Targeting Gene Fusion Events in Bladder Carcinoma

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Abstract

Studies over the past decades revealed the driving role of fusion genes in tumorigenesis. With the advent of sequencing methods, a surge in the identification of novel fusions genes has been evident. These events may also rearrange gene promoters to amplify the expression of oncogenes or to decrease the expression of tumor suppressor genes. Several gene fusion events are determined in bladder carcinoma including well characterized FGFR3–TACC3 and FGFR3–BAIAP2L1 fusion genes. These fusion genes generate chimeric proteins which retain the complete sequence of FGFR3 except the final exon fused in-frame to different C-terminal regions of the TACC3 and BAIAP2L1. The presence of fusion genes offers promising targetable molecules for treatment, resulting in improved patient outcome. Oncogenic FGFR3 is a druggable gene fusion signifying that it may aid in selection of patients for FGFR-targeted therapy in bladder carcinoma.

Keywords: Urothelial carcinoma; Next-generation sequencing; FGFR receptor; Clinical trial

Introduction

Bladder carcinomas show diverse molecular landscapes with poor clinical outcome and present several challenges in clinical management. No clinically targeted treatment has been approved so far for bladder carcinoma. Numerous studies reported on determining the landscape of single nucleotide variations, insertions, deletions, and copy number alterations in bladder carcinoma [1-11]. Although these genomic alterations comprised of large fraction of the mutation burden in tumors, gene fusions or translocations play a key role in tumorigenesis. Fusion genes were initially discovered in hematologic malignancies and have been recently reported in various other tumors. FGFR3–TACC3 gene fusions were observed in a variety of tumors including adenoe- and squamous cell carcinoma of the lung glioma, glioblastoma multiforme (GBM), bladder carcinoma, esophageal carcinoma, cervical carcinoma, gastric carcinoma and nasopharyngeal carcinoma (NPC) [12-26].

FGFR3-TACC3 fusion products induce aneuploidy and chromosome instability in GBM [18]. It promotes cell proliferation and anchorage independent cell growth by increasing STAT3 and ERK activation in GBM cell lines [19]. It has also been suggested that the transforming ability of FGFR3-TACC3 fusion results from loss of miRNA regulation in GBM [19]. FGFR3-TACC3 fusion activates Akt and ERK signaling pathways further promoting cell proliferation, colony formation and transforming ability in two NPC cell lines (HNE1 and HK1) [26]. FGFR3- BAIAP2L1 fusion genes were reported in bladder and lung carcinomas [27]. It induces growth signals via activation of MAPK cascade and inhibits tumor-suppressive signals via the TP53/RBI/CDKN2A pathways [27]. Figure 1 depicts the product of well characterized fusion genes, FGFR3– TACC3 and FGFR3–BAIAP2L1 in bladder carcinoma.

Literature Review

FGFR3-TACC3 gene fusion in bladder carcinoma

FGFR3-TACC3 was widely reported in patients with bladder carcinoma contributing to 3% cases of advanced tumor as reported by Ross et al. and Weinstein et al., 3.5% by Wu et al., 3.2% by Helsten et al. and 2.2% by Williams et al. Among 43 bladder carcinoma cell lines, Williams et al. and Wu et al. reported FGFR3– TACC3 fusions in 3 cell lines RT4, RT112 and LUCCC2 [20,28]. FGFR3-TACC3 fusion appeared at various genomic locations in bladder carcinoma [20,21,25,28,29] (Table 1). The loss of exon 19 was apparent in all the fusions. The breakpoints in FGFR3 were majorly seen at intron 18 retaining the kinase domain of FGFR3 with varying joining points in TACC3 like exon 4, 8, 11 or intron 10 retaining the entire coiled coil region of TACC3 (Figure 1A). The fusion gene products were found to be involved in constitutive dimerization and stabilization of kinetochore fibres during mitosis [20]. Williams et al. observed that the chimeric protein was highly activated and induce signaling via MAPK pathway and lacked the ability to activate PLCγ1 [20]. Lombardi et al. identified nine pathways significantly regulated in a cell line expressing FGFR3-TACC3 fusion. These pathways were involved in chaperon activation, TP53 expression and degradation, depolymerisation of nuclear lamina, MET negative regulation, modulation of bacterial toxins and regulation of receptor tyrosine kinase pathways. They also identified five pathways regulated only by stimulation of the wild-type FGFR3, which were involved in TP53 activity regulation, netrin mediated repulsion signals, apoptotic execution phase, activation of KTN1 by RHO GTPases and apoptotic cleavage of cellular proteins [30].

FGFR3–BAIAP2L1 gene fusion in bladder carcinoma

The FGFR3-BAIAP2L1 fusion genes were identified by Williams et al. and Wu et al. and the breakpoints in FGFR3 are seen at exon 18 retaining the kinase domain of FGFR3 with joining points in BAIAP2L1 at intron 1 or exon 2 [20,28]. The FGFR3– BAIP2L1 fusion retains the entire kinase domain of FGFR3, with IMD domain, SH3 domain and a putative WW domain interacting motif, of BAIAP2L1.

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### Table 1: Summary of the gene fusions in bladder carcinoma.

The table combines various studies identified several gene fusion events in bladder carcinoma. The most frequently studied gene fusion in bladder carcinoma is **FGFR3-TACC3** and is undertaken for clinical trial.

| Fusion Genes       | Ref     | Tissue/Cell Line | Number of Samples/Cell Lines | Number of Samples/Cell Lines Harboring Fusion Genes | Breakpoint of Fusion Partner 1 | Breakpoint of Fusion Partner 2 | Inhibitor/Clinical Trial |
|--------------------|---------|------------------|------------------------------|----------------------------------------------------|--------------------------------|--------------------------------|---------------------------|
| FGFR3-TACC3        | [21]    | Tissue           | 35                           | 1                                                  | NR                             | NR                             |                          |
|                    | [25]    | Tissue           | 131                          | 3                                                  | Intron 16 (2 cases) and Exon 17 (1 case) | Intron 10                      |                          |
|                    | [28]    | Tissue           | 85                           | 3                                                  | Exon 18                        | Exon 11                        |                          |
|                    | [20]    | Tissue           | 126                          | 4                                                  | RT112                          | Intron 10                      |                          |
|                    | [23]    | Tissue           | 43                           | RT4                                              | Intron 18                      | exon 4                         | JNJ-42756493/ NCT01703481 [31] |
|                    | [11]    | Tissue           | 46                           | LUC2                                             | Intron 18                      | Intron 10                      |                          |
|                    | [32]    | Tissue           | 105                          | T4V6 and T112                                    | NR                             | NR                             |                          |
|                    | [20]    | Cell lines       | 43                           | SW780                                            | Exon 18                        | Intron 1                        | NA                        |
|                    | [28]    | Cell lines       | 2                            | SW780                                            | Exon 18                        | Exon 2                         | NA                        |
|                    | [33]    | Tissue           | 250                          | 1                                                | NR                             | NR                             | NA                        |
| GFGR3-BAIAP2L1     | [21]    | Tissue           | 412                          | 9                                                | NR                             | NR                             |                          |
|                    | [11]    | Tissue           | 9                             | NR                                                | NR                             | NR                             |                          |
|                    | [1]     | Tissue           | 5                            | NR                                                | NR                             | NR                             |                          |
|                    | [4]     | Tissue           | 4                            | NR                                                | NR                             | NR                             |                          |
|                    | [2]     | Tissue           | 4                            | NR                                                | NR                             | NR                             |                          |
|                    | [3]     | Tissue           | 4                            | NR                                                | NR                             | NR                             |                          |

(NR- Not Reported, NA- Not Available)

**Figure 1:** **FGFR3-TACC3** and **FGFR3-BAIAP2L1** gene fusion products in bladder carcinoma.

This schematic representation shows fusion products of FGFR3-TACC3 and FGFR3–BAIAP2L1 gene fusions in bladder carcinoma. (A) Depicting three gene fusion products of FGFR3 isoform IIIb and TACC3. (B) Depicting gene fusion product of FGFR3 isoform IIIb and BAIAP2L1. The breakpoints are depicted by red arrows.
Clinical implications of gene fusions in bladder carcinoma

FGFR3 has been reported as an oncogene in majority of low-grade non-invasive bladder tumors and upregulated in invasive bladder tumors. FGFR3 fusions identified in a subset of bladder carcinoma with upregulated FGFR3 expression. FGFR3-TACC3 fusion contain part of TACC3 gene, encodes a microtubule-associated protein. The fusions lead to constitutively activation of tyrosine kinase domain and promotes aneuploidy. This fusion imparts oncogenic mechanism and can be a potential target for tyrosine kinase inhibitors in tumors [13,18]. Currently, FGFR3-TACC3 fusion is in a phase I clinical trial of the FGFR inhibitor JNJ-42756493 [20,31-33]. In addition, ASP5878 has the potential to be an oral targeted therapy against patients with bladder carcinoma harboring FGFR3 fusion and is also undergoing clinical trial (NCT02038673) [34]. Wu et al. observed that cell lines harboring FGFR3-TACC3 fusion, SW780 and RT4, were sensitive to FGFR kinase inhibitors (PD173074 and pazopanib) in vitro and in vivo. SW780 xenografts showed ERMK1/2 repression upon treatment with PD173074 while RT4 xenografts showed sensitivity to PD173074 treatment [28].

Discussion

Nakanishi et al. confirmed the antiproliferative activity of CHS183284/ Debio 1347, a selective FGFR inhibitor, against FGFR3–BAIAP2L1-positive SW780 cells. They demonstrated CHS183284/Debio 1347 induced apoptosis in SW780 by suppressing FRS and ERK phosphorylation and downregulating antionmRNA activity in SW780 and rat models. They observed FGFR3 or BAIAP2L1 knockdowns using siRNA showed effect on SW780 cells but not on J82 [27]. Wu et al. reported the sensitivity of SW780 (fusion harboring cell line) cells to PD173074 and pazopanib compared to mutation harboring cell lines. Above studies suggest that FGFR3 fusions are sensitive to FGFR inhibitors compared to FGFR3 mutations bearing cell lines and presence of fusions can be used for the selection of patients for FGFR-targeted therapy [27,28].

Conclusion

Bladder carcinoma is highly heterogeneous disease and historically associated with activating mutations in FGFR3 gene. However, FGFR3 gene rearrangements have recently been reported in a unique subset of bladder tumors. Targeting fusion genes would provide a strong impetus for the treatment of patients with bladder carcinoma. Targeting fusion-positive subset of patients from targeted FGFR inhibition would lead to a better treatment option.

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