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Ewing sarcoma: a chronicle of molecular pathogenesis☆

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Summary Sarcomas have traditionally been classified according to their chromosomal alterations regardless of whether they accompany simple or complex genetic changes. Ewing sarcoma, a classic small round cell bone tumor, is a well-known mesenchymal malignancy that results from simple sarcoma-specific genetic alterations. The genetic alterations are translocations between genes of the TET/FET family (*TLS/FUS*, *EWSR1*, and *TAF15*) and genes of the E26 transformation-specific (ETS) family. In this review, we intend to summarize a chronicle of molecular findings of Ewing sarcoma including recent advances and explain resultant molecular pathogenesis.

1. Introduction

Both singular and complex genetic abnormalities can induce mesenchymal tumors to arise from various cells of the bone and soft tissues [1]. In some sarcomas, singular genetic aberrations are highly specific and prevalent [2]. Among these sarcomas, Ewing sarcoma is a classic malignant small round cell tumor that has etiologic and characteristic chromosomal translocations between TET/FET (*TLS/FUS*, *EWSR1*, and *TAF15*) family genes and E26 transformation-specific (ETS) family genes [3]. In particular, *EWSR1* gene rearrangement has been reported to occur in ~90% of Ewing sarcoma cases [4].

Small round cell tumors comprise heterogeneous neoplasms composed of relatively small, round to oval, closely packed undifferentiated cells (Fig. 1A) [5]. Ewing sarcoma is a representative small round cell tumor that expresses CD99 in the membrane, which differentiates it from other small round cell tumors that demonstrate similar microscopic and/or immunohistochemical features [5].

In this review, we will focus on providing a large picture of the pathogenesis of Ewing sarcoma in the perspective of molecular alterations, while covering other aspects as well including but not limited to the protein expression patterns, target gene regulation, and epigenetic modifications.

2. CD99 expression and Ewing sarcoma

2.1. CD99 serves as a diagnostic marker of Ewing sarcoma

Because *MIC2* overexpression was identified in Ewing sarcoma, the transmembrane protein CD99 (cluster of differentiation 99, also known as single-chain type 1 glycoprotein), which is encoded by *MIC2*, has been routinely used as an

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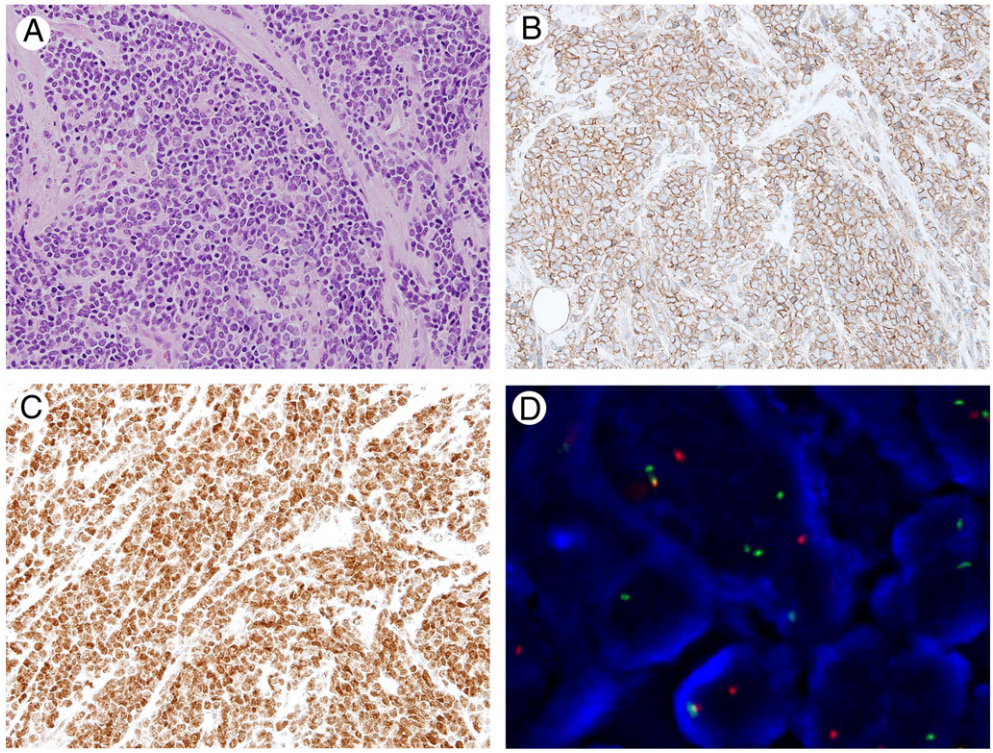

Fig. 1 Ewing sarcoma. A, Small round cells with scant cytoplasm, round nuclei and fine chromatin. B, CD99-positive tumor cells with diffuse and membranous patterns. C, Strong nuclear expression of FLI1 in tumor cells. Original magnification × 200. D, Fluorescence in situ hybridization assay result for *EWSR1* break-apart showing separated green and orange signals. Original magnification × 1000.

immunohistochemical diagnostic marker [6–9]. CD99 expression in the cytoplasmic membranes of tumor cells is highly specific and is found in 100% of Ewing sarcomas (Fig. 1B) [10,11]. However, CD99 expression is also found in other types of small round cell tumors including poorly differentiated synovial sarcoma, mesenchymal chondrosarcoma, lymphoblastic lymphoma/leukemia, acute myelogenous leukemia, granulocytic sarcoma, desmoplastic small round cell tumor, and rhabdomyosarcoma [10–19]. In addition, pancytokeratin, CD117 (C-kit), and CD56 (NCAM), which are used to diagnose other small round cell tumors, are also variably expressed in Ewing sarcoma [10,20,21]. Therefore, a confirmative diagnosis of Ewing sarcoma should involve analyses of immunoprofiles of other small round cell tumors and confirmation of an *EWSR1* gene translocation (Table 1).

Because most of the genetic translocations found in Ewing sarcomas are *EWSR1-FLI1* fusions [22,23], nuclear expression of FLI1 protein is usually observed in Ewing sarcomas (Fig. 1C). Several comparative studies that have analyzed CD99 and FLI1 protein expression profiles observed FLI1 immunoreactivity in 71% to 94% of Ewing sarcoma cases [10,24,25]. Similar to CD99 expression in a variety of small round cell tumors, FLI1 expression is also found in lymphoblastic lymphoma and vascular tumors [24,26]. Recently, the homeobox protein NKX2.2, which is a transcriptional target of EWSR1-FLI1, has been found to be a useful immunohistochemical marker for Ewing sarcoma. The identification of

Table 1 Differential diagnoses of small round cell tumors according to immunoprofiles

Immunoprofile	Differential diagnosis
CD99	Acute myelogenous leukemia
	Desmoplastic small round cell tumor
	Ewing sarcoma
	Granulocytic sarcoma
	Lymphoblastic lymphoma/leukemia
	Mesenchymal chondrosarcoma
	Poorly differentiated synovial sarcoma
	Rhabdomyosarcoma
Pancytokeratin	Desmoplastic small round cell tumor
	Ewing sarcoma
	Poorly differentiated synovial sarcoma
	Rhabdomyosarcoma
CD117	Acute myelogenous leukemia
	Ewing sarcoma
	Granulocytic sarcoma
	Melanoma
	Rhabdomyosarcoma
CD56	Ewing sarcoma
	Diffuse large B-cell lymphoma
	Natural killer/T-cell lymphoma
	Neuroblastoma
	Rhabdomyosarcoma
FLI1	Ewing sarcoma
	Lymphoblastic lymphoma/leukemia