World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i14.3960

World J Gastroenterol 2014 April 14; 20(14): 3960-3966
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (8): Gastric cancer

New insights into the functions and localization of the homeotic gene *CDX2* in gastric cancer

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Supported by The National Natural Science Foundation of China, No. 81060201; Natural Science Foundation of Guangxi Zhuang Autonomous Region of China, No. 2011GXNSFA018273 and No. 2013GXNSFAA019163; and the Key Health Science Fund of Guangxi Zhuang Autonomous Region of China, No. 1298003-2-6
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Received: September 26, 2013 Revised: December 22, 2013
Accepted: February 20, 2014
Published online: April 14, 2014

Abstract

Gastric cancer is one of the most frequent cancers, and it ranks the third most common cancer in China. The most recently caudal-related homeobox transcription factor 2 (CDX2) is expressed in a large number of human gastrointestinal cancers. In addition, gastric epithelial cell mutations in CDX2 result in tumor promotion, which is characterized by cellular drug resistance and a high proclivity for developing cancer. A series of publications over the past years suggests a mechanism by which CDX2 overexpression results in multidrug resistance. CDX2 appears to forward control regenerating IV and the multidrug resistance 1 expression signaling pathway for regulation of cell drug resistance.

Key words: Caudal-related homeobox transcription factor 2; Gastric cancer; Intestinal metaplasia; Apoptosis; Drug resistance

Core tip: This review elucidates the relationship between caudal-related homeobox transcription factor 2 (CDX2) and gastric carcinoma, and promotes research to establish whether CDX2 induces drug resistance in gastric cancer. The review highlights that CDX2-positive expression should be a useful maker for diagnosis for patients with intestinal-phenotype gastric cancer, because of this useful maker, future drug and gene therapy targets in gastric cancer might be influenced.

Yan LH, Wei WY, Xie YB, Xiao Q. New insights into the functions and localization of the homeotic gene *CDX2* in gastric cancer. *World J Gastroenterol* 2014; 20(14): 3960-3966 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i14/3960.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i14.3960

INTRODUCTION

Caudal-related homeobox transcription factor 2 (CDX2) is a member of the caudal type homeobox gene family. The encoded protein is a major regulator of intestine-specific genes and is involved in cell growth and differentiation, but also has several other functions, including early embryonic development of the intestinal tract, and intestinal inflammation and tumorigenesis[1-3]. We showed that multidrug resistance was reversed in gastric cancer SGC7901/DDP cells *in vitro* and *in vivo* by CDX2 down-

regulation[4]. Overexpression of CDX2 in HT-29 cells revealed increased resistance to the known substrates of multidrug resistance protein (MDR1), vincristine and paclitaxel, which was reversed by MDR1 inhibitor verapamil[5], thereby supporting cell growth. However, high expression of CDX2 significantly reduces tumorigenicity in BGC-823 cells[6], and CDX2 may play a growth-suppressive or proapoptotic role in gastric cancer cells. These findings suggest that a unique feature of *CDX2* gene is that it plays opposing functions with regard to the regulation of cell growth and death in gastric cancer. However, the molecular networks connecting CDX2 to its function and regulation in gastric cancer remain largely unknown.

IDENTIFICATION OF CDX2

Several studies have demonstrated that CDX2 is largely present in intestinal homeostasis and inflammation[7,8]. The first description of the caudal homeobox gene was in *Drosophila* by Mlodzik *et al*[9]. Six years later, James and Kazenwadel[10] reported *CDX2* gene expression in the intestinal epithelium of adult mice. They found that all nine homeobox genes were expressed in different regions of the intestine, with a unique expression profile for each gene, and CDX2 was present in a single copy in the mouse genome. Suh and Traber[11] further showed that the intestine-specific homeobox gene, CDX2, was a transcription factor that regulated both proliferation and differentiation in intestinal epithelial cells. Rao *et al*[12] showed that overexpression of CDX2 in intestinal epithelial cells increased migration in wound healing, while a more recent work of Gross *et al*[13] indicated that decreased CDX2 expression enhanced intestinal cell migration. A similar phenomenon also occurred in gastric cancer (GC). Silberg *et al*[14] showed that ectopic expression of CDX2 induced gastric intestinal metaplasia in transgenic mice. Our recent research[15] found that overexpression of CDX2 inhibited cell growth and proliferation, blocked entry into the cell cycle S phase, reduced motility and invasion of MGC-803 cells, and increased the rate of apoptosis in GC cells *in vitro*. Moreover, Dang *et al*[16] found that loss of CDX2 predominantly altered the expression of genes involved in intestinal glandular differentiation and adhesion, but disruption of CDX2 in MKN45 cells did not significantly affect their tumorigenic potential.

CDX2 contains two conserved protein domains that play different roles. The Caudal-like protein activation region is thought to mediate transcription activation, which consists of the N termini of proteins belonging to the caudal-related homeobox protein family. The level of activation caused by mouse CDX2 is affected by phosphorylation at serine 60 *via* the mitogen-activated protein kinase pathway[17]. In this region, *CDX2* gene always has homeodomains that interact with the DNA-binding domain of DNA replication-related element binding factor, which is an 80-kDa polypeptide homodimer that plays an important role in regulating cell-proliferation-related genes[18]. Another conserved protein domain is the protein kinase and catalytic domain, which contains the catalytic domain of the serine/threonine kinase (STK), mitogen-activated protein kinase (MAPK)/MAK/MRK overlapping kinase. The protein kinase superfamily is mainly composed of the catalytic domains of serine/threonine-specific and tyrosine-specific protein kinases. It also includes the RIO kinases, which are atypical serine protein kinases, aminoglycoside phosphotransferases, and choline kinases[19]. When the catalytic domain of STKs is activated, these proteins catalyze the transfer of the γ-phosphoryl group from ATP to hydroxyl groups in specific substrates such as serine, threonine, or tyrosine residues of proteins[20]. Duncan *et al*[21] have reported that protein kinase and caspase networks induce alterations in cell survival and frequently accompany transformation and tumorigenesis.

Subsequent studies have shown that CDX2 controls the transcription of cellular genes that are essential for gastric intestinal metaplasia. CDX2 contains catalytic domain of MAPK, which is involved in various key cellular activities. And the MAPK signaling pathways have been implicated in the pathogenesis of cancer, which plays a key role in several steps of tumorigenesis including cancer cell proliferation, migration, and invasion[22]. Cell cycle progression is related to mutable transcription factors and cofactors. Several studies have shown that CDX2 is modified post-translationally, which seems to regulate its activity and modulate its interactions with other transcription factors and cofactors[17,23].

ROLE OF CDX2 IN GASTRIC INTESTINAL METAPLASIA

Gastric intestinal metaplasia is a multifocal regenerative lesion characterized by the presence of intestinal cell types, such as goblet, Paneth and absorptive cells, alone or in combination, within the gastric mucosa[24]. The ectopic intestinal glands are completely reorganized, with displacement of the proliferative zone from the neck region down to the base of the crypt, thus resembling the normal intestine, concomitant with alterations in the stromal sheath surrounding the metaplastic gland, which also acquires an intestinal phenotype[25]. Intestinal metaplasia is thus generally accepted as a preneoplastic lesion conferring increased risk for gastric cancer development[26], and its cause-effect relationship with *Helicobacter pylori* (*H. pylori*) infection is indisputable. However, intestinal metaplasia arises in only approximately 30% of infected individuals, from which only around 7% will develop gastric cancer[27]. Although low, these percentages acquire particular importance in countries where the prevalence of infection remains high, such as Asia[28], where approximately 75% of the population is infected. Over the past two decades, several animal models of developing intestinal metaplasia have been reported. The Mongolian gerbil model is the best for recreation of all gastric histological events following *H. pylori* infection leading to intestinal

metaplasia and ultimately gastric cancer, thus corroborating the causal role of infection in preneoplastic lesions and cancer development. Several studies show that after long-term infection these animals develop intestinal metaplastic lesions that resemble human disease[29,30], which develop into gastric adenocarcinoma.

Recently, the induction of an ectopic intestinal phenotype in the stomach has also been achieved in animal models by manipulating downstream events in the carcinogenic cascade. Two mouse cell lines have been developed to help understand the causal role of ectopic CDX2 expression in the stomach for development of extensive intestinal metaplasia[14]. In these models, CDX2 is under the control of promoters from different gastric-specific genes that are transcribed during embryonic development[14]. The promoter such as H^+/K^+-ATPase b-subunit[31], is only active postnatally. Both models display extensive intestinal metaplasia, presenting all intestinal cell types except Paneth cells, as well as several intestine-specific gene products typical of the different lineages. These two models suggest two separate pathways for metaplastic development. Expression of CDX2 during fetal development may affect the undifferentiated endodermal cells of the foregut, normally devoid of this protein, and thus interfere with determination of cell fate, resulting in the induction of intestinal rather than gastric differentiation in a subset of these cells. Conversely, fresh expression of CDX2 in differentiated parietal cells suggests cellular transdifferentiation, with loss of gastric marker expression and gain of intestinal markers.

Other mouse models have been shown or suggested to exhibit aberrant development of an intestinal phenotype in the stomach. The gastrin knockout mouse shows achlorhydria and develops intestinal metaplasia, with CDX2 expression, and gastric tumors[32,33]. Homozygous mutation of the SHP2-binding site within the interleukin (IL)-6 family receptor gp130 led to the development of two metaplastic lineages, spasmolytic polypeptide-expressing metaplasia (SPEM) and intestinal-like cells, as determined by the presence of acidic mucins and clear brush border morphology, but with no evidence of goblet cell differentiation[34]. Early stages of intestinal transformation of the fetal stomach are found in both Sonic Hedgehog homozygous null[35] and Gli3 null embryos, which lack this downstream effector of Hedgehog signaling[36], as assessed by alkaline phosphatase activity. However, these changes do not have an overall impact on gastric differentiation. Finally, intestinal differentiation with associated goblet cells and expression of CDX2 appear in subcutaneously grafted gastric cells derived from $Runx3^{-/-}$ mouse fetuses[37]. The same genotype in another mouse strain results in the loss of chief cells, SPEM, and an intestinal phenotype with CDX2 expression, without apparent inflammation and with increased malignant potential[38].

CDX2 SEEMS LIKELY AS AN ONCOGENE IN GASTRIC CANCER

CDX2 may have a unique role compared to other CDXs, showing characteristics of both an oncogene and a tumor suppressor[39-41]. Many researchers report that CDX2 is an inhibitor of cancer cell growth. Cell growth inhibition by CDX2 is associated with significant cell cycle arrest at the G_0/G_1 phase and CDX2 suppresses cell proliferation by controlling the G_1 and S checkpoints and inducing a specific block in cell cycle progression, after which the cells are not committed to complete the rest of the cell cycle. Many genes that are regulated in a cell-specific manner have CDX2-binding sites as their promoters, and in some cases CDX2 induces their expression directly. Some of these gene products play a direct regulatory role in the cell cycle, for example, Cdc2 and cyclin E[42,43]. Moreover, CDX2 was also forced to express by IL-6, tumor necrosis factor-α and IL-1β[44,45]. A further study showed that CDX2 promoter activity is increased by IL-6 in a MEK/ERK and phosphoinositide 3-kinase (PI3K)-dependent manner, and deletion of CDX2 binding sites in the promoter sequence results in loss of IL-6-induced promoter activity[46]. IL-6 increases CDX2 protein expression in gastric intestinal metaplasia cells that is sufficient to induce cell death. Enforced expression of CDX2 *in vitro* causes apoptosis in several cell types[6,47]. In addition, apoptosis induced by PTEN upregulation in gastric cancer cells has been shown to be dependent on CDX2, by triggering PI3K/Akt inactivation. Therefore, it was surprising to find that gastric expression of CDX2 alone was sufficient to induce intestinal metaplasia in mice, and that these mice represented a powerful tool to investigate the molecular mechanisms that promoted intestinal metaplasia[14]. Moreover, as gastric cancer in humans is often preceded by intestinal metaplasia, the phenotype described here strongly suggests involvement of CDX2 in the initiation of the process leading to intestinal neoplasia of the gastric mucosa. Several lines of evidence suggest that CDX2 has the potential to function as an oncogene in gastric carcinoma, promoting the proliferation of cells beyond their normal constraints[4,5].

For some time, this apoptotic activity of CDX2 was thought to be similar to that described for another cancer-related protein, c-Myc[48,49]. Elevation of c-Myc occurs in many tumors, resulting in potent growth promotion[50]. This effect of c-Myc can, however, only occur if the cell is also receiving appropriate survival signals, for example, leptin[51]. If not, deregulation of c-Myc will cause programmed cell death[52]. This model, however, does not completely hold true for CDX2 because mutants of CDX2 have been described, which although unable to promote cell cycle progression, retain the ability to induce programmed cell death[53]. In summary, it appears that *CDX2* acts as an oncogene in gastric cancer.

CDX2 INDUCES DRUG RESISTANCE IN GASTRIC CANCER

Regenerating protein (Reg) Ⅳ is a small, 17-kDa secreted C-type lectin that is expressed in normal enteric neuroendocrine cells and some goblet cells[54]. Reg Ⅳ is expressed in approximately 37% of gastric cancers and is detectable in the sera of approximately 36% of gastric cancer patients. Expression of Reg Ⅳ is a marker for prediction of resistance to 5-fluorouracil-based chemotherapy in patients with gastric cancer[55]. Oue *et al*[56] showed that endogenous CDX2 and Reg Ⅳ expression was correlated in gastric cancer cell lines and primary tissue, and gastric intestinal metaplasia. In addition, using an endoplasmic-reticulum- regulated form of CDX2 led to rapid induction of Reg Ⅳ expression after 4-hydroxytamoxifen treatment. Reporter gene assays revealed an important role for consensus CDX2 DNA binding elements in the Reg Ⅳ promoter region in its transcription, and subsequent chromatin immunoprecipitation assays showed that CDX2 bound directly to the Reg Ⅳ promoter[47]. These results indicate that CDX2 protein directly regulates Reg Ⅳ expression in gastric cancer and intestinal metaplasia of the stomach. Reg Ⅳ may exert its function *via* the epidermal growth factor receptor (EGFR) signaling pathway in gastric cancer. Overexpression or silencing of Reg Ⅳ influences the level of EGFR phosphorylation[57]. The EGFR signaling pathway plays an important role in the normal physiological function of cells, such as apoptosis, migration and differentiation. The signaling pathways downstream of EGFR are also central to the biology of gastrointestinal cancer. A major recent discovery has been that two major pathways mediate signal transduction through EGFR: the RAS/RAF/MAPK/ERK and the PI3K/AKT/PTEN/mTOR pathways[58]. Forced expression of Reg Ⅳ in gastric cancer cell lines also induces expression of the phosphorylated form of EGFR, Bcl-2, Bcl-XL, survivin, and the phosphorylated form of AKT[57]. Therefore, this indicates that CDX2 protein directly regulates Reg Ⅳ expression, and Reg Ⅳ activates the EGFR/Akt/AP-1 signaling pathway to improve the survival rate of cancer cells. The intestinal phenotype of gastric cancer frequently expresses EGFR[59], therefore, it is suggested that this Reg-Ⅳ-activated pathway plays an important role in this subtype of gastric cancer.

Besides, CDX2 also induces expression of the MDR1 gene by which CDX2 directly regulates expression of the gene through binding to elements in the promoter region[5]. In fact, it has been reported that postoperative chemotherapy is not beneficial for patients with intestinal phenotype gastric cancer[60]. Taken together, it is possible that in intestinal phenotype gastric cancer, expression (or ectopic expression) of CDX2 induces Reg Ⅳ and MDR1 expression, resulting in an increase in drug resistance.

CDX2 IS A USEFUL MAKER FOR FUTURE DRUG AND GENE THERAPY IN GASTRIC CANCER

Whether CDX2-positive expression can be considered as a prognostic factor for gastric cancer has been in dispute for a long time. Several investigators reported that CDX2 was an independent prognostic indicator for gastric carcinoma[61,62]. However, we showed that no significant correlation could be determined between CDX2 and clinicopathological parameters such as tumor size, invasion and lymph node metastasis in gastric cancer[63]. This suggests that CDX2 does not affect the progression of human gastric cancer. These conflicting results were likely due to small sample sizes. Meta-analysis has recently been applied to identify prognostic indicators in patients with malignant diseases[64,65]. Recently, we carried out a meta-analysis that is believed to be the first study to estimate systematically CDX2 expression and its relationship with clinicopathological characteristics and 5-year survival rate of gastric cancer patients. The results indicated that CDX2 overexpression was significantly associated with sex, lower clinical stage, tumor differentiation, lower rate of vascular invasion and lymph node metastasis, as well as higher 5-year survival rate[66]. Several investigators have reported that CDX2 expression is associated with specific morphological and mucin phenotypes of gastric epithelial dysplasia, and decreased progressively with advanced gastric cancer stage, suggesting a possible tumor suppressor role for CDX2[67-69]. However, sample sizes in the meta-analysis were too small, and whether CDX2-positive expression is significantly associated with good prognosis in patients with intestinal phenotype gastric cancer remains to be fully investigated in the future.

CONCLUSION

Ectopic expression of CDX2 occurs in the stomach and promotes intestinal metaplasia of the mucosal epithelial cells, which is an important early event in gastric tumor formation. In addition, CDX2-positive gastric cancer patients also have a higher 5-year survival rate than CDX2-negative patients. Therefore, CDX2 may be an important factor that affects the prognosis of gastric malignant tumors. CDX2 has attracted increasing interest because of its importance in modulating various cellular processes in cell growth or survival, differentiation and apoptosis *via* the regulation of gene expression. Even minor changes in nuclear CDX2 levels and/or its activities may have a significant effect on gene regulation, and thereby cellular responses, during disease pathogenesis and treatment. Therefore, an understanding of the regulatory mechanisms is of importance in intestinal phenotype gastric cancer. As few studies have reported the relationship be-

tween clinicopathological parameters and CDX2 in intestinal phenotype gastric cancer, large-sample clinical studies are needed. Elucidation of the CDX2/MDR1/Reg Ⅳ pathway is a potentially important advance in molecular oncology. In view of the high frequency of *CDX2* mutations in human gastric tumors, new and/or existing pharmacological agents directed against components of this pathway may have therapeutic benefit.

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ISSN 1007-9327