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Research Paper

Somatic *FGFR3* Mutations Distinguish a Subgroup of Muscle-Invasive Bladder Cancers with Response to Neoadjuvant Chemotherapy

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ABSTRACT

The administration of neoadjuvant chemotherapy (NAC) preceding radical cystectomy benefits overall survival for patients with muscle-invasive bladder cancer (MIBC). However, the relationship between the genetic profiling of MIBC and NAC response remains unclear. Here, a mutation panel of six cancer-associated genes (*TSC1*, *FGFR3*, *TERT*, *TP53*, *PIK3CA* and *ERBB2*) and an immunohistochemistry (IHC) panel containing eight bladder cancer (BC) biomarkers (EGFR, RRM1, PD-L1, BRCA1, TUBB3, ERCC, ERCC1, aberrantly glycosylated integrin α3β1 (AG) and CK5/6) were developed. BC samples from patients who showed a pathologic response ($n = 39$) and non-response ($n = 13$) were applied to the panel analysis. *ERBB2*, *FGFR3* and *PIK3CA* exclusively altered in the responders group (19/39, 48.7%), in which *FGFR3* mutations were significantly enriched in patients with a response in the cohort (14/39, 35.9%; $P = 0.01$). Additionally, strong expression of ERCC1 was associated with a pathologic response ($P = 0.01$). However, positive lymph node metastasis ($P < 0.01$) and lymph-vascular invasion (LVI) ($P = 0.03$) were correlated with a non-response. Overall, the data show that *FGFR3* mutations and elevated expression of ERCC1 in MIBCs are potential predictive biomarkers of the response to NAC.

1. Introduction

Bladder cancer (BC) is one of the most common urological malignancies worldwide [1] (Ferlay, 2012) with an estimated 429,800 new cases and 165,100 deaths per year [2]. BC is clinically diagnosed into two major subtypes, non-muscle-invasive bladder cancers (NMIBCs) and muscle-invasive bladder cancers (MIBCs) [3]. NMIBCs have a low rate of progression to invasion (10%–15%) but show a high rate of recurrence (50–70%), and the five-year survival is ~90% [3]. MIBCs (stage T2 and above) have a less favorable prognosis, with a five-year survival <50% and a common progression to metastasis. Radical cystectomy with pelvic lymph node dissection remains the standard treatment, which has not improved for several decades, and new approaches to systemic therapy are urgently needed [2, 3].

To address recurrence and metastasis of bladder cancer, the concept of neoadjuvant chemotherapy (NAC) has evolved. After two to four cycles of chemotherapy, patients received surgery. The results of randomized and prospective studies demonstrated an overall survival (OS) benefit of 5–8% [4–6] compared with surgery alone. Although NAC improves pathological down-staging and OS, approximately only 15–40% of patients achieved a pathological response, defined as the absence of muscle-invasive disease and lymph node metastasis (<pT2 and pN0) [7]. Nonresponding patients, who are unlikely to derive a clinical benefit, are exposed to substantial toxicity and the potential delay of surgery [3, 5]. The identification of predictive NAC response biomarkers is critical to providing precision medicine to patients with MIBCs. Here, we

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Research in Context

Patients with muscle-invasive bladder cancers (MIBCs) are likely progressed to metastasis and have a five-year survival <50%. Neoadjuvant chemotherapy (NAC) has been demonstrated to have an overall survival benefit of 5-8% for MIBC patients. However, the relationship between genetic background and MIBC chemosensitivity remains debatingable. Yang et al. identified that the mutation of *FGFR3* and the elevated expression of ERCC1 were correlated with NAC response in MIBC patients.

demonstrated that mutation of *FGFR3* and strong expression of ERCC1 are correlated with NAC response in MIBC patients.

2. Materials and Methods

2.1. Study Design and Participants

Fifty-two MIBC patients were randomly selected for this NAC study between 2008 and 2017 from Renji Hospital, School of Medicine, Shanghai Jiao Tong University. Conventional NAC with a 21 d cycle of cisplatin and gemcitabine was administered to all patients in the study. Patients received cisplatin on d1 and gemcitabine on d1 and d8. Fifty-two patients were included in the cohort, in which 39 patients showed a pathologic response (partial response: ypT1, ypTa or ypTcis, $n = 33$; complete response: ypT0N0, $n = 6$), and 13 patients displayed a non-response (≥ ypT2).

2.2. Sample Preparation

The primary BC and matched peripheral blood samples for the cohort were obtained from Renji Hospital, School of Medicine, Shanghai Jiao Tong University with informed consent and approval by the Research Ethics Board of Shanghai Jiao Tong University. The genomic DNA from the tumor and matched peripheral blood samples was isolated according to the manufacturer's protocol (QIAGEN). Semi-quantitative PCR of *TERT, FGFR3, TP53, PIK3CA, ERBB2* and *TSC1* were performed using the former DNA templates with the primer sequences listed in Supplementary Table 1. All PCR products were examined by Sanger sequencing, and the putative SNPs for BC samples were selected according to the reference sequence of the matched peripheral blood samples.

2.3. Immunohistochemistry (IHC)

IHC was performed as previously described [8]. Briefly, sections (4 μm) were deparaffinized and rehydrated. After antigen retrieval, the sections were treated with 3% H_2O_2 solution, and incubated with

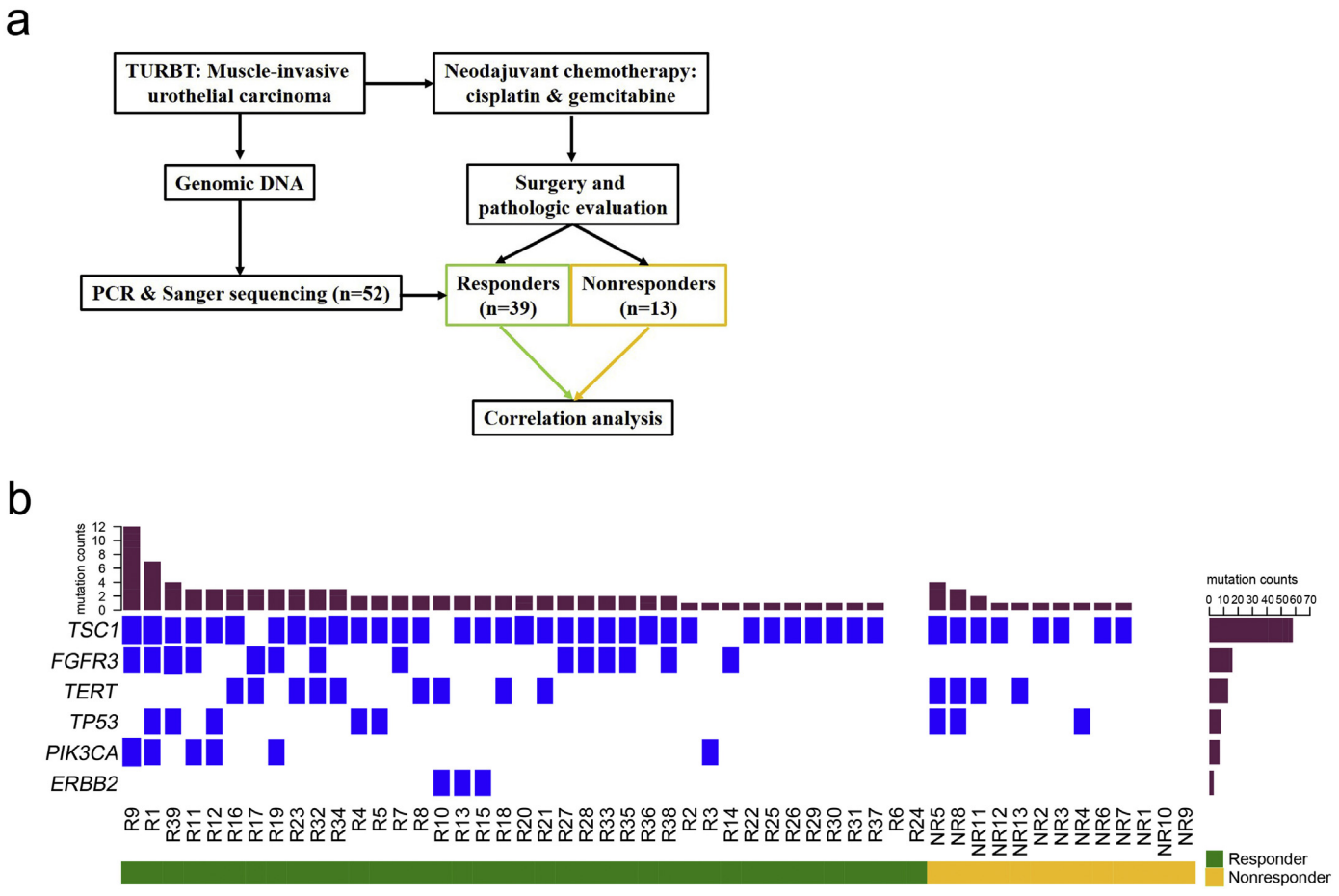

Fig. 1. Study design and mutation rates of key genes in fifty-two muscle-invasive bladder cancer patients. a. Fifty-two patients were split into responders and nonresponders based on their pathologic response to neoadjuvant chemotherapy. TURBT, transurethral resection of bladder tumor. b. The alteration landscape of the aggregate cohort ($n = 52$ patients) are displayed in the center. Each column represents a tumor, and each row represents a gene. *TERT, FGFR3, TP53, PIK3CA, ERBB2* and *TSC1* are listed on the left and the center panel is divided into responders (left and green) and nonresponders (right and orange). The mutation rates (top) and mutational frequency (left) are also summarized.

Table 1
Clinical characteristics of the bladder carcinoma patients.

	Total (52)	Nonresponder (13)	Responder (39)	*P* value
Female	10	0	10	0.175
Age	62.6	62.9	62.5	0.857
Follow-up	10.0	5.2	11.5	0.020
pT > 1	11	11	0	< 0.001
pN > 0	4	4	0	0.003
pCIS = 1	15	1	14	0.078
LV1 > 0	6	4	2	0.029
OS = 1	4	1	3	1.000
EGFR > 1	50	12	38	1.000
RRM1 > 1	46	10	36	0.580
PD-L1 > 1	44	12	32	0.560
BRCA1 > 1	48	10	38	0.134
TUBB3 > 1	51	12	39	1.000
ERCC1 > 1	48	9	39	0.011
BCMab1 > 1	30	5	25	0.196
CK5/6 > 1	0	0	0	1.000

10% bovine serum albumin for 30 min. Then, the sections were incubated with the primary antibody (EGFR, RRM1, PD-L1, BRCA1, TUBB3, ERCC1, aberrantly glycosylated integrin α3β1 (AG) or CK5/6) at 4 °C overnight, and incubation with corresponding secondary antibody and subsequently staining with a DAB kit (ZSGB Bio) were performed. The nucleus was counterstained with hematoxylin. The staining intensity was assessed by two independent experienced genitourinary pathologists using a 0–3 scoring system.

2.4. FGFR3 Mutation Status in Multiple Independent Cohorts

The *FGFR3* mutation status in The Cancer Genome Atlas (TCGA) urothelial bladder cancer dataset was determined using the TCGA data portal (http://cancergenome.nih.gov). The mutation frequencies of *FGFR3* in the Kim et al. and Guo et al. studies were obtained from the cBioPortal for Cancer Genomics (http://www.cbioportal.org).

2.5. Statistical Analysis

The correlation between genetic alterations and NAC response was analyzed using a Fisher's exact test. Analysis of the genetic alterations found in *TERT, FGFR3, TP53, PIK3CA, ERBB2* and *TSC1*, and the expression of EGFR, RRM1, PD-L1, BRCA1, TUBB3, ERCC1, AG and CK5/6 were performed using the Benjamini-Hochberg method and GraphPad Prism software version 5. The patient demographics, tumor characteristics and pathological findings were analyzed using the Mann-Whitney *U* test or Fisher's exact test. In the survival analysis, average FGFR3

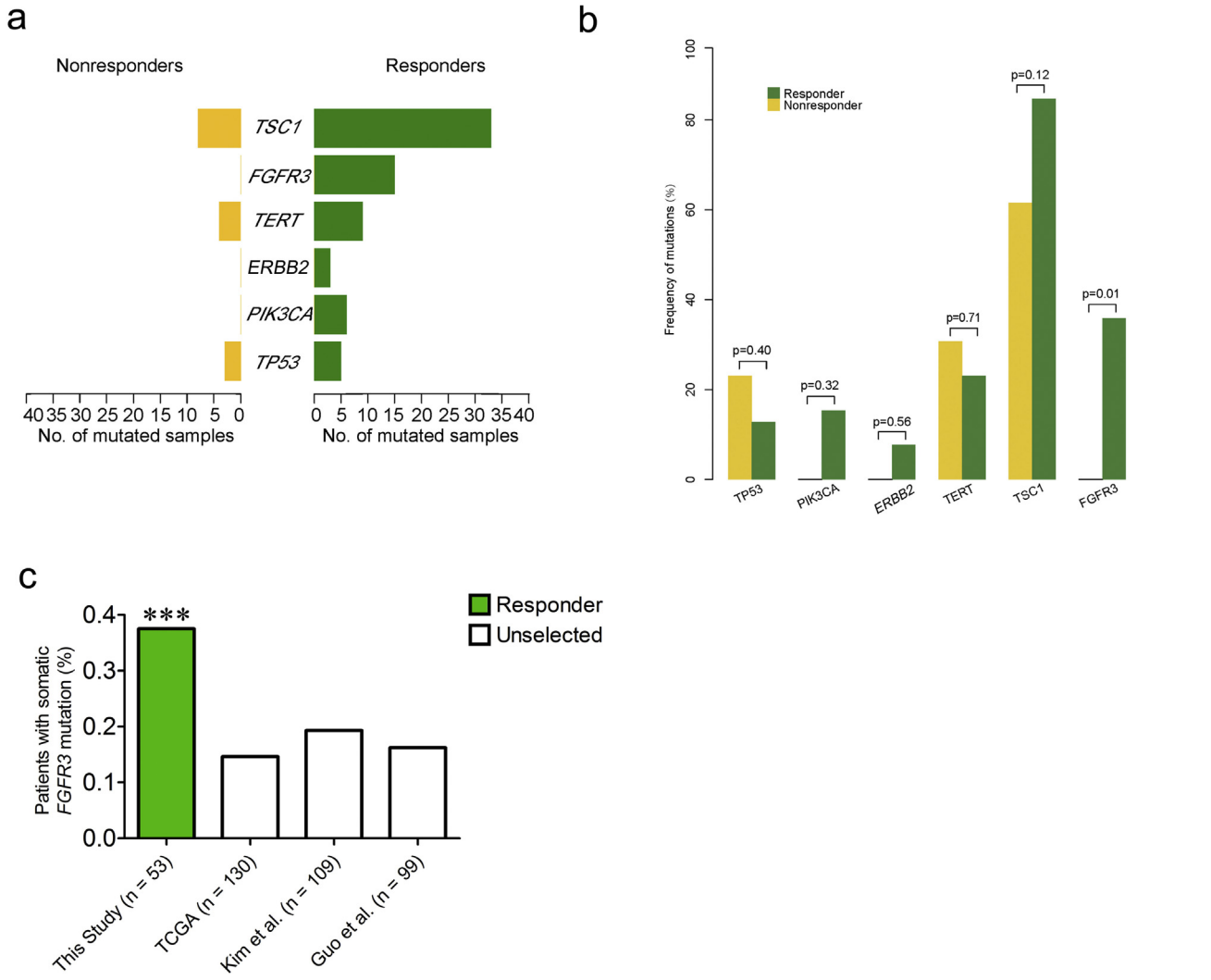

Fig. 2. *FGFR3* significantly altered in the responder group of muscle-invasive bladder cancer patients. a and b. *FGFR3*, *ERBB2* and *PIK3CA* somatic mutations exclusively occurred in the responder group. Only *FGFR3* demonstrated significant enrichment in patients with a response in the cohort. c. *FGFR3* somatic mutations were significantly enriched in the responder cohort compared with the unselected TCGA, Kim et al. and Guo et al. urothelial carcinoma cohorts.

expression was calculated initially. BC samples with high FGFR3 expression were defined as the high group, and the remaining samples were defined as the low group. The OS of each group was analyzed using a Kaplan-Meier analysis, and the difference between the two groups was examined using the log-rank test [9]. A P value <0.05 (*, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$) was regarded as statistically significant.

3. Results

3.1. Mutational Analysis of MIBCs Using a Six Gene Panel

Fifty-two MIBC patients were enrolled in this study to receive NAC. Six patients showed a complete response (ypT0N0), 33 patients displayed a partial response (ypT1/a/cis) and 13 patients were resistant (≥ ypT2) to NAC (Fig. 1A, Table 1 and Supplementary Table 2). The pretreatment tumor DNA from each sample was analyzed using a mutational panel of six genes (*TSC1*, *FGFR3*, *TERT*, *TP53*, *PIK3CA* and *ERBB2*) associated with tumorigenesis and drug resistance in BC. Divided into two groups, the mutational spectrum of the response (complete response & partial response) and non-response samples were depicted in a heat map (Fig. 1B).

3.2. FGFR3 Mutations Correlated with the Response to Neoadjuvant Chemotherapy

To identify the distinct altered genes between responders and non-responders, genes with different mutation frequencies were uncovered using contrast analysis (Fig. 2A). *FGFR3* (14/39, 35.9%), *PIK3CA* (6/39, 15.4%) and *ERBB2* (3/39, 7.7%) exclusively altered in the responder group (Fig. 1B and 2A). The mutations of *FGFR3*, *PIK3CA* and *ERBB2* were significantly enriched in the responder group (48.7% of cases, 19/39; Fig. 2B, $P < 0.01$).

Interestingly, *FGFR3* exhibited a significant difference between two groups (Fig. 2B, $P = 0.01$). The somatic *FGFR3* mutation frequency in the responder group was also compared with three unselected BC populations: 131 cases from TCGA [10], 109 cases from a United States patient cohort [11][10] and 99 cases from a Chinese patient cohort [12] (Fig. 2C). Compared with these unselected populations, *FGFR3* mutations were significantly enriched in the responder group (14/39, 35.9% of cases; Fig. 2C, $P < 0.001$; binomial test). Specifically, *FGFR3* mutated in 13 partial responders (13/33; nine pT1 and four pTcis) and one complete responder (1/6; pT0) in this cohort, and the mutation rate of *FGFR3* showed no significant difference between the two groups ($P = 0.39$, Fisher test). These results suggested that *FGFR3* alterations were associated with the response, especially the down-staging of BCs using NAC.

3.3. Somatic FGFR3 Mutations in Cisplatin-Based Chemotherapy Responders

In our study, four missense *FGFR3* mutations were found, including a well-known activating alteration c.746C > G (p.S249C) and three additional mutations (c.1114G > T, p.V372C; c.895G > A, p.G299S; c.1231G > A, p.V411 M) (Fig. 3A and B). To determine the relative abundance of somatic *FGFR3* mutations in other tumor types, TCGA data from 19 tumor types ($n = 4429$) were queried [13]. Somatic *FGFR3* mutations

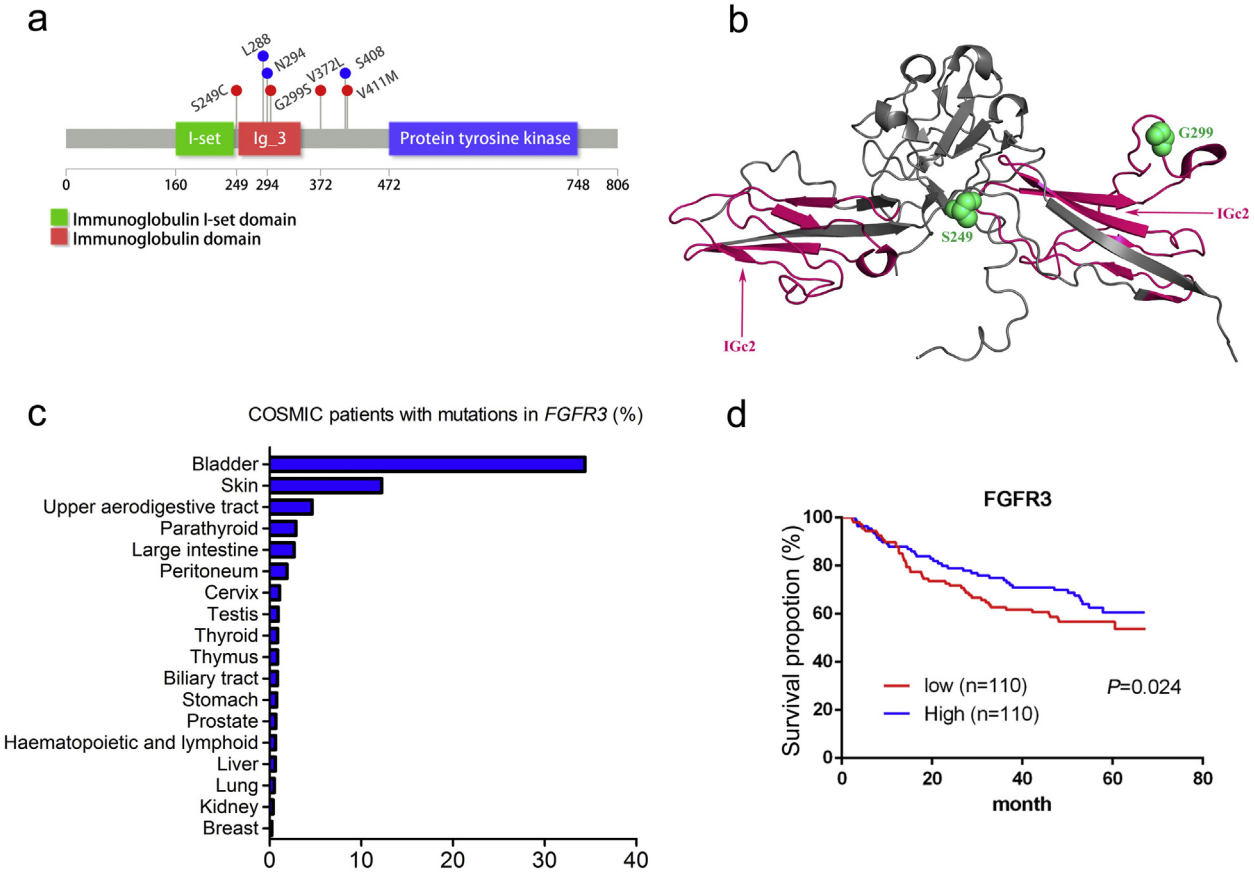

Fig. 3. *FGFR3* mutation mapping and distribution across tumor types. a. A stick plot of FGFR3 showing the locations of mutations in the responders. Red, somatic mutations. Blue, synonymous mutation. b. Structure of the immunoglobulin domain of FGFR3 (PDB code, 1RY7) with mutations identified in the responder cohort. c. The somatic *FGFR3* mutation frequency in multiple tumor types from COSMIC. d. Kaplan-Meier curves comparing OS between BC patients expressing high or low levels of FGFR3 using the log-rank test. n, patient number.

were observed at low frequencies (<5%) in 17 other tumor types except for BC and skin cancer (Fig. 3C). In the survival analysis, patients expressing higher levels of *FGFR3* had a longer mean survival time than those expressing lower levels of *FGFR3* (Fig. 3D). These results suggested that somatic mutations of *FGFR3* could predict the pathological response of BC patients to NAC.

3.4. Protein Expression Analysis of MIBCs Using an IHC Panel

The pretreatment tumor samples were analyzed with an IHC panel containing eight BC biomarkers (EGFR, RRM1, PD-L1, BRCA1, TUBB3, ERCC1, AG and CK5/6) (Supplementary Table 2). Among these biomarkers, only strong expression of ERCC1 was significantly correlated with the MIBC patient response to NAC ($P < 0.05$, Table 1). However, the expression of EGFR, RRM1, PD-L1, BRCA1, TUBB3, AG and CK5/6 was not associated with response ($P > 0.05$, Table 1).

3.5. Lymph Node Metastasis and Lymph-Vascular Invasion are Associated With Non-Response to NAC

The clinical characteristics including sex, age, OS and concomitant carcinoma *in situ* showed no significant differences between responders and nonresponders at baseline ($P > 0.05$; Mann-Whitney test) (Table 1). However, lymph node metastasis (pN) and lymph-vascular invasion (LVI) were correlated with a non-response ($P < 0.05$; Mann-Whitney test) (Table 1).

4. Discussion

NAC is emerging as an effective treatment for MIBCs. In the clinic, NAC can shrink tumor size and restrain tumor metastasis, as well as contributing to tumor down-staging and patient OS [2]. In this study, *FGFR3, PIK3CA* and *ERBB2* exclusively altered in the response cohort, in which the mutation of *FGFR3* was significantly enriched in the responder group. Additionally, strong expression of ERCC1 was significantly correlated with the MIBC response to NAC. However, pN and LVI were correlated with a non-response.

MIBCs are divided into basal, luminal and p53-like subtypes according to their molecular signature. The relationship between molecular subtype and chemosensitivity remains debatable [3]. McConkey et al. and Seiler et al. revealed an absolute survival benefit from NAC in patients with basal subtype tumors [14, 15]. However, Choi et al. reported that p53-like MIBCs were consistently resistant to neoadjuvant MVDC, while basal and luminal types showed no significant difference in drug sensitivity to NAC [16]. Our previous study found a significant survival benefit conferred to patients with the luminal subtype of MIBC that received NAC [17]. In this study, MIBCs with *FGFR3* mutations displayed a response to NAC (cisplatin and gemcitabine) that represented the luminal type of MIBCs. Consistent with our results, Rosenberg et al. reported that the response to atezolizumab was significantly greater in the TCGA luminal cluster II subtype than in the other subtypes (34% *versus* 10% for subtype I, 16% for subtype III and 20% for subtype IV) in the IMvigor 210 cohort 2 trial [18]. A possible reason for this discrepancy might result from the different subtyping method of BCs and the distinct combination of the drugs applied during NAC.

Previous studies have indicated that the alteration of *ERCC2* was significantly enriched in BC patients who responded to cisplatin [19]. Groenendijk et al. demonstrated that *ERBB2* missense mutations exclusively occurred in responders [20]. Furthermore, Plimack et al. reported that defects in DNA repair genes (*ATM*, *RB* and *FANCC*) predicted the response to neoadjuvant cisplatin-based chemotherapy in MIBC [21]. *FGFR3* belongs to the fibroblast growth factor receptor (FGFR) family and regulates cellular proliferation, migration and differentiation. The deregulation of *FGFR3* and its receptors is correlated with the pathogenesis of many cancers originating from different tissues [22]. Activating *FGFR3* mutations frequently occur in BC and were reported to correlate with drug sensitivity in lung adenocarcinoma [23]. Here, we identified that *FGFR3* exclusively altered in the responder cohort (14/39, 35.9%), with one well-known activating mutation (c.746C > G) and three additional alterations (c.1114G > T, c.895G > A and c.1231G > A). Additionally, *PIK3CA* and *ERBB2* altered exclusively in the responders, a finding that requires validation in a larger cohort. In conclusion, our findings demonstrate that *FGFR3* mutations could predict the pathologic response of BC patients to NAC and provide a promising biomarker to aid clinicians in treatment decisions.

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Conflicts of Interest

There are no conflicts of interest.

Author Contributions

C.H. and L.C. designed and supervised the study. K.X., Z.X. and W.H. searched literature. Z.R. and C.H. developed the methodology. Y.Z., Q.X., G.Y., Q.X., W.Y. and S.C. performed the experiments and analyzed the data. Y.Z., Z.R. and L.C. wrote and reviewed of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2018.06.011.

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