

Suggested Role for Neutrophil Extracellular Traps Formation in Ewing Sarcoma Immune Microenvironment

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Abstract : Ewing sarcoma (EWS) is a highly aggressive cancer with a survival rate of 70-80% for patients with localized disease and under 30% for those with metastatic disease. Tumor-infiltrating neutrophils (TIN) can generate extracellular net-like DNA structures known as neutrophil extracellular traps (NETs). However, little is known about the presence and prognostic significance of tumor-infiltrating NETs in EWS. Herein, we investigated 46 patients diagnosed with EWS and treated in the Tel Aviv Medical Center between 2010 and 2021. TINs and NETs were identified in diagnostic biopsies of EWS by immunofluorescent. In addition, NETs were investigated in neutrophils isolated from peripheral blood samples of EWS patients at diagnosis and following neoadjuvant chemotherapy. The relationships between the presence of TINs and NETs, pathological and clinical features, and outcomes were analyzed. Our results demonstrate that TIN and NETs at diagnosis were higher in EWS patients with metastatic disease compared to those with local disease. High NETs formation at diagnosis predicted poor response to neo-adjuvant chemotherapy, relapse, and death from disease ($P < .05$). NETs formation in peripheral blood samples at diagnosis was significantly elevated among patients with EWS compared to pediatric controls and decreased significantly following neoadjuvant chemotherapy. In conclusion, NETs formation seems to have a role in the EWS immune microenvironment. Their presence can refine risk stratification, predict chemotherapy resistance and survival, and serve as a therapeutic target in patients with EWS.

Keywords : Ewing sarcoma, tumor microenvironment, neutrophil, neutrophil extracellular traps (NETs), prognosis

Conference Title : ICPO 2024 : International Conference on Pediatric Oncology

Conference Location : Tokyo, Japan

Conference Dates : March 18-19, 2024