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The histogenesis of Ewing Sarcoma

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Ewing Sarcoma is the second most frequent malignant bone tumor in adolescents and young adults. The majority of Ewing sarcoma arises in the bone, but 15-20% of Ewing sarcoma originates in the soft tissue surrounding bones [1,2].

Chromosomal translocation is a hallmark of Ewing Sarcoma and has long been considered the primary cause in its development. Around 85% of Ewing sarcoma harbors a t(11:22)(q24:q12) translocation resulting in the fusion of the N-terminal portion of the EWS gene with the C-terminal portion of the FLI1 gene, one of five ETS family genes [3]. The EWS-FLI1 fusion gene behaves as an aberrant transcription factor to induce or suppress a number of genes modulating transformation, differentiation, cell growth and signal transduction [4,5]. Through direct interactions with RNA processing proteins, EWS-FLI1 also regulates alternative splicing of RNA to impact diverse oncogenic cellular processes (e.g., favoring expression of a TERT isoform with enhanced telomerase activity) [6].

Unlike other sarcomas, such as osteosarcoma and fibrosarcoma, which present some lineage-specific differentiation, Ewing sarcoma is histologically classified as composed of uniformly undifferentiated small round basophilic cells. However, the specific cell type from which Ewing sarcoma is one of the biggest medical mysteries of our time and still under debate. When first reported by James Ewing, in his first reports on the tumor in 1921, proposed an endothelial origin for the sarcoma on the basis of its cellular morphology and the rareness of stroma [7]. In 1971 a myelogenous origin of Ewing sarcoma was proposed given ultrastructural features resembling developing myelocytes [8]. Since then, several hypotheses regarding the histogenesis of Ewing sarcoma have been advanced, with neural crest cells and mesenchymal stem cells receiving the most attention as the putative cells of origin.

The hypothesis of neural crest origin is supported by several lines of evidence. Observational studies reveal that various neural lineage markers, such as neuron-specific enolase and S-100, associated with the neuroectodemal linage are expressed in Ewing sarcoma [9]. Ultrastructural features, such as neurosecretory granules, have been observed with electron microscopy in some Ewing sarcomas [10]. The genome expression profile of Ewing sarcoma is more similar to that of neural crest stem cells than other cell types such as mesenchymal stem cells [11]. A spectrum of neural crest developmental genes is significantly upregulated by ectopic expression of the EWS-FLI1 chimeric protein in a rhabdomyosarcoma cell line, driving the cells to become less differentiated and develop the observed phenotype of Ewing sarcoma [12]. In addition, Ewing sarcoma cell lines undergo neural differentiation upon treatment with various differentiation-inducing agents [13].

On the other hand, there is a growing body of evidence supporting a mesenchymal stem cell origin of Ewing sarcoma. CD99 is a relatively specific marker of Ewing sarcoma and is detected at low levels in mesenchymal stem cells and upregulated by EWS-FLI1 [14]. When the EWS-FLI1 fusion protein is expressed in marrow-derived stromal cells, it represses both osteogenic and adipogenic differentiation of bone marrow stromal cells [15]. Ectopic EWS-FLI1 expression in murine primary bone marrow-derived mesenchymal stem cells leads to cell transformation and engraftment of Ewing sarcoma-like tumors *in vivo* [16,17]. These engineered tumors have a similar cellular morphology and express similar cell surface markers to Ewing sarcoma. The knock-down of EWS-FLI1 expression in Ewing Sarcoma results in convergence of the tumor gene expression profiles to that of mesenchymal stem cells [18]. Furthermore, the core EWS-FLI1 transcriptional signature, identified across multiple model system through comparative analysis, shared some characteristics with published mesenchymal stem cell data [19].

To our knowledge, all attempts to identify the Ewing sarcoma cell of origin have relied on the overexpression of EWS-FLI1 in various progenitor cells. EWS-FLI1 expression in these model systems may drive pathology across a number of cell types even if Ewing Sarcoma does not typically arise from these cell types. Distinct cellular phenotypes of Ewing sarcoma may be the result of the relative expression of EWS-FLI1 rather than a reflection of the cell of origin. Current advances to generate chromosome fusions by CRISPR/Cas9 methodology may provide a new approach to answer this mystery [20,21].

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