Krüppel-like factor 4

Subjects: Biotechnology & Applied Microbiology

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breast cancer colorectal cancer

1. Introduction

Krüppel-like factor 4 (KLF4) is a transcription factor very important in various developmental processes and disease states. Although the most recent review of its key roles in development, cellular reprogramming and cancer appeared in 2017 [1], since then many new reports have explored the roles played by KLF4 in cancer. These discoveries shed new light on the functioning, regulation and significance of KLF4 in various types of cancer. The emerging picture is very complex and indicates that many aspects of KLF4 functioning must be taken into account before any conclusions can be made. On the other hand, many results are very promising, not only from the point of view of basic research, but also because they can potentially find clinical applications. In the present review we focus on the role of KLF4 in the most common types of cancer [2], as the vast majority of recent reports are concerned with these cancer types.

Traditionally, the role of KLF4 in cancer has been to act primarily as a tumor suppressor, that is, to drive terminal differentiation and inhibit cellular proliferation. However, recent studies analyzing data from cancer patients, in vitro tissue and cell culture experiments, murine models of metastasis and also of conditional (tissue-specific deletion) animal models indicate that the role of KLF4 is actually much more extensive than originally believed, and is extremely dependent on the microenvironment in which KLF4 drives its cadre of transcriptional targets. Moreover, recent findings (primarily from *Cre-lox* dependent *Klf4*-deletion) indicate that loss of KLF4 acts as a “sensitizing” mutation, in that tissue homeostasis is often only marginally perturbed, however when a further stressor (such as environmental factor/toxin exposure, further genetic mutation etc.) is applied, the disruptions to tissue homeostasis are far more pronounced than they are in tissues with normal KLF4 function. In this way, KLF4 may be considered to act not only as a tumor suppressor, but more broadly, as a critical “cell stability molecule”, and an important maintainer of tissue homeostasis.

2. Colorectal Cancer

The broadly described role of KLF4 in colorectal cancer (CRC) remains controversial. Many studies have shown that KLF4 plays a tumor-suppressive role in CRC [3]. The reduced expression of KLF4 in human CRC tissues has

been associated with increased growth of CRC cells, lymphatic node metastasis, reduced tumor cell differentiation, and tumor recurrence. CRC patients with lymph node metastasis display reduced KLF4 expression. Furthermore, the downregulation of KLF4 is associated with poor prognosis in human CRC patients, decreased overall survival as well as disease-free survival [3].

KLF4 inhibits CRC cell proliferation through upregulation of N-Myc downstream regulated gene 2 (NDRG2) by binding to the *NDRG2* promoter. Lower expression of KLF4, as well as NDRG2, in CRC patients was correlated with poor overall survival [4]. KLF4 acts as transcriptional repressor of GINS complex subunit 4 (GINS4), a prognostic biomarker promoting the growth of CRC. The expression of GINS4 is significantly elevated in CRC tumor samples [5].

Loss of KLF4 in CRC tissues is associated with epithelial-mesenchymal transition (EMT). There is a marked decrease in KLF4 expression in CRC tumor samples obtained from patients, which is also observed in the mouse model. The same study has shown a negative correlation between KLF4 levels and mesenchymal markers both in human patients and in mice treated with azoxymethane and dextran sodium sulfate (AOM/DSS). These markers include TWIST, β-catenin, claudin-1, N-cadherin, SNAI2 and vimentin. in CRC patient tumor sections. However, the expression of KLF4 is positively correlated with the epithelial marker E-cadherin [6].

The intestinal epithelium-specific deletion of *Klf4* in mice increases genetic instability and accelerated progression of colitis-associated colorectal cancer (CAC). Mice with intestinal epithelium-specific deletion of *Klf4* ($Klf4^{\Delta IS}$) treated with AOM and DSS developed significantly more adenomatous polyps and carcinomas in situ in comparison to treated control $Klf4^{fl/fl}$ mice. The tumors and polyps in these mice display an increased number of mitotic cells with more than 2 centrosomes [7]. On the other hand, the expression of KLF4 is specifically increased in colorectal epithelial cancer cell lines, Caco-2 and HCT116, but not in the other human colorectal epithelial cell lines. Overexpression of KLF4 was induced in the HCT166 cell line with the help of small activating RNAs. This promoted migration and invasion of cells. It was found that the underlying molecular mechanism included the induction of EMT and nuclear translocation of β-catenin [8].

The analysis of cell proliferation and tissue remodeling from the cohort of colorectal cancer patients have also predicted KLF4 to be a driver of tissue remodeling in CRC via myeloid cell infiltration [9]. KLF4 can also indirectly modulate the actin cytoskeleton morphology via activity of RhoA in order to inhibit cellular migration and invasion of the human colon cancer cell line RKO [10].

The well-described role of microRNA in colorectal cancer and its significance in cancer prognosis and treatment was reviewed elsewhere [11]. The relationship between some specific microRNAs and KLF4 in these neoplasms is also well known. KLF4 is a direct target of miR-543, miRNA highly expressed in CRC samples and cell lines, and associated with tumor size, TNM stage and metastasis. These studies have shown an obvious inverse correlation between miR-543 and KLF4 expression in CRC tissues. By targeting KLF4, miR-543 facilitates colorectal cancer proliferation and metastasis [12]. MiR-25-3p, miR-103 and miR-107, all promote metastasis of CRC by targeting KLF4 [13]. Furthermore, miR-25-3p also regulates KLF4 in endothelial cells, as it can be transferred into them from

CRC cells via exosomes. By targeting KLF2 and KLF4, miR-25-3p regulates the expression of VEGFR2, ZO-1, occludin and claudin-5, and in this way it promotes vascular permeability and angiogenesis [14].

MiR-7-5p negatively regulates KLF4 which results in increased proliferation and migration of CRC cells Moreover, KLF4 overexpression rescued the suppressive effects of miR-7-5p on CRC cell proliferation and migration [15]. MicroRNA-10b, a key regulator of metastasis in many human tumors, regulates KLF4 expression and in this way it controls the metastasis and proliferation of CRC cells [16]. KLF4 is directly involved in the regulation of miR-153-1 expression. The long non-coding RNA, Taurine up-regulated 1 (TUG1), negatively regulates KLF4 expression. TUG1 interacts with EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit). This regulation contributes to the growth, metastasis and EMT of CRC in mice in vivo [17].

KLF4 regulates stemness and mesenchymal properties of CRC stem cells through the TGF-β1/Smad/snail pathway in $Lgr5^{+}CD44^{+}EpCAM^{+}$ colorectal cancer stem cells (CSCs), which are responsible for initiating and sustaining tumor development and progression [18]. It appears that KLF4 participates in the response of cancer cells to chemotherapy. KLF4 is very important for maintaining the stemness in cancer cells. KLF4 enhances the expression of survival proteins hTERT and HMGB1 (high mobility group box 1) which sensitizes cancer cells to cisplatin cytotoxicity. In the presence of cisplatin, expression of HMGB1 and hTERT is negatively regulated by KLF4. What is more, KLF4 promotes the cisplatin-mediated G2/M cell cycle arrest while a knock-down of KLF4 induces cisplatin-mediated S-phase arrest compared to control. In cisplatin-treated and KLF4 knock-down HCT-15 cells, compared to the empty vector control, the level of reactive oxygen species was decreased, accounting for increased cell survival. Therefore it appears that increasing KLF4 expression might sensitize drug-resistant cancer cells to chemotherapy [19]. Sijunzi decoction is a traditional Chinese medicine product used in the prevention and treatment of CRC. KLF4 is a likely molecular target of this medical product [20].

KLF4 mediates the effects of mesalazine, also known as 5-aminosalicylic acid (5-ASA), an aminosalicylate anti-inflammatory drug [21], on the β-catenin pathway in colon cancer cells. The treatment with 5-ASA–induces μ-protocadherin expression, and KLF4 is a direct regulator of μ-protocadherin in this context. The underlying molecular mechanism involves miR-130a and miR-135b, as these microRNAs target KLF4 and 5-ASA treatment suppresses their expression [22]. KLF4 p.A472D mutation contributes to acquired resistance to cetuximab, a human-mouse chimeric IgG1 mAb that targets the extracellular domain of epidermal growth factor receptor (EGFR) and is effective in treating RAS wild-type and BRAF V600E wild-type patients with metastatic CRC [23].

In HCT116RR, derived radio-resistant cancer cells, KLF4 directly interacts with the human telomeric RAP1 protein [24]. The silencing of RAP1 reverses the radio-resistant phenotype in these cells and increases their sensitivity to radiotherapy. Increased RAP1 levels were associated with a poor survival rate, indicating that RAP1 could serve a marker for survival prediction in these types of cancer [24], although the precise relationship between RAP1 and KLF4 needs to be investigated further. B-cell-specific Moloney murine leukemia virus insertion site 1 (BMI1) deficiency sensitizes cells to radiation treatment by modulating the expression of KLF4 and leads to enhanced radiosensitivity in microsatellite stable colorectal cancers [25]. In summary, KLF4 serves as a tumor suppressor in CRC and sensitizes CRC cells to various forms of treatment. It seems to be involved in a wide variety of molecular

pathways and cellular processes. The overall picture of these interactions is very complicated and calls for further research to unravel all its nuances.

3. Breast Cancer

The role of KLF4 in breast cancer is complex; it has been reported that KLF4 has dual function as either a tumor suppressor or an oncogene, in a context-specific manner. Recent work revealed that in triple-negative breast cancer (TNBC) KLF4 is a repressor of the *EGFR* gene leading to a decrease in both total and phosphorylated EGFR levels in MDA-MB-231 and MDA-MB-468 cells. Furthermore, overexpression of KLF4 inhibits migration, invasion and growth of TNBC cells in vitro and increases the sensitivity of these cells to erlotinib [26]. Additionally, the group of TNBC patients with high KLF4 expression have more favorable prognostic factors (overall survival and disease-free survival rates) than patients characterized with low KLF4 expression [27]. It should be noted that KLF4 is a favorable prognostic indicator for patients with other subtypes of breast cancer as well (classified on the basis of the estrogen receptor (ER) and HER2 status) [28]. Lu et al. investigated a novel mechanism of KLF4 regulation in breast cancer cells, involving covalent head-to-tail looped RNA, originating from the euchromatic histone lysine methyltransferase 1 (circEHMT1). They found that KLF4-dependent inhibition of migration and invasion of breast cancer cells is regulated by miR-1233-3p which is a target of circEHMT1 [29]. Other studies revealed interesting mechanisms of KLF4 regulation in breast cancer cells, involving DEAD-BOX (DDX) RNA helicase (DDX3X). Data showed that DDX3X directly interacts with *KLF4* mRNA and negatively regulates its splicing. The DDX3X knockdown in MCF7 cells drives the cell cycle arrest by increasing KLF4 protein levels [30].

Nuclear factor I-C (NFI-C) appears to be an essential factor for the maintenance of epithelial differentiation and inhibits EMT and metastasis of breast cancer cells by regulating KLF4. NFI-C directly interacts with the *KLF4* promoter and stimulates its transcriptional activity which in consequence induces mesenchymal-epithelial transition (MET) [31]. Importantly, KLF4 is a key inducer of MET in normal mammary epithelial cells and breast cancer cells, through its ability to activate the epithelial program by triggering E-cadherin expression [32]. Other mechanisms suggesting protective role of KLF4 in breast cancer involve human 1-acylglycerol-3-phosphate O-acyltransferase 9 (AGPAT9). AGPAT9 inhibits breast cancer cell proliferation, migration and invasion both in vitro and in vivo through the KLF4/*Homo sapiens* longevity assurance homolog 2 of yeast LAG1 (LASS2)/ vacuolar-H^+-ATPase (V-ATPase) signaling pathway [33]. Results showed that the LASS2 expression is activated by KLF4 and LASS2 is its target gene. Moreover, the LASS2 inhibition of the V-ATPase activity occurs through LASS2 interaction with the c subunit of the V-ATPase proton pump (ATP6V0C) [34][35]. The above findings indicate that KLF4 suppresses breast cancer development. Conversely, there are also reports suggesting that KLF4 plays an oncogenic role in mammary tumorigenesis. An in vitro and in vivo study performed by Zhou and colleagues showed that breast cancer cell metastasis is promoted by ATXN3 (Ataxin-3, ATX3, AT3 or MJD), which is a novel deubiquitinating enzyme of KLF4 [36]. They also found that a member of the F-box protein family (FBXO32) mediates KLF4 ubiquitination and degradation, and in consequence suppresses breast cancer tumorigenesis [37].

In the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced carcinogenesis model KLF4 expression is up-regulated. Furthermore, KLF4 can bind to the promoter of S100 calcium binding protein A14 (*S100A14*) gene,

increasing its mRNA and protein levels, which promotes breast cancer cell motility [38]. The study of the role of KLF4 in glycolytic metabolism and proliferation in breast cancer cells revealed that KLF4 is a stimulator of glycolytic metabolism. KLF4 directly binds to the phosphofructokinase platelet gene (*PFKP*) promoter and activates its transcription, while KLF4 knockdown decreases PFKP expression resulting in reduced glucose uptake and lactate production in vitro. Additionally, there is a statistically significant positive correlation between KLF4 and PFKP expression in breast cancer tissues [39].

The expression of KLF4 is significantly and inversely correlated with brain, but not bone, metastasis-free survival [40]. Using a mouse model it was demonstrated that miR-7-2 suppresses brain metastasis by inhibiting KLF4 expression. In addition, further in vitro experiments showed that miR-7 reduces the ability of invasion and self-renewal of cancer stem cells (CSCs) by modulating KLF4 expression [40]. In agreement with these findings the silencing of WNT1-inducible signaling pathway protein 2 (WISP2) signaling in human breast adenocarcinoma MCF7 cells resulted in miR-7 inhibition and elevation of KLF4 expression. The above mechanism is responsible for the reduction in breast cancer cells susceptibility to the cytotoxic T-lymphocyte (CTL)-mediated lysis [41].

Other studies revealed that dual specificity tyrosine phosphorylation regulated kinase 2 (DYRK2) negatively regulates the formation of breast CSCs, and KLF4 is a key mediator in this process. Moreover, androgen receptor (AR) activates KLF4 expression by binding to the *KLF4* promoter and this process is DYRK2-dependent [42]. KLF4 may influence tumor response to chemotherapy. KLF4 regulates chemoresistance in breast cancer cells. Cisplatin treatment elevates KLF4 protein levels, which led to reduced sensitivity of breast cancer cells to this drug [43]. In addition, patients with locally advanced breast cancer with high KLF4 expression have lower pathologic complete remission (pCR) rates after neoadjuvant chemotherapy [44]. Thus the overall picture of KLF4 involvement in breast cancer is even more complicated than in CRC. As in CRC, KLF4 serves as a tumor suppressor in breast cancer and sensitizes breast cancer cells to various forms of treatment, but it can also act as a tumor promoting factor in breast cancer. There are many molecular pathways and cellular processes responsible for the involvement of KLF4 in breast cancer. Certainly, more studies are necessary to shed more light on this topic.

4. Hepatocellular Carcinoma

According to the latest findings, in hepatocellular carcinoma (HCC) KLF4 performs a tumor suppressive role [45][46][47]. It inhibits proliferation, migration, invasion and EMT of HCC cells [45]. The expression of KLF4 is reduced in HCC tumors, in comparison with the surrounding non-tumorous tissues, and is negatively correlated with the number of tumors, grades of differentiation, and stages of LNM (lymph node metastasis) and TNM (tumor node metastasis) [45][48]. High KLF4 levels in tumor tissues are associated with both better overall survival rate and recurrence-free survival rate, while low KLF4 expression may mean a poor prognosis for HCC patients [45][48]. KLF4 may thus become not only a valuable prognostic biomarker but may also be a therapeutic target in HCC [45][48][49].

KLF4 is very unstable in living cells. Its half-life is only about two hours, as it is rapidly ubiquitinated and degraded in proteasomes [50]. In HCC, this process is regulated by tumor necrosis factor receptor-associated factor 7

(TRAF7), which acts as an E3-ubiquitin ligase. TRAF7 promotes HCC migration and invasion through ubiquitination and subsequent degradation of KLF4 [51]. KLF4 expression in HCC is negatively regulated by a number of microRNAs: miR-9-5p, miR-10b, miR-18a and miR-124 [52][53][54][55]. Histone methyltransferase SET8 binds to KLF4 and suppresses its expression [46]. Subsequently, KLF4 redirects carbohydrate flux from glycolysis to mitochondrial respiration. The underlying molecular mechanism involves the activation of sirtuin 4 (SIRT4) expression by KLF4, which binds directly to the *SIRT4* promoter and positively regulates its expression [46]. KLF4 activity as a transcriptional transactivator is negatively regulated by DEAD box RNA helicase 17 (DDX17), which displays a tumor promoting function in HCC [56].

The expression of KLF4 can also be regulated at the level of splicing. Splicing factor 3b subunit 4 (SF3B4) is frequently overexpressed in HCC samples, where it promotes cancer development [57]. At the molecular level, SF3B4 overexpression triggers SF3B complex to splice *KLF4* primary transcript to nonfunctional skipped exon mature transcripts [57]. All the above findings indicate that the mechanisms of regulation of KLF4 activity are complex, and that simply measuring the levels of KLF4 expression is insufficient to appropriately investigate its involvement in HCC.

Monoglyceride lipase (MGLL; EC 3.1.1.23) is one of the targets of KLF4 regulation relevant for the development of HCC [58]. The expression of MGLL is decreased in HCC samples, both at the mRNA and protein levels [59]. Patients with low MGLL expression have lower 5-year overall survival rate, and overexpression of MGLL suppresses HCC cell migration [58]. KLF4 directly binds to the *MGLL* promoter and positively regulates the expression of *MGLL* in HCC cells [59]. KLF4 also directly binds to the promoter of the gene coding for Ring1- and YY1-binding protein (RYBP), a tumor suppressor, and positively regulates its expression [60]. miR-31 is yet another direct target of KLF4 regulation in HCC [61]. KLF4 positively regulates the expression of tetraspanins CD9 and CD81 [62]. These proteins are surface markers of exosomes, and they act as tumor suppressors in HCC where they inhibit cell proliferation by negatively regulating the MAPK/JNK signaling pathway [62].

KLF4 represses the expression of another Krüppel-like factor, KLF11, by directly binding to its promoter, whereas KLF11 inhibits the expression of Smad7 through direct binding to its promoter, and this in turn triggers EMT in HCC cells [55]. Interestingly, KLF4 can also directly bind to the Smad7 promoter but, unlike KLF11, it positively regulates its transcription [47]. In this way KLF4 suppresses oncogenic transforming growth factor beta (TGF-β) signaling, and therefore loss of KLF4 expression in primary HCC cells may contribute towards the activation of oncogenic TGF-β signaling and subsequent tumor progression [47]. KLF4 positively regulates the expression of P-cadherin, which acts as a tumor suppressor in HCC [63]. P-cadherin functions in HCC by modulating glycogen synthase kinase 3 beta (GSK-3β) signaling, thus adding yet another signaling pathway to those influenced by KLF4 [63].

Increased expression of KLF4 in HCC cells contributes towards their resistance to sorafenib, a protein kinase inhibitor approved for the treatment of HCC [64]. KLF4 and epidermal growth factor receptor (EGFR) constitute a positive feedback loop, where KLF4 directly binds to the *EGFR* promoter and positively regulates its transcription, while nuclear EGFR directly binds to the *KLF4* promoter and increases its transcription. However, the underlying molecular mechanisms remain elusive. KLF4 might induce the resistance to sorafenib by inducing CSCc, because

CSCs have strong chemoresistance to antitumor agents [64]. KLF4 is a well-known Yamanaka factor, one of four core factors known to possess the ability to “re-program” differentiated cells into a more immature state, and its ectopic expression can reprogram various differentiated cells to pluripotent stem cells [65]. The overexpression of KLF4 in the HCC cell line HuH7 can induce a CSC-like phenotype in non-CSC cells by upregulating the expression of EpCAM (epithelial cell adhesion molecule) and CD133/Prominin-1 [66]. However, these latter studies were carried out in only one cell line and, as the authors agree, their investigations will have to be repeated in a series of HCC cell lines with different genetic and epigenetic backgrounds before any far-reaching conclusions can be proposed.

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