Macrophage repolarization by host defence peptide and co-delivery with doxorubicin to suppress the growth of triple-negative breast cancer

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Triple-negative breast cancer (TNBC) is an aggressive and challenging subtype of breast cancer characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor-2 (HER2). While chemotherapy remains the most common treatment for TNBC, its limitations—including recurrence, metastasis, and resistance—underscore the need for combination therapeutic strategies such as immunotherapy. Host defense peptides (HDPs), are a class of naturally occurring compounds with emerging anticancer potential. Since HDPs are known to play a critical role in modulating immune responses, we designed and developed disulfide bridge-linked antimicrobial peptides (termed mCA4) based on the host defense protein chicken Angiogenin 4 (chAng4). mCA4 demonstrated significant potential to re-polarize RAW-264.7 murine macrophages from pro-tumorigenic phenotype to anti-tumorigenic phenotype. Treatment of macrophages with mCA4 resulted in an increased expression of pro-inflammatory cytokines (TNF-α, IL-1β) and a decreased expression of anti-inflammatory cytokines (IL-10, TGF-β). Co-culturing mCA4 activated RAW-264.7 macrophages with TNBC cells (4T1) led to the suppression of anti-inflammatory pathways (STAT-3 and STAT-6) and the activation of a pro-inflammatory pathway (STAT-1), resulting in significantly increased apoptosis of TNBC compared to treatment with doxorubicin (DOX) alone *in-vitro*. These findings suggest that mCA4 may offer a promising therapeutic strategy for reprogramming the immune microenvironment in TNBC and enhancing anti-tumor immunity.