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Review Article

Krüppel-like factor 8 emerges as an important regulator of cancer

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Abstract: Krüppel-like factor 8 (KLF8) is a young member of the KLF transcription factor family proteins. It is highly overexpressed in several types of human cancers and regulates various cellular processes important for tumor progression. Increasing evidence has made KLF8 a new focus in cancer research and a potential target for cancer therapy. This review highlights the role of KLF8 in cancer by summarizing the up-to-date studies into its structure, function as a dual transcription factor, target genes and mechanisms of expression and modifications.

Keywords: Krüppel-like factor 8 (KLF8), cancer

Introduction

There are 17 members in the KLF protein family. Many of them have been shown to play a role in cancer [1]. Some of these transcription factors act as transcriptional activators, some act as transcriptional repressors and other members have a dual role in both activating and repressing gene expression. All of the KLF proteins share three highly conserved Cys2His2 zinc finger motifs in DNA (CACCC GT-box or GC-rich element) binding domain at their C-terminus with diverse N-terminal regulatory elements [2].

KLF8 possesses highly conserved zinc finger domains at its C-terminus that binds to the CACCC region of target gene promoters [3]. KLF8 was first reported as a transcriptional repressor of beta-globin gene expression [3]. It has subsequently been identified as a critical regulator of cell proliferation, oncogenic transformation, epithelial to mesenchymal transition (EMT), tumor invasion and metastasis. Although considered widely expressed, KLF8 expression is barely detectable in most normal cell and tissue types, but highly increased in a number of human cancer types. Thus, KLF8 has emerged as an important cancer-regulating protein.

The structure of KLF8 protein

KLFs are named after homology with Krüppel protein of *Drosophila melanogaster*. KLF8 is present in most of the species. In human KLF8 is located in the chromosome X [4]. Human KLF8 protein consists of 359 amino acid residues. It was first isolated from the K562 leukemia cell line [5]. A typical transcription factor contains three essential domains for its activity, 1) a nuclear localization signal to transport the protein into the nucleus, 2) a DNA binding domain to interact with promoter DNA and 3) a transcriptionally regulatory domain to regulate gene expression. The DNA binding domain is highly conserved in all KLF proteins. In some cases the Zinc finger domains also mediate protein-protein interaction.

As depicted in **Figure 1**, KLF8 protein shares with KLF3 and KLF12 a C-terminal binding protein (CtBP) interacting domain in its N-terminus [3]. CtBP is a transcriptional co-repressor protein. The Pro-Val-Asp-Leu-Ser (PVDLS) motif (86-90 aa) in KLF8 N-terminus is recognized by CtBP. KLF8 interaction with CtBP triggers KLF8 transcriptional repression activity. Along with its

transcriptional repression activity, KLF8 also acts as a transcriptional activator [5, 6]. The glutamine residues Q118 and Q248 of KLF8 are essential for KLF8 transcriptional activation function [7]. The two putative classical nuclear localization signals (NLS) flanking the zinc finger domains do not regulate KLF8 nuclear localization [8]. The post translational modifications such as sumoylation and acetylation of KLF8 do not appear to impact the nuclear localization of KLF8, either. The serine 165 (S165) and lysine 171 (K171) residues of KLF8 are critical for its nuclear localization. The C-terminal zinc finger domains 1 and 2 bind to importin-beta, a protein which imports cytosolic proteins to the nucleus. The exact role of the S165 and K171 residues in regulating nuclear localization of KLF8 remains to be determined. However, it is speculated that PKC may phosphorylate KLF8 at the S165 residue, facilitating the localization of the protein to the nucleus. Inhibition of PKC activity by specific PKC inhibitor decreases the nuclear localization of KLF8 [8]. These sites are also important for cellular function of KLF8 as KLF8 mutant without these regions failed to activate cyclin D1 expression compared to wild type KLF8 [8]. New DNA synthesis was also decreased in cells expressing these mutants. Poly (ADP-Ribose) Polymerase 1 (PARP-1) is an important protein involved in DNA repair, post translational modification known as PARylation, DNA transcription, chromatin modeling and cancer progression [9-11]. PARP-1 has been widely accepted as a therapeutic target for cancer treatment [11]. Recently PARP-1 has been identified as a protein interacting with the Zn finger motifs 1 and 2 of KLF8 [12]. This interaction helps stabilize KLF8 protein in the nucleus. In PARP-1 null cells KLF8 half-life is significantly reduced and the level of ubiquitinated KLF8 is significantly increased. KLF8 interaction with and PARylation by PARP-1 is critical for its nuclear localization. PARP-1 interaction prevents nuclear exporting protein CRM1 from binding to KLF8 and thus inhibits KLF8 export out of the nucleus. Inhibition of the interaction between KLF8 and PARP-1 leads to the cytoplasmic localization of KLF8. It is believed to be caused by increased KLF8 transport by CRM1 to the cytoplasm where KLF8 is ubiquitinated and subsequently degraded presumably by proteasome [12]. Activation of cyclin D1 promoter by KLF8 was significantly reduced when PARP-1 was knocked down or inhibited. KLF8 transcriptional activity can be restored by re-expressing PARP-1 in PARP-1 null cells indicating that KLF8 interaction with PARP-1 and PARylation in the nucleus are crucial for KLF8 transcriptional activity and cellular function [12] See **Figure 1**.

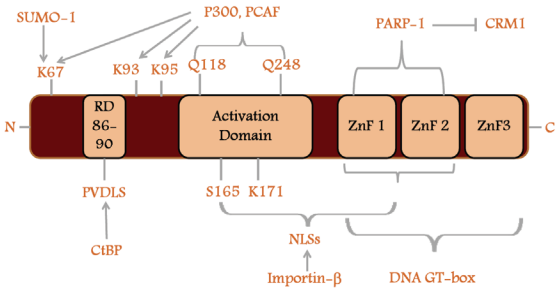

Figure 1. Schematic structure of KLF8 protein. KLF8 interacts with the transcriptional co-repressor C-terminal binding protein (CtBP) through its repression domain (RD or PVDLS motif), with the transcriptional co-activators P300 and PCAF histone acetyltransferases through its activation domain (AD centered on Q118/Q248), with target DNA GT-box sequence via the three C2H2 zinc-finger (ZnF) motifs. KLF8 also binds to importin through its nuclear localization signal sequences and PARP-1 at the ZnF region to regulate its nuclear localization. The acetylation sites and sumoylation site of KLF8 are also shown.

The expression and modifications of KLF8

Understanding the mechanisms behind the elevated expression of KLF8 in cancers is the key to finding important signal pathways leading to KLF8 activation in cancer. It has been reported that KLF8 expression is regulated at both transcriptional and post-translational levels. KLF8 acts as the downstream target of FAK which, activated by integrin signaling, enhances cell proliferation, cell migration through several intermediate transducers such as Src and PI3K [13]. KLF8 expression is highly elevated in FAK over-expressing cells of both mouse and human origins [5, 14]. Integrin-mediated cell adhesion was also able to upregulate KLF8 expression. These observations gave rise to an assumption that KLF8 activates cyclin D1 to regulate cell proliferation as a downstream mediator of FAK. Subsequent studies demonstrated that the FAK-dependent regulation of KLF8 is mediated by SP1 transcription factor which activates KLF8 gene expression by directly binding and activating KLF8 gene promoter. The signaling from FAK to SP1 is mediated by PI3K-AKT and ERK MAP-kinase pathways [15]. KLF8 promoter contains

GT- box (CACCC) regions, consensus binding sites for KLF transcription factors. Indeed, KLF3 can directly repress whereas KLF1 directly activates KLF8 gene promoter [16]. In the presence of these three KLF members, KLF8 transcription is repressed by KLF3. In this context, KLF1 also activates KLF3 transcription [16]. A recent study has identified a cross-talk between Wnt and KLF8 signaling to nuclear β-catenin function in human liver cancer cells [17].

Post-translational modifications are an essential mechanism for the regulation of protein expression and function. KLF8 can be modified by various such mechanims including sumoylation, acetylation ubiquitylation and PARylation. KLF8 is sumoylated by small ubiquitin like modifiers SUMO-1, SUMO-2, and SUMO-3, primarily by SUMO-1. When sumoylated at Lys67, the function of KLF8 as a transcriptional activator or repressor is limited. These results suggest that KLF8 is sumoylated when its function is not needed in the cell [6]. Acetylation was found to be another important post-translational modification of KLF8. KLF8 is acetylated at lysine93, lysine95 and lysine67 by histone acetyltransferase P300 and PCAF co-activators. Acetylation at the Lysine93 is mediated by P300, whereas acetylation at the lysine67 and lysine95 is mediated by both P300 and PCAF. Lysine67 is a common site for both sumoylation and acetylation, thus the sumoylation and acetylation at the lysine67 counteract each other [18]. CtBP recruits E2 and E3 ligase to enhance sumoylation and thus it positively regulates sumoylation. Acetylation at lysine93 and lysine95 inhibits CtBP binding to KLF8 repression domain (86PVDLS90) and thus indirectly inhibits sumoylation. Further using lysine67, lysine93, lysine 95 mutants it was proved that acetylation at these sites promotes the cyclin D1 expression and cell cycle progression by KLF8. A balance between sumoylation and acetylation appears to be critical for KLF8 function in cellular processes [18]. KLF8 PARylation by PARP-1 is a third post translational modification which is required for its transcriptional activity and localization in nucleus to bind to gene promoters [12]. In the absence of PARP-1 function, KLF8 undergoes ubiquitylation and subsequent degradation presumably by proteasome in the cytoplasm [12]. Till date KLF8 phosphorylation has not been well studied although it was predicted that phosphorylation at Serine165 by PKC may play a role in the nuclear localization and cellular function of KLF8. Treatment with PKC inhibitor results in less nuclear localization of KLF8 and a decrease in cyclin D1 expression [8].

KLF8 functions as a dual transcription factor

KLF8 was initially identified as a transcriptional repressor [3]. KLF8 represses gene expression through binding to a co-repressor CtBP to its PVDLS domain (aa86-90). This domain is known as repression domain (RD) (**Figure 1**) [3]. It was also shown that KLF8 is widely expressed in all human tissues. KLF8 was found to bind to CACCC region or GT-box region of target gene promoters. CtBP binding to the PVDLS domain of KLF8 triggers its transcriptional repression of beta-globin gene promoter reporter containing a tandem of GT-boxes. Consistently, a systematic screening for KLF proteins that bind and regulate gamma-globin gene promoter suggested that KLF8 is a transcriptional repressor of gamma-globin gene expression [19]. Interestingly, mutational disruption of the PVDLS domain could not completely abolish KLF8 transcriptional repressor activity suggesting that KLF8 acts as a repressor in both CtBP-dependent and independent manners [3]. KLF8 was then shown to be highly overexpressed in FAK overexpressing cells and to transcriptionally activate cyclin D1 gene promoter to promote cell cycle progression [5]. KLF8 binds directly to a GT-box on cyclin D1 promoter and activates its expression [5]. KLF8 knockdown significantly decreases cyclin D1 expression and the cell cycle progression [5]. Later it was found that KLF8 also activates gene expression by recruiting the co-activators P300 and PCAF to its activation domain containing the core residues of Q118 and Q248 [7]. P300 and PCAF in turn acetylate the histones to activate gene promoter [7]. Mutation in this KLF8 activation domain completely abolishes KLF8 transcriptional activating activity. Both transcriptional activation and repression functions of KLF8 labeled it as a dual transcription factor. KLF8 plays an important role in cell proliferation as a dual transcription factor by activating cyclin D1 expression [20-22]. KLF8 directly represses KLF4 expression to activate cell proliferation [6]. Given the tumor suppressor role of KLF4 [23], repression of KLF4 by KLF8 could contribute to tumor progression. KLF8 directly binds to a GT-box on E-cadherin promoter and represses its activity [24, 25]. E-cadherin is a marker of epithelial cells and a tumor suppressor [25],

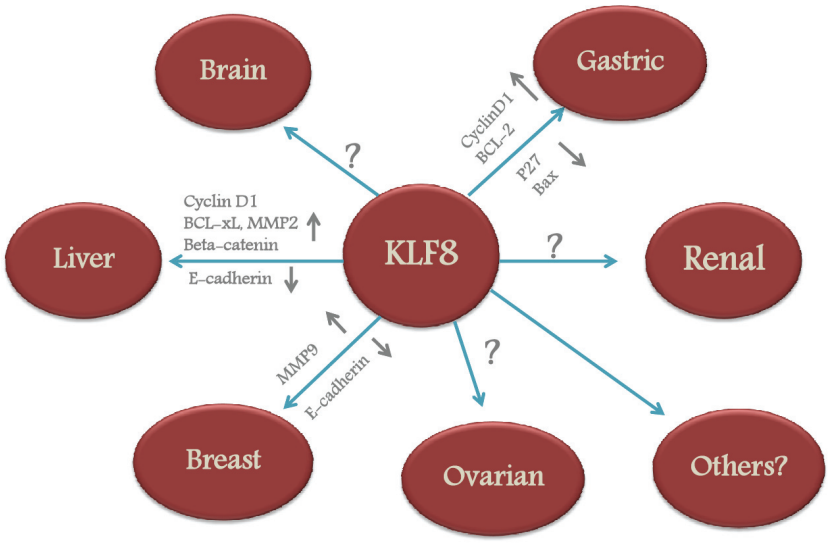

Figure 2. KLF8 regulated human cancer types. Involved KLF8 target genes of transcriptional activation (upward arrows) or repression (downward arrows) are indicated.

loss of its expression leads to loss of cell-cell contact resulting in epithelial to mesenchymal transition (EMT) which is a critical early step of cancer cell invasion and metastasis. Recently it was found that KLF8 directly binds to GT-box 3 on MMP9 promoter and transcriptionally activates its expression [26]. Matrix metalloproteinases (MMPs) are protease enzymes which break down the extracellular matrix proteins and promote cell invasion into other tissues. Increase in MMP expression and catalytic activity leads to cancer cell invasion and metastasis. Taken together, KLF8 appears to target tumor suppressors for transcriptional repression and tumor promoting genes for transcriptional activation for an overall effect favoring tumor progression. The downregulation of E-cadherin and upregulation of N-cadherin, MMP 2 and 9 as well as integrins have also been correlated to the expression of KLF8, along with the other EMT-promoting factors including Snail, TWISTs and ZEBs, during the implantation stage of bovine embryogenesis [27].

KLF8 in cancer

Since the initial descriptions of KLF8 as a regulator of beta-globin and cyclin D1 transcription [3, 5], several reports have been followed to demonstrate the aberrant overexpression of KLF8 in various types of human cancer including breast [24, 26, 28], ovarian [15, 28], renal [28, 29], liver [17, 30], gastric [31] and brain [20-22] cancer (**Figure 2**). Various signaling pathways regulating KLF8 and its target genes associated with cancer have been identified (**Figure 3**). Initial effort began with a study of the role of KLF8 in oncogenic transformation of NIH3T3 cells [28]. In that report, tetracycline regulated inducible overexpression of KLF8 caused the transforming phenotypes including loss of contact inhibition and serum independent growth [28]. On the other hand, overexpression of a KLF8 inhibiting mutant clearly reduces the ability of v-Src to transform NIH3T3 cells and KLF8 regulation of cyclin D1 expression appears to play a partial role [28]. KLF8 directly represses the tumor suppressor gene KLF4 which may also contribute to the transformation [6]. Cancer cells are benign when they are localized in their origin. Cancer becomes malignant when cancer cells invade the extracellular matrix and migrate to different locations. This process is known as metastasis if the cell migration takes the route of blood or lymph circulation. EMT is a process during which epithelial cells are transformed into fibroblast-like cells that are more motile and invasive [25]. EMT plays a critical role in tumor metastasis. On one hand, EMT allows a few cancer cells to dissociate and migrate away from the primary tumor mass. On the other hand, it renders the cancer cells ability to survive the circulation by avoiding anoikis- an apoptotic process triggered by cell detachment from extracellular matrix that kills particularly epithelial cells. Cancer cell migration, invasion and metastasis are the most malignant stages of cancer. E-cadherin and MMP9 are two of the most important mediators in these stages. During EMT E-cadherin expression is decreased and the expression of mesenchymal markers such as N-cadherin and vimentin is increased. KLF8 directly represses E-cadherin expression and triggers subsequent EMT process in both canine kidney epithelial cell line MDCK and human mammary epithelial

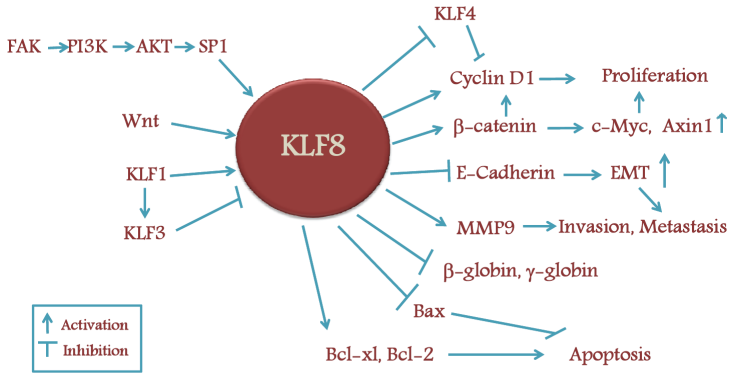

Figure 3. KLF8 signaling. Upstream regulators, downstream target genes and cellular processes are shown.

cell line MCF-10A [24]. This induction of EMT by KLF8 does not appear to depend upon other EMT inducer proteins such as Snail. KLF8 directly activates MMP9 gene promoter by binding to a GT-box to increase MMP9 expression and catalytic activity [26]. KLF8 overexpression leads to increased breast cell migration and invasiveness. KLF8 knockdown in highly metastatic breast cancer cell line significantly decreases the lung metastatic rate in nude mouse [26]. In ovarian cancer cells KLF8 transduces FAK to PI3K to AKT to SP1 signaling to upregulate cyclin D1 expression and enhance the cell cycle progression [15]. The recent discovery of PARP-1 binding to KLF8 in the nucleus in both breast and ovarian cells [12] suggests a potentially interesting cooperation between KLF8 and PARP-1 in these cancer cell types. Besides breast and ovarian cancer, role of KLF8 has been identified in a few other cancer types. It was reported that KLF8 protein and mRNA is highly overexpressed in human renal cell carcinoma (RCC) tissues compared to that in the adjacent non-tumorous renal tissues [29]. Silencing KLF8 expression in the RCC 786-0 cells induces apoptosis and inhibition of invasion *in vitro* and tumor growth in nude mice [29]. In human hepatocellular carcinomas (HCC), the aberrant overexpression of KLF8 was correlated with the metastatic potential, post-surgical recurrence of the HCC tumors and poor survival studied in more than 300 patient cases [30]. Using tissue microarray analysis of the patient specimens and several KLF8-genetically modified HCC cell lines, the study demonstrated that in HCC cells KLF8 promotes proliferation and invasion and inhibits apoptosis by inducing the upregulation of cyclin D1 expression, the expression switch of EMT marker genes, the activation of MMP2, the transcriptional repression of caspases 3 and 9 and activation of Bcl-xL [30]. Related to this study, a most recent report has suggested a role of KLF8 in mediating Wnt to β-catenin signaling to activate the transcription of c-Myc, cyclin D1 and Axin1 and promote HCC cell proliferation [17]. In gastric cancer, the KLF8 expression was found highly elevated in gastric cancer tissues from 80 patients and in human gastric cancer cell lines compared to the adjacent nontumor gastric tissue and normal gastric epithelial cells [31]. KLF8 knockdown in the cancer cells resulted in reduced xenografted tumor growth in nude mice with decreased expression of cyclin D1 and BCL-2, the upregulation of P27 and Bax expression and apoptosis in the tumor cells [31]. The first implication of the role of KLF8 in cancer was from an early study in which the U-251MG human glioblastoma cells were used [14]. That study showed that the expression of KLF8 in the cells depends upon the expression and activity of FAK and correlated to the increase/decrease of cyclin D1/p27 and the cell cycle progression. Subsequently, a recent study demonstrated that the U251 glioblastoma cell growth can be induced to undergo apoptosis by knocking down the expression of KLF8 [22]. In the meantime, a group from Germany reported the positive expression of KLF8 in human gliomas of all grades irrespective of the proliferation rate assumed by Ki67 staining, and knocking down KLF8 in the U87-MG glioma cells dramatically inhibited the cell proliferation [21].

In summary, studies to date have demonstrated a critical role of KLF8 in the regulation of a variety of cellular processes favoring tumor progression of many cancer types. While this certainly suggests that KLF8 could be used as a potential future molecular target for cancer therapy, many questions regarding the tumor-promoting or oncogenic role and mechanisms of KLF8 remain to be answered by additional studies using well-defined experimental systems such as non-tumorigenic human cells of cancer origins and KLF8 genetically engineered mouse models.

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