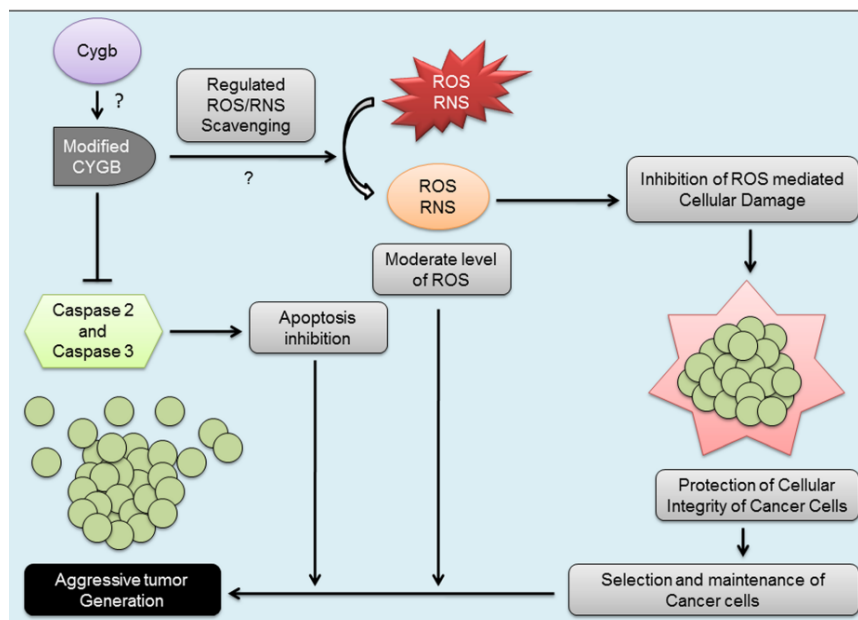


Figure 5. Possible Cygb oncogenic function.⁷

Modifications to Cygb may lead to the development of its oncogenic functions. Lower O₂ binding affinity, ROS activity, and/or nitric oxide dioxygenase activity impaired due to structural or post-translational modifications may alter its function in such a way as to make Cygb a strong oncogenic factor. Cygb's oncogenic function can be described through its ability to inhibit apoptosis factors such as caspase 2/3. Another way to help cancer cells is through their innate ability to annihilate ROS and RNS, thus protecting cellular populations in tumors from damage.

So it can be concluded that the alleged oncogenic function and tumor suppressor activity of Cygb shown in Figure 6.¹¹ Down-regulation of Cygb as a tumor suppressor gene in Figure 6 is shown to be influenced by various factors. The oncogenic function causes chemoresistance, cancer cell development, and aggressive phenotypes. The occurrence of downregulation of Cygb will also lead to the initiation of cancer cells.¹¹

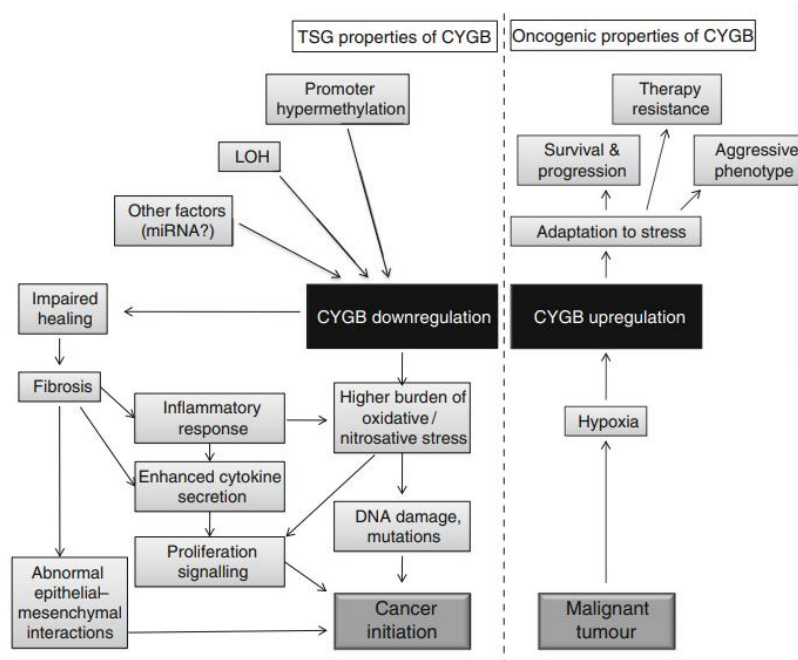


Figure 6 The alleged oncogenic function and tumor suppressor activity of Cygb.¹¹

Cygb expression can occur downregulation as a tumor suppressor gene or upregulation as an oncogenic function in this image influenced by various factors. The oncogenic function causes chemoresistance, cancer cell development, and aggressive phenotypes. The occurrence of downregulation of Cygb will also lead to the initiation of cancer cells. LOH: loss of heterozygosity.¹¹

CONCLUSION

In 2001 Cygb was identified by Kawada et al in hepatic stellate cells (HSC) which play an important role in the repair of damaged liver cell tissue and, therefore referred to as stellate cell activation-associated protein (STAP). Cygb is a globin with 6 coordination bonds (hexacoordinate globin). The gene encoding Cygb is located on chromosomes 17q25.3 in humans and 11qE2 in mice. Cygb is expressed throughout the tissues of mammals and is present in cells.

Cygb expression is regulated through upstream signals including oxidants (hydrogen peroxide, H_2O_2), oxygen pressure (O_2), growth and inflammatory factors (IL-1 β , FGF2), and cell-to-cell interactions (NOTCH 2 and 3). In addition, Cygb is a downstream target of tumor growth factor b (TGF-b), platelet-derived growth factor, protein kinase C, and EPO signaling. The potential functional roles of Cygb include the signaling of NO and nitrites, as antioxidants, regulation of apoptosis, and regulation of fibrogenesis.

Recent research reports that Cygb has several implications for cancer. In most cancer cells, Cygb expression is regulated by hypermethylation, indicating epigenetic control. In cancer cells, Cygb down-regulation occurs which indicates a possible role as a tumor suppressor gene. But, in some malignancies the opposite occurs, Cygb upregulation is related to resistance to hypoxia which shows Cygb has two sides or Janus faces related to its role in cancer cells.

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AUTHORS CONTRIBUTION

All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

Authors should make a conflict of interest disclosure statement or a declaration that they do not have any conflicts of interest.

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