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Novel mechanism of chemoresistance to paclitaxel in breast cancer

Background: Paclitaxel elicits both cytotoxic and pro-survival responses in tumor cells. The tumor-promoting effect of paclitaxel is a currently unrecognized determinant for decreasing the apoptotic effect of paclitaxel therapy. The likely mechanism for paclitaxel-dependent tumor-activating effects is the ability of paclitaxel to activate Toll-like Receptor-4 (TLR4) pathway. TLR4 is often over-expressed in malignant epithelial cells in which its signaling hyper-activates NF-kB, MAPK and PI3K pathways providing a pro-survival benefit to the residual cancer cells. The goal of this project was to identify the TLR4 role in paclitaxel resistance by correlating the expression profile of TLR4 pathway in a panel of breast carcinoma cells with sensitivity to paclitaxel therapy.

Methods: TLR4 mRNA levels were determined in 18 breast carcinoma lines by qRT-PCR. The functionality of TLR4 pathway was determined by measuring mRNA of downstream products (IL-6, IL-8, MCP-1 and TNFα) after stimulating cells with a natural TLR4 ligand, lipopolysaccharide (LPS), or paclitaxel. Protein levels were measured by ELISA. Cytotoxic assays were used to correlate the level of TLR4 expression and responsiveness to paclitaxel. TLR4-positive (MDA-MB-231) and negative (HCC1806) lines were engineered to stably down-regulate and over-express TLR4, respectively. The target expression in modified clones was determined by qRT-PCR and Western Blot. The modified lines were analyzed for functionality and altered responsiveness to paclitaxel in vitro as well as for tumor growth, metastasis and recurrence in vivo.

Results: TLR4 was expressed in 60% of human breast cancer cell lines. TLR4 receptor in MDA-MB-231 line was functional as demonstrated by up-regulation of inflammatory cytokines. LPS increased IL-6 and MCP-1 by 8-10 folds whereas IL-8 and TNF-alpha were increased by 40-45 folds. MDA-MB-231 line was ~5 fold more resistant to paclitaxel than HCC1806 lacking TLR4. Paclitaxel treatment not only drastically increases secretion of NF-kB dependent cytokines but also up-regulated the expression levels of their receptors suggesting establishment of novel autocrine pro-survival and proliferative positive loops. Anti-TLR4 antibody inhibited paclitaxel stimulating effects by nearly 100%. Mice implanted with MDA-MB-231 line lacking TLR4 expression showed significant tumor growth delay and absence of recurrence.

Conclusions: These data show that paclitaxel up-regulates both inflammatory cytokines and their receptors in human breast carcinoma cells, likely through activation of the TLR4 pathway. Inflammatory pathway signaling increases survival and proliferation in TLR4-positive cells, suggesting that activation of this pathway in malignant cells maintain chronic inflammation and promote tumor growth and metastasis through both paracrine and autocrine loops. This study suggests that tumor resistance to paclitaxel might be determined by TLR4 expression, and that blocking TLR4 might significantly improve tumor response to paclitaxel therapy.

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