



## Chemotherapy Sensitivity of Gastric Cancer

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### Keywords

ATP-Binding cassette transporters; Chemotherapy; Chemoresistance; Chemosensitivity; Stomach neoplasm; Stem cells; MiRNA

### Introduction

Gastric cancer is one of the most common and fatal malignancies in East Asia despite decreased incidence in the West [1]. It was estimated that 986,600 new cases were diagnosed in 2008, which is the fourth leading form of cancer and accounts for more than 8% of total cancers [2]. The patients of early diagnosed disease can benefit, even get long survival, from the local resection with lymphadenectomy, especially D2 gastrectomy. But the high mortality rate for gastric cancer remains as an important problem which is due to increased advanced cases of relapse and metastasis after gastrectomy. Adjuvant therapies major in chemotherapy and radiotherapy were paid more and more attention. The efficacy of adjuvant chemotherapy for gastric cancer, whether neoadjuvant chemotherapy or postoperative chemotherapy, was testified by more clinical studies including perioperative chemotherapy [3] and postoperative adjuvant chemoradiotherapy [4], for improving disease-free survival and overall survival. However, chemotherapy resistance is another popular question for metastatic gastric cancer who receives multimodal treatment. Therefore, what is the mechanism of chemotherapy resistance and how to resolve the chemotherapy resistance are the key approaches to improve disease-free survival and overall survival and to decrease mortality rate for gastric cancer patients.

Chemotherapy resistance is usually divided by two classes that is inherent resistance and acquired resistance and acquired chemotherapy resistance accounts for greater than 90% of failed treatments in advanced cancer patients, especially for gastric cancer [5]. The causes to chemotherapy resistance could be due to either genetic or epigenetic factors, such as aberrant expression of drug resistance-related gene, proteins and signaling pathway in cancer stem cells and miRNAs level changes, except some biological metabolic enzymes, including thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), thymidine phosphorylase (TP), and orotate phosphoribosyltransferase (OPRT) for 5-FU, which can affect chemotherapy efficacy on some degree. In this review, the aberrant expression gene, proteins and signaling pathway in cancer stem cells and the role of microRNA (miRNA) in anticancer drug resistance will be explored in light of current knowledge.

### Chemotherapy Sensitivity and Cancer Stem Cell

Chemotherapy sensitivity is opposite to chemotherapy resistance, furthermore either is increasing one is decreasing. So we will obtain the higher chemotherapy sensitivity by overcoming the chemotherapy resistance. The CSC hypothesis was thought inevitably when speaking of the chemotherapy resistance. Because all of us knew that CSCs are small part differentiated cell types of heterogeneous mixture which possesses the properties of resistance to toxic agents, unlimited self-renewal and asymmetric cell division. The accurate mechanisms causing chemotherapy resistance in CSCs are still poorly understood, but numerous studies have demonstrated that purported CSCs are more resistant to chemotherapy than non-CSCs [6]. There are CSCs or CSC like cells also in gastric cancer tissues or their cell lines like other cancers such as human acute myeloid leukemia, breast and brain tumors [7-9].

The CD44<sup>(+)</sup> gastric cancer cells had been isolated and tested that possessed the properties of self-renewal and the ability to produce differentiated progeny by now. In addition, the CD44<sup>(+)</sup> gastric cancer cells demonstrated properties of chemo- and radio-resistance. What's the cause of chemo-resistance in the CD44<sup>(+)</sup> gastric cancer cells? They may be intrinsically resistant to chemotherapeutic agents due to the expression of ABC transporters [10], although there are no related studies explored the relationship between the expression of ABC transporters and the CD44<sup>(+)</sup> gastric cancer cells

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Received Date: 26 Dec 2016

Accepted Date: 03 Apr 2017

Published Date: 14 Apr 2017

#### Citation:

Zhang H, Fan Q, Wei X. Chemotherapy Sensitivity of Gastric Cancer. *Clin Surg*. 2017; 2: 1400.

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resistance. Another study found that the CD44<sup>(+)</sup> stem cells isolated from cancer tissues with magnetic beads have resistance to 5-FU via high expression ALDH and the stronger the resistance, the higher the expression of ALDH. CD44<sup>(-)</sup> cells have low expression of ALDH. This suggests that ALDH are the major cause of drug resistance in the CD44<sup>(+)</sup> gastric stem cancer [11]. Furthermore, gastric cancer cells with high expression of ALDH have stronger resistance to 5-fluorouracil (FU) and cisplatin [12,13]. But resistance to 5-FU is studied in SP cells which were thought of another means of gastric cancer stem cell [14]. These results suggest that, relative to non-SP cells, SP cells have a significantly higher expression of ABCG2 and the anti-apoptotic protein Bcl-2. And the chemotherapy resistance characteristics of SP cells may be derived from their high expression levels of anti-chemotherapy proteins. Similar findings were also demonstrated by Fukuda "et al." [15], whose study revealed that SP cells in the gastric cancer cell strain MNK45 exhibited significantly higher resistance to cisplatin chemotherapy drugs than non-SP cells. The CSCs isolated from gastric cancer cell lines using the SP method have stronger drug tolerance for chemotherapy [16]. Whether MDR1 was involved in the chemotherapy sensitivity regulation of gastric cancer stem cell or not, there is no results showed by now. And there was no really causes found in whether the CD44<sup>(+)</sup> gastric cancer cells or SP gastric cancer stem cell.

Although there are some consistence of between the CD44<sup>(+)</sup> gastric cancer cells resistance and SP gastric cancer stem cell resistance, the cause to resistance of the two subpopulation cells is not universal. According to these findings, we can infer that the cause to gastric cancer cells resistance is not single factor such as some genes or proteins involved. Gastric cancer stem cells may provide the subpopulation cells with elementary signals such as Notch, PI3K/AKT and Hedgehog to obtain the resistance.

SomestudieshadalsofoundthatincreasesinAktactivityinresponse to chemotherapy. Treatment of human ovarian cancer cell lines with cisplatin increased Akt activity without measurable cytotoxicity [17]. Hayakawa "et al." [18] used small molecule inhibitors and genetic approaches to verify that the induction of Akt activity by cisplatin was responsible for the observed chemotherapeutic resistance. Another study of E-Ras found that its relation with chemo resistance because activation of the PI3K/AKT pathway and the acquisition of EMT have been reported to be related to chemo resistance [19-21]. So we think that modulation of the PI3K/Akt pathway is a common observation with the administration of chemotherapy, and suggest that in some cases, modulation of Akt activity may be directly responsible for the response to chemotherapy of gastric cancer. Notch signaling is another critical pathway for regulating cell-to-cell communication during embryogenesis, cellular proliferation, differentiation and apoptosis [22]. Targeting CSCs with inhibitors of Notch signaling promotes cell differentiation, increases sensitivity to chemotherapy, and reduces metastasis [23]. Dysregulated Notch signaling has been observed in many human cancers. Recently, it has been shown that Notch signaling is activated in human breast cancer, with the accumulation of Notch1 intracellular domain in tissue [22]. Notch signaling in breast cancer has also been shown to activate Akt [24] and surviving [25], which may be involved in mediating chemotherapy resistance. But there is no study results showed that Notch signaling had involved in mediating chemotherapy resistance of gastric cancer. This is not the only one result which involved in the chemotherapy of gastric cancer stem cells, another signaling Hedgehog was also tested which involved the same action. Clinical tumor samples from

a phase II trial of chemotherapy with or without vismodegib (VIS) for advanced gastric cancer were analyzed for CD44<sup>(+)</sup> gastric cancer tissue. In the chemotherapy alone group, high CD44 expression was associated with decreased survival, whereas in the chemotherapy plus VIS group, high CD44 expression was associated with improved survival [26]. And VIS is the inhibitor of Hedgehog, so we can think that Hedgehog signaling inhibition of overcome the chemotherapy resistance of CD44<sup>(+)</sup> gastric cancer tissue and cells.

## Chemotherapy Sensitivity and miRNA

MiRNAs are small, 19-23 nucleotide-long, highly conserved non-coding RNAs and widely expressed in all tissues and cells. They regulate target genes which are involved in development, apoptosis, metabolism and human diseases including cancers. More and more researches have shown that miRNAs had taken part in almost every step of carcinogenesis and progression. So they were broadly used in not only diagnosis and therapy of carcinoma but also determining or predicting of chemotherapy and radiotherapy resistance. How miRNAs affect the drug sensitivity of different cancer cells is still unknown. Some studies found that the function of the chemoresistance related miRNAs may be disturbed by mutation, misexpression or ectopic processing of miRNA genes, causing ectopic expression of target proteins which are involved in cancer drug responses and resulting in changes of chemosensitivity in many kinds of cancers [26-29].

A study reported that miR-138 might mediate drug resistance, at least in part, through regulation of MDR1 in the vincristine induced, multidrug-resistant leukaemia cell line HL60/VCR [30]. Another study found that the expression of miR-331-5p and miR-27a was inversely correlated with MDR1 expression. Transfection of exogenous miR-27a or miR-331-5p, or a combination of these two miRNAs, down-regulated MDR1 and increased sensitivity of the K562-resistant cancer cells to DOX [31]. That miR-21 may regulate other target mRNAs in this cell line but not PTEN and that miR-21 has multiple downstream effects potentially contributing to its impact on anticancer drug sensitivity in a lung cancer cell line using Western Blot assessment of target protein and mRNA [31]. Functional analysis of the role of miR-34a in EWS cells indicated that when miR-34a expression was enforced, cells were less proliferative, less malignant, and sensitized to DXR and VCR [32]. Not all other tumors have chemoresistance related miRNAs, but some chemoresistance related miRNAs were found in gastric cancer. Xia and colleagues reported that 10 out of 342 human miRNAs (Let-7a, miR-15b, miR-16, miR-17-5p, miR-20a, miR-23b, miR-106a, miR-106b, miR-196a, miR-320) were downregulated more than 2-fold in a multidrug-resistant gastric cancer cell line, another 2 miRNAs were upregulated more than 2-fold (miR-302b, miR-492). Furthermore, a decrease in Bcl-2 protein level but not mRNA level was detectable in precursor transfected cells indicating a direct inhibition of Bcl-2 by miR-15b and miR-16 [33]. Our study results showed that there are aberrant miRNAs in SP cells of gastric cancer cells. But we didn't investigate the relationship between the aberrant miRNAs and chemoresistance of gastric cancer SP cells [34], so it is very necessary to explore whether the aberrant miRNAs involved in chemoresistance of gastric cancer SP cells. Kun Liu "et al." [35]. found that decreased let-7i expression was significantly associated with poorer response to chemotherapy and shorter OS of patients with GC. They thought let-7i might be a novel therapeutic target for modulating chemotherapeutic sensitivity and a potent biomarker for predicting tumor response and survival

in advanced GC patients and in p53-mutant human gastric cancer cells which express high levels of Bcl-2 and very low levels of miR-34, restoration of miR-34 (a-c) expression resulted in a downregulation of Bcl-2, Notch1 and HMGA2 – in slightly differing extents. Furthermore, a significant increase in caspase-3 activity was observed. Mir-34 was thereby demonstrated to be involved in the network and tumor suppressing pathways of p53 as a downstream target of p53 [36]. Another study through investigating drug resistance to cisplatin and 5-fluorouracil in 90 patients with gastric cancer and comparing patients' miRNA expression before and after chemotherapy, Kim "et al." [37] found that high expression of let-7g, miR-342, miR-16, miR-181, miR-1 and miR-34 indicated sensitivity to chemotherapy, and high expression of miR-518f, miR-520a, miR-520d, miR-519e, miR-363 and miR-517 indicated resistance to chemotherapy. By predicting miRNAs, they used a new method for choosing chemotherapy regimen and monitoring its effects, and even reversing the chemotherapy resistance through transfecting specific pre-miRNA. MiRNA-15b and miRNA-16 are downregulated severely in the multidrug resistant gastric carcinoma cell line SGC7901/VCR. By improving miRNA-15b and miRNA-16 expression levels, sensitivity to vincristine was enhanced. So they can predict the occurrence of resistance to chemotherapy and radiotherapy [33,37,38]. In fact, miRNA regulation of chemotherapy resistance in gastric cancer was a many crisscross network consisted of functional genes and cell signaling pathways. Some of them miRNA were found by now, there are much of work need to be done future [39].

## Perspectives

Gastric cancer patients will obtain more benefit from the treatment except the operation involved, especially more efficient chemotherapy in future. So it is essential to explore and understand exact and key mechanisms of chemotherapy resistance to make better of the survival and life quality of gastric cancer patients.

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