Targeting ER stress responses to unleash T cell immunity against ovarian cancer

Minkyung Song, Ph D.

Dept. of Integrative Biotechnology, College of Biotechnology and Bioengineering,
Sungkyunkwan University, 16419, Rep. of Korea

T cell-based immunotherapies have emerged as a novel approach to overcome conventional cancer treatments. However, tumor-induced immunosuppression restrains the optimal T cell responses in aggressive ovarian cancer. Therefore, unveiling and targeting the major mechanism that tumors exploit in T cells to control their function is crucial for developing successful ovarian cancer immunotherapies.

We previously reported the Endoplasmic Reticulum (ER) stress induced in unfavorable tumor microenvironment as a major immunosuppressive mechanism in ovarian tumor infiltrating T cells. The subsequent activation of signaling pathway operated by ER membrane resident sensor, IRE1a, and its downstream target transcription factor, XBP1 controlled their mitochondrial function and anti-tumor activity. Single cell RNA sequencing analysis using intratumoral T cells isolated from mice lacking XBP1 selectively in T cells further revealed specific regulatory roles of XBP1 in transcriptional program within heterogenous T cell sub-populations. XBP1-deficient mice bearing ovarian cancer demonstrated superior anti-tumor immunity, delayed malignant progression, and increased overall survival. In addition, transfer of ex vivo expanding tumor-reactive T cells lacking XBP1 into ovarian cancer bearing recipients showed prolonged overall survival compared to mice receiving wild-type counterparts. Hence, this knowledge uncovers new immune therapeutic targets in the tumor microenvironment, which will facilitate to devise the next generation T cell-based immunotherapy against ovarian cancer.