

The Function of Stress-induced Transcriptional Regulator p8 in Solid Tumors

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ABSTRACT

Abnormal transcriptional regulation of the tightly sophisticated collaboration under stressful conditions is a critical aspect of tumorigenesis and progression. The transcriptional regulator p8 or NUPR1 (nuclear protein-1) or Com1 (candidate of metastasis-1) is one of the proteins related to the high mobility group. p8 is first identified during acute pancreatitis, and its expression is upregulated in certain types of solid tumors. p8 can be induced in response to intracellular and extracellular stresses with variant functions depending on contextual cues. On one hand, p8 plays an important role in the progression of several solid tumors, including thyroid, breast, brain and pancreatic tumors. On the other hand, p8 also acts as a tumor suppressor in some kinds of solid tumors including prostate and colorectal tumors. Deciphering the mechanisms of p8 regulation and its function will provide new strategies for solid tumors treatment with more efficacy.

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Key words: Solid tumor; Tumorigenesis; Transcriptional regulator; p8

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INTRODUCTION

During the progression of solid tumor, abnormal transcriptional regulation of the tightly sophisticated collaboration becomes co-opted by mechanisms that are currently unclear. p8, also known as NUPR1 (nuclear protein-1) or Com1 (candidate of metastasis-1), is a transcriptional regulator^[1] which was first discovered to be strongly induced during the acute phase of pancreatitis^[2]. Human p8 encodes a small, highly basic and unfolded 82-amino acid polypeptide with a theoretical molecular mass of 8872.7 Da^[2] and a pI of 9.98. p8 contains a N-terminal PEST (Pro/Glu/Ser/Thr-rich) region suggesting a regulation of p8 at the protein level by the ubiquitin/proteasome system^[2,3], and a basic helix-loop-helix motif^[3] followed by a canonical bipartite nuclear localization signal^[4] at its C-terminus suggesting its nuclear localization. In fact, p8 localizes throughout the whole cell and its subcellular localization depends on cell growth conditions^[5]. p8 has an abundant expression in liver, pancreas, prostate, ovary, colon, thyroid, spinal cord, trachea and adrenal gland, with moderate expression in heart, placenta, lung, skeletal muscle, kidney, testis, small intestine, stomach and lymph node, and with low expression in brain, spleen, thymus and bone marrow. No p8 mRNA was detected in peripheral blood leukocytes^[4]. p8 has an isoform with 100 amino acids produced by alternative splicing, named isoform a. The importance of the 18 amino acid region that is absent in the shorter isoform is not clear, and the expression and functional difference between these isoforms remain unknown. By now, the shorter isoform, isoform b has been the focus of all the biochemical and molecular biological studies.

p8 is conserved with homologs in mammals^[4], *Drosophila*^[6], *Xenopus*^[7], and other vertebrate and invertebrate organisms, except yeast. The human p8 shows an overall similarity of approximately 75% with rat and mouse p8^[4]. Numerous data base searches indicate that p8 shares no strong homology with other proteins except HMG I/Y, a member of the high mobility group of non-histone chromatin proteins. Not only structurally similar to HMG proteins, p8 also

exhibits some biochemical properties similar to HMG proteins, such as isoelectric point, hydrophilicity plot, heat stability, and charge distribution.

Although p8 has a basic helix-loop-helix motif, it binds DNA weakly without apparent preference for DNA sequence. After phosphorylated by PKA, p8 can bind DNA with a much higher affinity^[8]. Moreover, p8 can undergo acetylation, sumoylation and bears a PEST sequence which is required for degradation by the ubiquitin^[1,3,9-13]. These facts, together with the known nuclear localization of p8, indicated that p8 is in fact a transcriptional regulator.

p8 is a stress-induced protein and seems to be turned on by divergent stresses, such as systemic LPS or CCl₄^[14,15], demyelination-inducing agents^[16], serum withdrawal^[6], and chemical inducers of cell cycle arrest^[5]. Expression of p8 can also be induced in response to TGF^[10], TNF^[9,17], glucose^[18], cannabinoids^[13], 1,25-dihydroxyvitamin D₃^[19], angiotensin, and ET^[20], which suggested that p8 is a complex molecule with diverse physiological and biological functions.

p8 AND SOLID TUMOR

Initially, p8 was identified as a stress gene^[1]. And then, Ree *et al.*^[21,22] found that Com1, which is identical to human p8, is involved in tumor progression and metastasis. Recently, Cano *et al.*^[23] found that p8 status affects drug sensitivity of pancreatic ductal adenocarcinoma (PDAC) in mice. A lot of reports have showed that p8 plays a role in tumor progression, although there are some controversies over its exact function. p8 can promote or inhibit tumor growth, which seems to be dependent on the tumor type. It is interesting that, the results of studies with p8 *in vitro* are not always the same as *in vivo*, which may due to the fact that the function of p8 can be affected by microenvironment. However, it is confirmed that p8 plays an important part in tumor progression and metastasis^[24,25].

p8 Promotes Tumor Progression

Primary studies about the function of p8 in tumor progression was done by Vasseur *et al* who found that after overexpression of both the ras^{V12} mutated protein and the E1A oncogene, mouse embryo fibroblasts (MEFs) from p8^{+/+} mouse could form colonies in soft agar and dispersed tumor in nude mice. However, p8^{-/-} MEFs could not. Restoration of p8 in p8^{-/-} MEFs led to tumor formation^[26]. All these phenomenon suggested that p8 is required for the organization and development of tumors.

p8 was first found to be expressed in acute phase of pancreatitis, and then Su *et al* found p8 was strongly induced in pancreatic tumor and demonstrated p8 is involved in the development of pancreatic tumor, reflecting its mitogenic activity^[27]. Later, it is reported that p8 expression controls pancreatic tumor cell migration, invasion, and adhesion, which are required for tumor cell metastasis through down-regulation of CDC42 expression. Knocking-down p8 in pancreatic tumor cells *in vitro* decreased migration and invasion while increasing cell adhesion; overexpression produced the opposite effect^[28]. Recently, p8 was found to be able to promote tumor progression and metastasis by inhibition of homotypic cell cannibalism (HoCC)^[29], apoptosis^[24], and autophagy^[30,31]. The inactivation of p8 promoted HoCC which is negatively correlated to metastasis^[29]. p8 can inhibit apoptosis so as to protect cell from stress-induced death through a pathway dependent on transcription factor RelB and immediate early response 3 (IER3)^[24]. p8 partially regulates AURKA expression, which limits autophagy-associated cell death^[30], indicates that p8 may play an important role in regulation of autophagy which affects cell survival.

p8 was also found to be expressed and related to the metastasis of

breast tumor^[21,22]. The expression of p8 has an inverse relationship with apoptosis^[32]. It is reported that, p8 formed a complex with p53 and p300 and bound the p21 promoter and transcriptionally upregulated p21 expression together with phosphorylation of Rb and upregulation of the anti-apoptotic protein, Bcl-xL, p8 expression imparts breast tumor cell growth and survival advantage, and also, p8 conferred resistance to two chemotherapeutic drugs of Taxol and doxorubicin^[33].

Overexpression and cytoplasmic localization of p8 protein is related to disease progression of papillary carcinoma, suggesting p8 plays a role in tumor progression^[34]. p8 can also inhibit apoptosis and promote cell growth in colorectal tumor cell^[35]. Moreover, the expression of p8 is necessary for the maintenance of the transformed phenotype of pituitary GH3 cells, and the reexpression of p8 in a subset of lactotropes led to prolactinomas formation *in vivo*^[36]. Recently, Guo *et al* found that RNAi knockdown of p8 inhibits human non-small cell lung tumor growth *in vitro* and *in vivo*^[37], suggesting p8 might be a promising target for gene silencing therapy in non-small cell lung tumors.

Together, these data suggest that p8 can mediate the expression of some specific gene to inhibit apoptosis, autophagy and HoCC, therefore, confer the resistance of stress to tumor cell so as to promote tumor progression.

p8 Acts as a Tumor Suppressor

There are also some reports approved or proved that p8 can inhibit tumor progression. This seems quite controversial regarding of the previous discussions. However, p8 is a very unique protein, which has a smaller molecular weight and less stable structure, and may recruit different partners to execute variant functions^[38].

Although Vasseur *et al* have previously reported that p8 plays an important role in controlling the growth of transformed MEFs^[26], and then, they noted in another paper that p8 acts as a tumor inhibitor in normal MEFs. MEFs expressing p8 arrest their growth more readily after serum withdrawal than MEFs lacking p8. p8 facilitates p53 and p21 accumulation in response to adriamycin, so as that p8^{+/+} MEFs are also more sensitive to adriamycin-induced apoptosis^[5].

Carracedo *et al* found that in pancreatic tumor cells, p8 mediated the upregulation of endoplasmic reticulum stress-related genes in response to cannabinoid treatment, leading to the reduction of tumor cell spreading and growth^[39]. Jiang *et al* found that the levels of p8 in ER-β positive tumors were positively correlated the overall survival of the patients^[40], and p8 could interact with ER-β which made it a tumor suppressor role in breast tumor cells and is involved in estrogen-regulated cell growth^[41]. Similar to the founding in breast tumor, p8 is aberrantly expressed in human colon tumor at both the protein and mRNA levels^[42]. While the p8 transcript is increased in tumor tissues compared with normal tissues, low levels of p8 transcript are seen in aggressive tumors^[42]. In prostate tumor cells, p8 levels are inversely correlated with the invasiveness and growth *in vitro* and the overexpression of p8 reduced the growth of prostate tumors *in vivo*, suggesting p8 is a potential tumor suppressor in human prostate tumor^[25]. Ceramide-dependent upregulation of the stress-induced protein p8 and its downstream targets (ATF-4, CHOP, and TRB3) related with the ER stress could mediate the proapoptotic effect of cannabinoids on brain tumor cells, and also, a decreased activation of the p8-regulated proapoptotic pathway led to resistance to cannabinoid treatment *in vivo*^[1].

Taken together, these data show that p8 can inhibit tumor progression, promote apoptosis so as to inhibit cell spreading and growth. Thus, while contrasting in function, p8 appears to participate

in functions related to cell growth and survival control in tumor cells. Whatever the potential function of p8 in tumor cells might be, the molecular mechanism for this gene transcriptional regulation confers has so far remained elusive, but could provide therapeutic targets for tumor treatment and diagnosis.

FUNCTIONAL MECHANISM OF p8

Several findings in tumor cells reveal an association of p8 expression with tumor progression and metastasis through the following processes.

p8 and Cell Cycle

When exposed to stress, cells can respond by activating various cytoplasmic pathways whose nature depends on cell type and the nature of the stress, and then, convey a signal to the nucleus to modulate gene expression so as to determine whether a cell re-enters the cell cycle, undergoes cell cycle arrest or enters into apoptosis. Vasseur *et al* found that p8-deficient fibroblasts grow faster, serum-deprivation induced cell cycle arrest is enhanced in normal fibroblasts compared to p8-deficient fibroblasts^[43]. The expression of the cyclin-dependent kinase inhibitor p27 is decreased in p8-deficient fibroblasts, and intracellular levels and activities of Cdk2 and Cdk4 are lower in normal fibroblasts compared to p8-deficient ones, so p8 appears to regulate the cell cycle upstream from the cyclin dependent kinases. Malicet *et al* found that p8 regulates degradation of p27 through interaction with Jab1, a component of the COP9 signalosome complex^[44]. As p8 plays an important role in Jab-1 mediated translocation of p27 from the nucleus to the cytoplasm, it can regulate cell cycle probably through the increased translocation of p27 (Figure 1A). Although p8-induced cell cycle arrest may suggest it is a tumor suppressor, cell cycle arrest is also required for the epithelial to mesenchymal transition (EMT). During this process, tumor cells transform from epithelial phenotype to mesenchymal phenotype with higher motility, migration, and proteolytic properties, which are essential for invasion and development of metastasis.

p8 and Programmed Cell Death

p8 Inhibits Apoptosis

In the above paragraphs, we have discussed that p8 is associated with programmed cell death. Through the yeast- two hybrid system, prothymosin- α , a highly acidic protein, is identified to be a molecular partner of p8. Prothymosin- α , which is very similar to p8, has an unstable tertiary structure and is involved in many cellular processes. p8 and prothymosin- α can form a stable heterodimeric complex, which inhibits mitochondria-dependent apoptosis by preventing apoptosome formation and thus, caspase 9 activation^[38] (Figure 1B). Therefore, the complex of p8 and prothymosin- α can be a new antiapoptotic target for tumor treatment.

p8 Induces Autophagy

Carracedo *et al* found that treatment with $\Delta 9$ -tetrahydrocannabinol (THC) induces an (ER) stress which leads to the neo-synthesis of ceramide in glioma and pancreatic tumor cells^[1]. And then, high intracellular ceramide levels induce the expression of the p8 gene as well as three of its key target genes, including the activating transcription factor-4 (ATF4), the C/EBP homologous protein (CHOP), and the pseudo-kinase TRB3. Through the interplay of these gene products, the ER-stress signal can be transduced. The activation of the p8/TRB3 pathway inhibits Akt activity leading to the inhibition of mTOR activity, which induces ER stress-associated

autophagy^[45] (Figure 1C). Consequently, activation of p8 may help tumor cells survive ER-stress caused by accumulation of misfolded proteins, hypoxia, or starvation, but if their capacity is inadequate to survive, cells would enter programmed cell death, such as autophagic cell death or apoptosis^[40].

p8 Regulates Accessibility to Chromatin

Gironella *et al* found the interaction between p8 and MSL1^[46]. The MSL1 nuclear factor is a component of MSL complex which has histone deacetylase (HDAC) and acetyl-transferase (HAT) activities^[47]. When p8 is overexpressed, it can bind MSL1 and inhibit acetylation of lysine 16 of histone H4, which is MSL1-dependent^[46]. Thus, through interaction with MSL1, p8 may regulate the histone acetylation/deacetylation of the related target genes. Moreover, it is reported that p8 can form a complex with transcription co-activator p300, and then this complex can interact with PTIP (Pax2 transactivation domain interacting protein) so as to eliminate its repression of target gene transcription^[11] (Figure 1D). In breast epithelial cells, p8 can bind p53 and p300, and this complex can recognize p21/Waf1 promoter and activate p21 transcription^[33] (Figure 1D). In summary, through interaction with different binding partners, p8 may regulate their accessibility to chromatin so as to conduct transcriptional regulation of target genes, and consequently tumor progress is reprogrammed.

Future Directions and Perspectives

In conclusion, p8 is a complicated biological molecule which can make opposite effects based on the physiological condition. On one hand, p8 can make tumor more invasive and resistant to cell death. On the other hand, it can also act as a tumor suppressor. Although much effort has been made to explore the functions and functional mechanism of p8, much remains to be discovered. Previous study was mainly done *in vitro*, developing transgenic mice with p8 deletion^[48] or excessive p8 expression will complement the existing functional study of p8. The lack of a stable structure represents a handicap for structural study and identification of possible nuclear and cytosolic interactors which would be key to create the genetic networks regulated by or requiring the presence of p8.

As tumor is a growing epidemic in the whole world, p8 is emerging as a multifaceted cell regulator which plays an important role in the pathological process of solid tumors, it will be crucial to further determine the functional mechanism of p8. Upcoming investigations leading to a detailed understanding of p8 functions will provide theoretical basis for developing new therapeutic treatment of solid tumors.

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CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

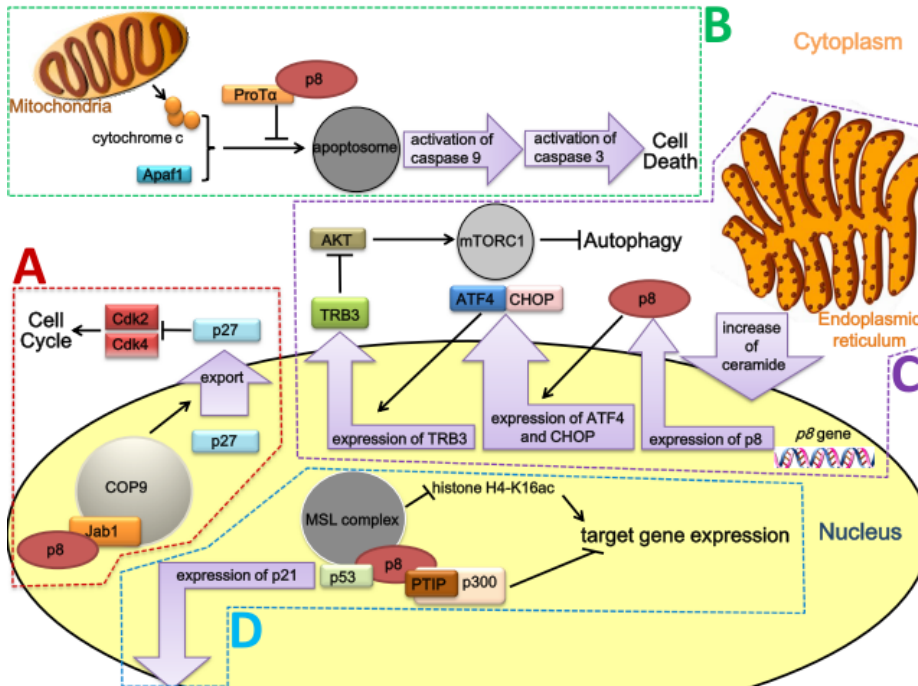


Figure 1 Functional mechanism of nuclear protein p8. A p8 suppresses cell cycle progression. p8 interacts with the Jun activating binding protein 1 (Jab1) leading to the export of p27 checkpoint regulator from nucleus to cytoplasm where it binds and inhibits cyclin-dependent kinases Cdk2 and Cdk4 which allow cell cycle progression. B p8 inhibits programmed cell death. When exposed to pro-apoptotic stress, cytochrome c is released from the mitochondria and binds to apoptotic protease activating factor-1 (Apaf1) to form the apoptosome complex which activates pro-caspase 9 and pro-caspase 3, leading to apoptotic cell death. p8 can bind to prothymosin- α (ProT α) and inhibit the formation of apoptosome complex. C p8 is involved in autophagy caused by the ER-stress response. ER-stress upregulates the level of intracellular ceramide to induce p8 expression which induces expression of the activating transcription factor-4 (ATF4), the C/EBP homologous protein (CHOP), and the pseudo-kinase TRB3. TRB3 inhibits Akt and mTORC1 pathways and induces autophagy process consequently. D p8 mediates several target genes regulation. p8 interacts with the male-specific lethal protein (MSL) complex, therefore regulates histone acetylation and/or deacetylation, so as to control chromatin accessibility and gene transcription. p8 also binds to transcription factors PTIP (Pax2 transactivation domain interacting protein) and p300 to control gene expression. p8 can also control the expression of cyclin dependent kinase inhibitor p21 through interaction with p53.

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