

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 fusion 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 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; FGF 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 adeno- 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/RB1/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 LUCC2 [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 PLC γ 1 [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, apoptic execution phase, activation of KTN1 by RHO GTPases and apoptic cleavage of cellular proteins [30].

FGFR3-BAIAP2L1 gene fusion in bladder carcinoma

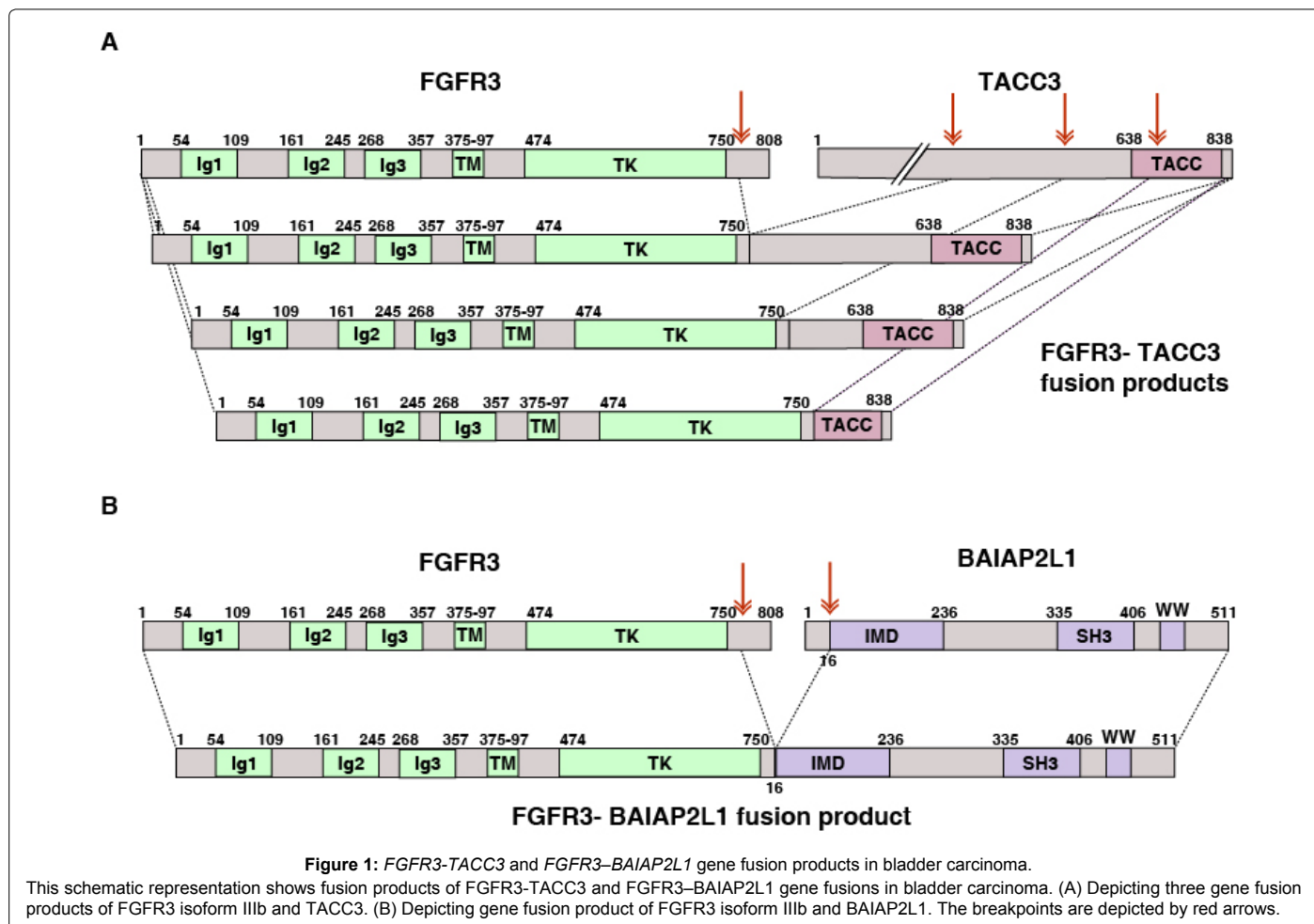
The *FGFR3-BAIAP2L1* fusion genes were identified by Williams et al. and Wu et al. and the breakpoints in *FGFR3* are seen at exon 18 retaining the kinase domain of *FGFR3* with joining points in *BAIAP2L1* at intron 1 or exon 2 [20,28]. The *FGFR3-BAIAP2L1* fusion retains the entire kinase domain of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

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Fusion Genes	Ref	Tissue/Cell Line	Number of Samples Analyzed	Number of Samples/Cell Lines Harboring Fusion Genes	Breakpoint of Fusion Partner 1	Breakpoint of Fusion Partner 2	Inhibitor/Clinical Trial
<i>FGFR3-TACC3</i>	[21]	Tissue	35	1	NR	NR	JNJ-42756493/ NCT01703481 [31]
	[25]	Tissue	131	3	Intron 16 (2 cases) and Exon 17 (1 case)	Intron 10	
	[28]	Tissue	85	3	Exon 18	Exon 11	
	[23]	Tissue	126	4	NR	NR	
	[20]	Cell lines	43	RT112	Intron 18	Intron 10	
				RT4	Intron 18	exon 4	
		Tissue	46	1	LUCC2	Intron 18	
[11]	Cell lines	30	T4V6 and T112	NR	NR		
[32]	Tissue	105	1	NR	NR		
<i>FGFR3-BAIAP2L1</i>	[20]	Cell lines	43	SW780	Exon 18	Intron 1	NA
	[28]	Cell lines	2	SW780	Exon 18	Exon 2	
<i>TPM1-ALK</i>	[33]	Tissue	250	1	NR	NR	NA
<i>ITGB6-LOC100505984</i>	[11]	Tissue	412	9	NR	NR	NA
<i>AFF1-PTPN13</i>				5	NR	NR	
<i>PPARG-SYN2</i>				4	NR	NR	
<i>GPR110-TNFRSF21</i>				4	NR	NR	
<i>TSEN2-PPARG</i>				4	NR	NR	
<i>FGFR3-TNIP2</i>				[32]	Tissue	105	

(NR- Not Reported; NA- Not Available)

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.

(Figure 1B) [20]. A detailed list of fusion genes in bladder carcinoma is provided in Table 1.

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 *FGFR3* inhibitor JNJ-42756493 (NCT01703481) and has demonstrated partial response in a bladder carcinoma patient with *FGFR3-TACC3* translocation [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 *in vivo*. SW780 xenografts showed ERK1/2 repression upon treatment with PD173074 while RT4 xenografts showed sensitivity to PD173074 treatment [28].

Discussion

Nakanishi et al. confirmed the antiproliferative activity of CH5183284/ Debio 1347, a selective *FGFR* inhibitor, against *FGFR3*-*BALAP2L1*-positive SW780 cells. They demonstrated CH5183284/ Debio 1347 induced apoptosis in SW780 by suppressing FRS and ERK phosphorylation confirming its antitumor activity in SW780 and rat models. They observed *FGFR3* or *BALAP2L1* 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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