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Advances in chromosomal translocations and fusion genes in sarcomas and potential therapeutic applications

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ABSTRACT

Chromosomal translocations and fusion genes are very common in human cancer especially in subtypes of sarcomas, such as rhabdomyosarcoma, Ewing's sarcoma, synovial sarcoma and liposarcoma. The discovery of novel chromosomal translocations and fusion genes in different tumors are due to the advancement of next-generation sequencing (NGS) technologies such as whole genome sequencing. Recently, many novel chromosomal translocations and gene fusions have been identified in different types of sarcoma through NGS approaches. In addition to previously known sarcoma fusion genes, these novel specific fusion genes and associated molecular events represent important targets for novel therapeutic approaches in the treatment of sarcomas. This review focuses on recent advances in chromosomal translocations and fusion genes in sarcomas and their potential therapeutic applications in the treatment of sarcomas.

Introduction

Tumor development is driven by complex processes based on numerous genetic changes, in which chromosomal translocation is one of the most important mechanisms for producing oncogenes. Chromosomal translocations have long been found in hematological malignancies [1]. With the development of cytogenetic technology, the examination of genetic changes has been extended to solid tumors. As a result, a substantial number of characteristic chromosomal translocations causing fusion genes were discovered in sarcomas. Fusion gene protein products can influence cell survival, growth and migration [2]. In recent years, advancements in next generation sequencing (NGS) technologies have innovated and enriched genetic investigations of sarcomas [3]. In contrast with previous techniques, NGS generates data in enhanced detail. In fact, genomic aberrations can be detected at a base pair resolution not only in genomic DNA sequencing level but also in transcriptome RNA sequencing level [4]. This level of detail has enabled the identification of many novel chromosomal translocations and fusion genes in sarcomas. As a result, there is an enhanced understanding of tumorgenesis, which has improved diagnostic approaches in sarcomas. More importantly, these breakthroughs have influenced the clinical treatment of sarcoma. The novel specific fusion genes and their related molecular drivers represent important targets for therapeutic strategies.

This review will highlight several recent advances in chromosomal translocations and fusion genes involved in sarcoma, and provide a summary of novel therapeutic approaches that could be useful in the future treatment of sarcomas.

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma, accounting for 10% of all childhood solid tumors. Rhabdomyosarcoma has two main histologic types including embryonal rhabdomyosarcoma (ERMS) occuring in 80% of cases, and alveolar rhabdomyosarcoma (ARMS) comprising 20% of cases and usually having an unfavorable prognosis. Survival rates have changed little in recent years [5].

The most important discovery in rhabdomyosarcoma was the fusion gene formed by chromosomal translocations in ARMS (Supplementary Table 1). Balanced nonrandom chromosomal translocations t(2;13)(q35;q14) and t(1;13)(p36;q14) have been revealed in nearly 75% and 10% of cases, respectively [6,7]. The fusion gene of t(2;13) translocation consists of PAX3 and FOXO1 genes [8], while t(1;13) contains PAX7 and FOXO1 genes [9]. Both fusion genes generate transcription factors with greater capacity to activate transcription when compared to their wild types [10].

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There are some other novel translocations in RMS (Table 1). t(2;2)(q35;p23), a novel translocation has been revealed in ARMS, which leads to a fusion of the genes PAX3 and NCOA1. The molecular product of this fusion gene has the same transactivation property with the PAX3-FOXO1 protein [11]. In a case of ERMS, a noncanonical translocation t(2;8)(q35;q13) was revealed and the fusion gene PAX3-NCOA2 was identified. This fusion gene not only inhibits myogenic differentiation but also promotes cell proliferation in RMS cell lines [12]. In the spindle cell variant of rhabdomyosarcoma (SRMS), the novel VGLL2-CITED2 and VGLL2-NCOA2 fusions were identified in most cases. SRF-NCOA2 and TEAD1-NCOA2 were found in a few cases [13]. A novel t(6;8)(p12;q11.2) chromosomal translocation was revealed in a case of SRMS [14]. A total of ten patients with these novel fusion genes were analyzed for the prognosis. All 10 patients have a favorable clinical outcome without metastasis and were alive at their median 7-year follow-up. This suggests that these novel fusion genes are less aggressive than the PAX3-FOXO1 fusion gene, and therefore these novel fusion genes represent potential biomarkers for low risk RMS. We can also find that all novel fusion genes do not contain the FOXO1 gene, which verified the deduction that FOXO1 gene is involved in RMS with higher malignant degree.

Despite the application of novel chemotherapy drugs and chemotherapeutic administration, outcomes of RMS patients have not significantly improved. Small molecule compounds are not able to directly disrupt the function of PAX-FOXO1 fusion proteins, which are the tumor specific therapeutic targets. Therefore, several studies have explored the downstream effects of this translocation protein. These downstream genes may become promising therapeutic targets (Table 3). The identified targets of PAX3-FOXO1 include tyrosine-protein kinase Met (c-Met), insulin like growth factor 1 receptor (IGF1R) [15] and fibroblast growth factor receptor 4 (FGFR4) [16]. FGFR4 and IGF1R enhance cell survival and stimulate myoblast growth in ARMS. A multi-institutional phase II study was conducted to evaluate the effect of the IGF1R monoclonal antibody R1507 in 36 RMS patients. One patient gave a partial response while six patients had a stable disease. Although R1507 has limited activity in patients, other IGF-1R inhibitors may play a role in the treatment of RMS and need to be evaluated. A small molecule inhibitor of FGFR4, such as PD173074, has been shown to suppress RMS tumorigenesis *in vitro* and *in vivo*. c-Met is a receptor tyrosine kinase (RTK) that is over-expressed in RMS and is involved in the development and progression of RMS. Furthermore, the inhibitor of c-Met, SU11274, could inhibit cell proliferation and block cell migration in RMS cells [17]. Therefore, c-Met and FGFR4 inhibitors may be effective targeting therapy reagents for RMS. It has been found that the PAX3-FOXO1 protein increased genomic amplification of MYCN. In tumor cells and xenograft murine, the inhibition of MYCN results in strong antitumor activity and shows promise for the treatment of RMS [18]. Fenretinide, a novel compound not yet applied in the treatment of ARMS, has been found effective against fusion-positive rhabdomyosarcoma *in vitro* and *in vivo*, which implies its potential as a therapeutic target for fusion genes [19]. In addition, PAX-FOXO1 fusion proteins can also destroy myogenic differentiation in rhabdomyosarcoma cells by affecting the function of genes such as p21, muscle creatine kinase, and myogenin [20]. To improve the prognosis and increase the survival rate of rhabdomyosarcoma patients, further efforts are needed and should identify novel therapeutic approaches involved in targeting fusion proteins.

In terms of inducing a targeted PAX3-FOXO1 chromosomal translocation in ARMS, CRISPR-Cas9 provides a novel mean and precisely creates the mouse models of chromosome translocation induced human sarcomas [21]. With this novel technology, the role of fusion genes in sarcomas could be identified easily and directly.

Histopathology cannot always predict the clinical outcome of RMS. The prognostic value of the PAX-FOXO1 translocation is one of the most important factors and will help in risk stratification of RMS. According to the report of the children's sarcoma committee, patients with PAX3-FOXO1 ARMS had a lower overall survival compared with those with PAX7-FOXO1 ARMS. Event-free survival was worse in fusion-positive ARMS patients compared with ARMS and ERMS patients that are fusion-negative [22]. These observed differences in prognosis may be due to the stronger transcriptional activity of PAX3 than PAX7 in the promoter region [23].

Ewing sarcoma family of tumors

The Ewing sarcoma family of tumors (ESFT) is the second most common type of primary malignant sarcoma. ESFT includes soft tissue Ewing's sarcoma, peripheral primitive neuroectodermal tumors and Askin's tumors, which had been considered to be

Table 1
Novel chromosomal translocations or fusion genes in sarcomas.

Tumor type	Translocation	Fusion gene	Reference
Alveolar rhabdomyosarcoma	t(2;2)(q35;p23)	PAX3-NCOA1	[11]
Embryonal rhabdomyosarcoma	t(2;8)(q35;q13)	PAX3-NCOA2	[12]
Spindle cell rhabdomyosarcoma		VGLL2-CITED2	[13]
		VGLL2-NCOA2	[13]
		TEAD1-NCOA2	[13]
		SRF-NCOA2	[13]
	t(6;8) (p12;q11.2)		[14]
Undifferentiated small round cell sarcomas	t(4;19)(q35;q13.1)	CIC-DUX4	[31]
	t(10;19)(q26.3;q13)		
		BCOR-CCNB3	[32]
		CIC-FOXO4	[33]
		EWS-NFATC2	[34]
		EWS-SMARCA5	[35]
		EWS-PATZ1	[36]
		EWS-SP3	[36]
Mesenchymal chondrosarcoma		HEY1-NCOA2	[70]
Extraskeletal Myxoid chondrosarcoma	t(9;16)(q22;p11.2)	FUS-NR4A3	[71]
Clear cell sarcoma	t(10;17)(q22;p13)	YWHAE-FAM22	[76]
		IRX2-TERT	[77]
	t(2;13)(q13;q22)		[78]
	t(3:17)(q29;p11.2)		[78]
Myxoid liposarcoma	t(2;4) (q23;p14)		[83]