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High-Level of Notch 1/Jagged 1 Level up Regulated Chemo-Resistance of Cisplatin in NSCLC

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ABSTRACT

Lung cancer is the top ranked cause of cancer death worldwide and lung cancer alone. Platinum-based chemotherapy increase survival rates and improves the life quality in patients, and many suggested pathways of the efficacy of cisplatin in treatment of NSCLC. This study aimed to identify the signaling pathway of Notch 1/ Jagged 1 in mechanistic action of cisplatin treatment of NCSLC. Fifty patients having NSCLC were enrolled in this study include 37 patient's male while females were 13 patients, with a median age of 42.5 years (range, from 33 to 76 years). Clinical factors such as sex, age, tumor site, size and grade, metastasis, and T.N.M. stage, were collected. Immunohistochemistry including the use of the method of avidinbiotin peroxidase on all tissues, while patient blood sample use for total RNA and reverse transcribed and Kaplan-Meier method used for plotted the survival curves.

The degree of Notch 1/Jagged1 protein-expression were mainly more in patient include male more than the female ($P<0.05$). It's clear; the expression levels of Notch1 proteins were in relation with grades of tumor and its pathological state. The expression levels of Notch 1/Jagged1 were strongly related (high or low) in patients not respond to chemotherapy and tumor progress or metastasis disease to lung or brain. The survival rate of patients with low expression Notch 1/Jagged 1 whom treated with cisplatin-based chemotherapy was 100% during 8-months of follow up. High Notch-1/Jagged-1 levels expression invert a poor prognosis of NSCLC patients and may represent a new strategy to decrease resistance of cisplatin based treated NSCLC patients.

Keywords: Cisplatin, NSCLC, Notch 1/Jagged1, Metastasis, Chemotherapy

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Introduction

Recently, after cardiovascular diseases, cancer is a main source of death in the wide world. every year, there is a million and a half people were diagnosed with cancer and more than half of a million-people died from this disease, which makes it a noteworthy general medical issue on the planet[1, 2].Most predominant cancers lead to deaths are lung, breast, prostate, colorectal and pancreatic cancer. With each other, in the United States these five types it forms about fifty percent of all cancer deaths in 2009[3].Most related death cancer type is lung cancer in the world and it alone with NSCLC as the main cause of cancer related death about 160,000 killed more than all other 4 cancers together[4]. So, the survival rate of lung cancer is very low and accounted about 8%-15%. While this survival rate in early-stage of this disease increases to 40%-55% after surgery[5, 6].Smoking becomes fundamental driver of lung cancer, in charge of over 80% of cases. Hazard factors including exposure to asbestos, arsenic, radon and indoor air contamination lead to the principally overweight of non-smoking related lung cancer in females[7].Acquired resistance of cisplatin treatment is yet a basic issue in clinical administration in the cancer patients. Late examinations have demonstrated that one of cisplatin resistance mechanisms related to Notch expression. Notch 1 higher than normal related to cisplatin resistance in Head and neck squamous cell carcinoma (HNSCC) patient in some publication[8, 9]. On the other part, secretase inhibition (GSI) mixed with cisplatin increase colorectal cancer cell death. Human ovarian cancer enhanced chemo-resistance to cisplatin in high expression of Notch 1[10].The proposal supported by these results that inactivation of Notch pathway could be a novel strategy in cisplatin chemotherapy. Jagged 1 was first identified as in a ligand that can be activate Notch receptors when it was cloned in the mammalian rat in 1995[11, 12].Jagged 1 gene is expressed in multiple organ systems in the body and its mutations causes the autosomal dominant disorder called Alagille syndrome (ALGS)[13]. ALGS is a disruption of genes lead to liver, heart, kidney, and other organs disorders.

Infancy or early childhood generally becomes evident to this disorder. Jagged 1 is a well-characterized main regulator of liver development and regeneration[14]. Jagged 1 expression has been observed to be up regulated and its levels inversely connected with patient's survival in breast-colon and cervical cancers[15]. Also, absence of Jagged 1 in human prostate malignant cells decrease invasion of it and in vivo cancer development. Jagged 1 is distinguished as a potential-metastasis-promoting gene related with poor survival through involving metastasis in lung cancer[16, 17].Lung adenocarcinoma sub-classification histopathological is challenging. So, in one research pathologists can sub-classification in only 41% cases of lung adenocarcinoma[18]. Nine genetic markers costly effective, Jagged 1 is one of them utilized to differentiate with very high accuracy all sub-types of non-small cell lung cancer[19]. The main objective of this study is to identify the signaling pathway of Notch 1/ Jagged 1 in mechanistic action of cisplatin treatment of NCSLC.

Methods and Patients

Study design

Fifty patients having NSCLC were enrolled in this study. They accomplished to the Al-Furat cancer center/Najaf between November 1, 2016 and July 1, 2017. Before receiving preoperative treatment, all samples were collected from patients. The study included 37 patients male while females were 13 patients, with a median age of 42.5 years (range, from 33 to 76 years). This study was implemented by the Ethics Committee of Kufa Medical College / University of Kufa and in conformity with the Ethical Guidelines of the Helsinki Declaration of 2004. From each patient or his / her legal relative the written parameters were obtained. Clinical factors include sex, age and size, site and grade of cancer were collected. There are 24 cases have cancer metastasis and have complications like SVC obstruction (n=3), brain tumor (n=2) and by MRI and pathological-analysis lymph node metastasis detected (n=12).

Samples collection

The samples were collected from patients who diagnosed as NSCL, and the serum refrigerated at − 20°C until used for further analyses, while, tissue specimens were collected from histopathological lab where the patients diagnosed as NSCLC.

Immunohistochemistry and Evaluation of Staining

Immunohistochemistry is very delicate process because it depends on the formation of conjugated compound (avidinbiotin peroxidase) on all samples. The specimens were placed in xylene material to get rid of adherent paraffin, after that the tissues were treated by different strengths of alcohol solutions to do dehydration process. All these processes were done before the inhibition of the activity of the conjugated enzyme(peroxidase) by using 0.5 percent of hydrogen peroxide in specific alcohol solution (CH3OH) for about ten minutes. Not exact conjugation was inhibited by expose sections with 10 % normal goat solution in po_4 buffer solution for one hour at room temperature. Prevented washing and sections were incubated with anti-Notch-1 or anti-Jagged-1 (1 ∶ 50) in po_4 buffer solution at 4 °C over-night in a moist container after that the sections observed with Imunoglobine G for two hours at room temperature and detection by complex of (Streptavidin peroxidase). The indicative color is brown it is show the activity of peroxidase that occurred by section incubation with 0.1% 3,3-diaminobenzidine in PO_4 buffer solution with peroxidase hydrogen 0.03% for 10 min at 25 °C. The samples of tissue were scored autonomously by couple of pathologists without the clinic pathology and result of the patients utilizing an immune reactivity result framework portrayed already[15].Depending on the results, Classification all NSCLC specimens into two groups: the (result 0–4) low expression group while (result 5–12 score) high expression group.

Real time Reverse Transcription P.C.R.

All RNA has been extracted and reverse transcribed. With PCR we use these primers:

Notch 1, forward primer (5′-CACCCATGACCACTACCCAGTT-3′) and reverse primer (5′-CCTCGGACCAATCAGAGATGTT-3′);

Jagged 1, forward primer (5′-AAGGACGTGGCCTCTGGT-3′) and reverse primer (5′-TCAGGCTCTCACCCTTGG-3′);

ß-acting, forward primer (5′-AAATCCCATCACCATCTTCC-3′) and reverse primer (5′-TCACACCCATGACGAACA-3′). Evaluation of primers by a virtual PCR, and concentration of the primer was optimized to avoid formation of primer dimer. And to avoid nonspecific amplification the dissociation curves were evaluated. Rt-PCR amplifications were done in the Mx4000 Multiplex QPCR System (Strata gene, La Jolla, CA) using 2×SYBR Green PCR Master Mix (Applied Biosystems). Also, analyzed and normalized data by the ß-acting expression in each blood sample20.

Table 1. Primer sequences of the different genes with their respective product sizes.

		Size of PCR
Gene	Primer Sequences	Product (bp)
ß-actin	F: 5′- AAATCCCATCACCATCTTCC-3′	437
	R: 5′- TCACACCCATGACGAACA-3′	
Notch 1	F: 5′-CACCCATGACCACTACCCAGTT-3’	490
	R: 5′-CCTCGGACCAATCAGAGATGTT-3′	
Jagged 1	F: 5′-AAGGACGTGGCCTCTGGT-3’	436
	R: 5′-TCAGGCTCTCACCCTTGG-3′	

Statistical analysis

Statistics were conducted with the SPSS Statistics program (Windows version 9.0). To assess whether the observed differences are statistically significant (mean ± SD, ANOVA), the related or non-related t tests are utilized where suitable. Kaplan-Meier method applied for plotted the survival curves, the significant p value (two sided) is less than 0.05.

Results

Correlation of Notch 1/Jagged 1 expression levels with tumor clinic pathological parameters

The levels of Notch 1/Jagged 1protein expression were significantly higher in male patients than in female patients (P<0.05). Higher levels of Notch 1/Jagged 1 protein expression were significantly associated with poorly differentiated tumors and advance stages of tumors mass and regional lymph node (LN) (P<0.05). Also, highly correlation was noticed with patient's age and pathological stages of NSCLC tumor as shown in table 2.

Table 2. Correlation of expression levels of Notch 1/Jagged 1 protein with tumor clinic pathological parameters

Clinic pathological parameters	Levels of Notch 1/Jagged 1 protein		
	High	Low	*P*
Age			
<30 years	1	1	0.0951
≥ 30 years	38	10	0.0031
Gender			
Male	26	5	0.0026
Female	13	6	0.0021
Stage			
I	0	4	0.0011
II	0	8	0.0021
II	1	14	0.0031
IV	22	1	0.0022
Tumor grade			
1	0	2	0.0031
2	0	4	0.0011
3	9	8	0.0021
4	24	3	0.004

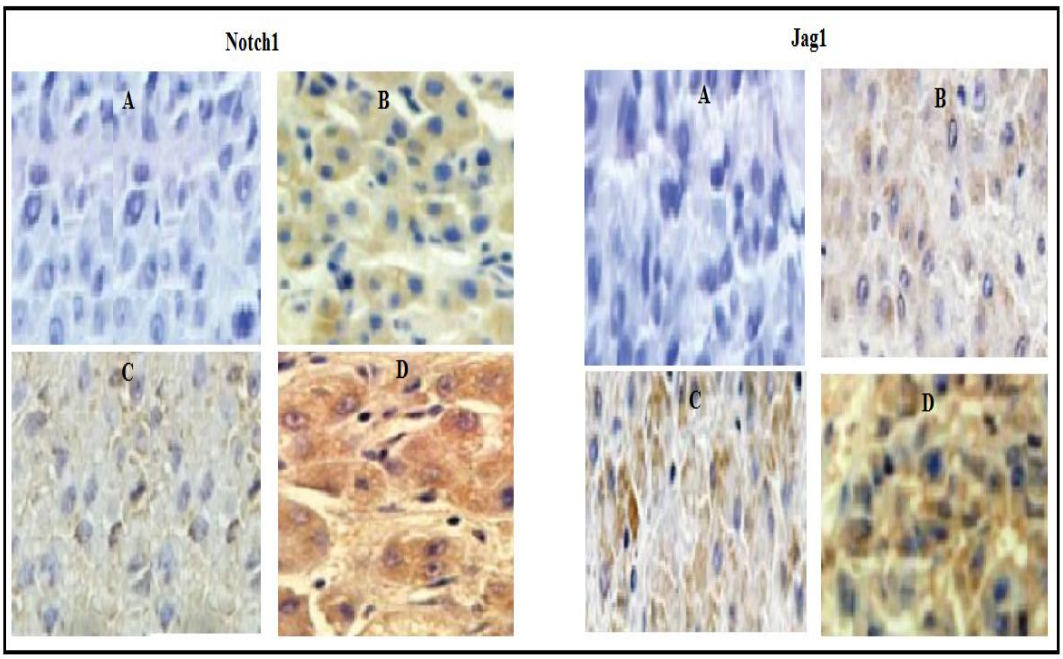


Figure 1. Expression of Notch 1 and Jagged 1

Over-Expression of Notch 1/Jagged 1 correlated with cisplatin response

The Notch 1/Jagged 1 expression levels were strongly related (high or low) with patients not respond to progress or metastasis disease to lung or brain as in Figures 1 and 2. In contrast, low expression levels of Notch 1/Jagged 1 were detected in the samples with good response to cisplatin-based protocol chemotherapy.

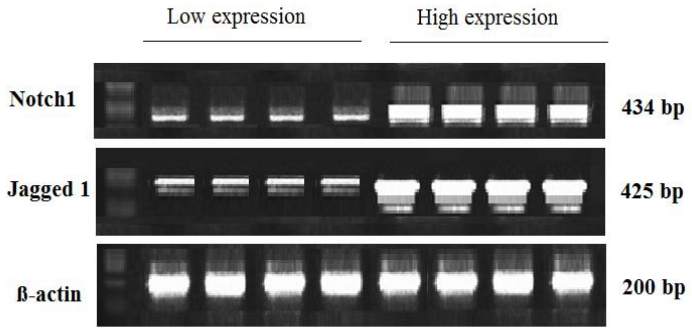
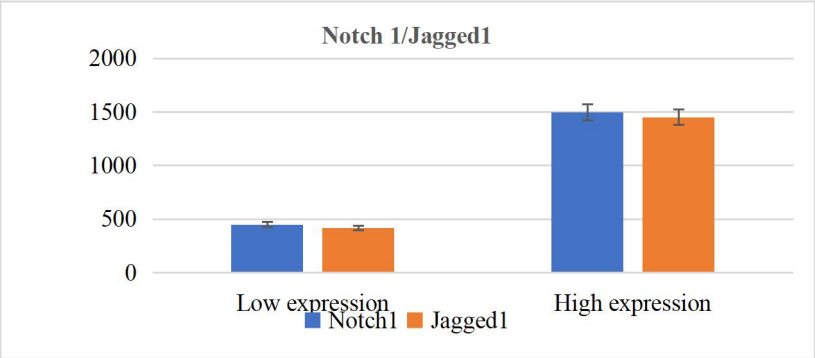


Figure 2. Role of the Notch 1 signaling pathway in failure of cisplatin treatment

The levels of Notch 1 and Jagged 1 were determined by quantitative polymerase chain reaction. B-acting served as an internal control. Data are expressed as mean ± standard error, $n = 50$; $^{*}P < 0.05$ versus Low expression.

Figure 3. Gel electrophoresis of PCR products. Notch 1 = 434 bp DNA ladder; Jagged 1 = 425 bp; β-acting gene control= 200pb



Low survival rate with high expression of Notch 1/Jagged 1

The survival rate of patients with low expression Notch 1/Jagged 1 whom treated with cisplatin-based chemotherapy was 100% during 8-months of follow up. While patients with high expression of Notch 1/Jagged 1 whom treated with same protocol with cisplatin-based chemotherapy had survival rate 57% through same treated period. The survival rates of patients were estimated by the Kaplan-Meier method and compared by using the log-rank test as in Figure 4.

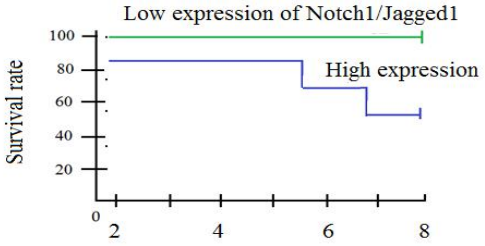


Figure 4. Effect of Notch 1/Jagged 1 on survival rate in patients with NSCLC.

Discussion

It is evident that Notch 1/Jagged 1 signaling pathway plays important roles in the pathogenesis of tumor activity and its microenvironment establishment (vascular invasiveness and immunological response)[21, 22].This signaling pathway may have deferent behavior in other tissue injury like in myocardial ischemia and reperfusion[23, 24].However, the use of complete Notch inhibitors was resulting in many clinical adverse events like gastrointestinal toxicity[25]. Furthermore, Crosstalk between many other proteins signaling pathways especially vascular endothelial growth factor (VEGF) and Notch 1 plays important role with the immune system and cancer cells activity. Interestingly, this biological crosstalk makes Notch 1 and its ligands Jagged 1 good preclinical and clinical approaches for combination protocols therapy [26, 27]. Moreover, because of dual effects Jagged 1 (anti-apoptotic and pro-apoptotic), the use of blockade combination therapy may have highly successful results compared with standard chemotherapy that are obtained from preclinical study in ovarian, pancreatic malignant tumor, cervical cancer and lymphoma[28, 29].Previous studies reported that over expression of Notch 1 with or without Jagged 1 *in vivo* or *in vitro* may be responsible for upgrading activity of malignant tumor cells[30, 31]. The presented data showed that Notch 1 and Jagged 1 have more expression in high grade tumors. Clinically, it was also found that lung cancer metastasis had more expression of both Notch 1 and its ligand Jagged 1. This is consistent with other study results[32]. Furthermore, other research study considered the clinical relationship between response to treatment with chemotherapy in breast cancer and over expression of both proteins (Notch 1/Jagged 1), it was found that Notch 1 regulate the levels of ESR1 in ER-positive breast cancer and may be involved in signaling pathway in the tamoxifen resistance. Suggesting Notch signaling pathway may represent a potential therapeutic target for breast cancer therapy[33, 35]. In the present study, we demonstrated that up regulation of both Notches 1/Jagged 1 correlated with survival rate. The Kaplan-Meier estimator curve, showed that the mortality rate more with high levels expression of Notch 1/Jagged 1. Moreover, this high expression is also associated with lymph nodes involvement and generalized patient's fatigability. Moreover, the presented data showed that expression of Notch 1/Jagged 1 are predominant expressed in adeno-NSCLC more than squamous-NSCLC with unclear mechanism. While, other data showed more expression of Notch 1 were observed in small cell lung cancer with plural effusion and metastasis to brain[36, 37]. The protocol of chemotherapy is one of the standard methods of treatment in many cancers and failure to response to chemotherapy may be responsible for cancer patient's recurrence and ultimately death. The cancer cross-resistance to treatment with chemotherapy is frequently a major issue regarding the successful use of cancer chemotherapy[38, 39].The mechanistic pathway for this resistance of chemotherapy has many proposals, including over expression of many proteins like (ABCG2/BCRP) in breast cancer[40]. To our knowledge, this study first time investigate the correlation between the over expression of Notch 1/Jagged 1 and response to treatment in NSCLC patients with cisplatin base chemotherapy. In the current study, it demonstrated that Notch 1/Jagged 1 expression has positive correlation between high expression and unfavorable patient prognosis in NSCLC treated with cisplatin base therapy and suggest a unique mechanism for failure response to cisplatin as anticancer drugs in patients with NSCLC.

Conclusion

The results of the current study concluded that high levels of Notch 1/Jagged 1 expression were correlated with a poor prognosis of NSCLC patients. Furthermore, Notch 1/Jagged 1 will provide a new approach to follow up NSCLC patients. Targeting Notch 1/Jagged 1 signaling pathway may represent a new strategy to decrease resistance of cisplatin based treated NSCLC patients.

Significance statement

This study discovered the over expression of Notch 1/Jagged 1 mostly related with advance stage of lung cancer and resistance to cisplatin.

This study will help the researchers to uncover the critical areas of immunological signaling pathway of NSCLC that many researchers were not able to explore. Thus, a new theory on explained the chemo resistance of NSCLC may be arrived at.

Compliance with Ethical Standards

Authors declare that they have no conflict of interest.

Informed consent was obtained from all individual participants included in the study.

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Authors' contributions

Yousif NG, Al-Huseini LA, Jassim MN, Sadique AM contributed to sample collection and sample management. Hadi NR, Al-Amran FG contributed to study design. Data were generated by Jassim MN, data interpretation by Yousif NG, Al-Huseini LA and drafting of the manuscript by Al-Huseini LA, Yousif NG supervised the research and writing processes. All authors have contributed to the manuscript and approved the final version of the manuscript for submission.

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