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Blockade of TLR4 by TAK-242 Inhibits Growth and Invasiveness in Human Breast Cancer Cells

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TLR4 is one of the most important receptors on the surface of innate immune system cells. When stimulated, it causes induction of two different pathways; both end up with NF-kB activation. In cancer cells, TLR4 is often overexpressed and its activation results in anti-apoptotic signaling, cell survival and chemo-resistance. TAK-242 is a small molecule inhibitor which specifically inhibits TLR4 and it has been used as a drug for septic shock treatment in clinical trials. In the present study, we investigate the effects of TAK-242 on four breast cancer cell lines: MDA-MB231, MCF7, BT-474 and SKBR3. The cytotoxicity of the inhibitor was investigated by MTT, colony formation and crystal-violet staining assays. Cell cycle analysis and annexin-PI apoptosis test were further carried out. The effects of TAK-242 on downstream pathways and the genes involved in cell cycle arrest, apoptosis, metastasis and survival were investigated by qRT-PCR. Basal expression levels showed that TLR4 was expressed at high level in MCF-7, MDA-MB231 and SKBR3 but not in BT-474 cells. Further analysis indicated that those cell lines which expressed higher levels of TLR4 were more affected by the drug and they showed higher apoptosis and cell cycle arrest. qRT-PCR showed up-regulation of pro-apoptotic (FAS-BAD) and down-regulation of anti-apoptotic (BCL2-SVV) genes, and genes involved in metastasis (MMP9) and pro-inflammatory cytokines (IL6). This study showed TAK-242 strongly affects cancer cell survival and invasiveness through TLR4 inhibition, which may suggest TLR4 inhibition as a method for cancer treatment.

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