Abstract citation ID: bvac150.1797

Tumor Biology

ODP543

Chemotherapy-induced extracellular HSP70 enhances pro-tumorigenic effects of macrophages in breast cancers.

Mio Yamaguchi, MHSc, Kiyoshi Takagi, PhD, Yasuhiro Miki, PhD, Erina Iwabuchi, PhD, Minoru Miyashita, MD, PhD, Hironobu Sasano, MD, PhD, and Takashi Suzuki, MD, PhD

Breast cancer is one of the most common types of malignancies in women worldwide. Cytotoxic chemotherapy has improved the prognosis of aggressive phenotype of breast cancer patients including triple-negative breast cancers. However, resistance to chemotherapy is an important problem. Tumor-associated macrophages (TAMs) are primary components of tumor microenvironment and promote tumor progression by releasing various cytokines. Pro-tumorigenic effects of TAMs are known to induce chemoresistance in breast cancers. On the other hand, we previously showed that pro-tumorigenic effects of TAMs were enhanced in breast cancer tissues following chemotherapy by immunohistochemical study. Here, we demonstrated that breast carcinoma cells exposed by chemotherapy induced pro-tumorigenic effects of TAMs. THP-1 human monocyte cell-derived macrophages were interacted with MDA-MB-231 and MDA-MB-453 human breast cancer cells treated with epirubicin (EPI), and conditioned media from them significantly promoted proliferation and migration of breast cancer cells. We found that the expression of heat shock protein (HSP) 70 in the cytoplasm of MDA-MB-231 cells was upregulated following EPI treatment. HSP70 is an intracellular molecular chaperone and recently described with extracellular actions in stressful conditions. However, extracellular HSP70 action on TAMs in breast cancer has remained largely unknown. MDA-MB-231 cells treated with EPI and EPI-resistant MDA-MB-231 subline promoted secretion of HSP70, especially exosomal HSP70. Then, HSP70 knockdown in MDA-MB-231 cells were performed using siRNA. Macrophages cultured with HSP70 suppressed conditioned media from MDA-MB-231 cells showed decreased expression of CD163, a marker of pro-tumorigenic macrophages. Furthermore, HSP70 suppressed conditioned media downregulated the expression of transforming growth factor (TGF)-beta and colony stimulating factor (CSF)-1 in MDA-MB-231 cells, which are known to increase pro-tumorigenic effects of macrophages. Then, we performed immunohistochemistry for HSP70 in 116 breast carcinoma tissues. HSP70 immunoreactivity in the cytoplasm of breast carcinoma cells was correlated with stage, lymph node metastasis, pathological T factor, histological grade, Ki-67 LI, and negatively correlated with ER and progesterone receptor (PR). Furthermore, immunoreactivity of HSP70 was increased in breast cancer patients who had received neoadjuvant chemotherapy. When we correlated HSP70 with clinical outcome, HSP70 immunoreactivity was correlated with increased risk of recurrences and breast-cancer-specific mortality. Importantly, macrophage infiltration was correlated with increased risk of recurrences only in the HSP70 positive group, but not in the HSP70-negative group, which indicates that HSP70 may be associated with the pro-tumorigenic effects of TAMs in breast cancers. Taken together, breast carcinoma cells promoted secretion of extracellular HSP70 following chemotherapy and it might induce chemoresistance by upregulating pro-tumorigenic effects of macrophages, directly or indirectly via regulation of cytokines expression in breast carcinoma cells. Extracellular HSP70 may be an important target to improve the prognosis of breast cancer patients.

Presentation: No date and time listed