IL-1α regulated the induction of proinflammatory cytokine expression in cancer-associated fibroblasts

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Cancer-associated fibroblasts (CAFs) have been shown to secrete high levels of proinflammatory cytokines. These proinflammatory cytokines, such as interleukin-6 (IL-6) and IL-8, were reported to assist cancer cell proliferation, angiogenesis and invasion. However, the mechanisms by which fibroblasts become proinflammatory ones during cancer progression are still not known. Here, we showed that through co-culturing with breast cancer cells for at least three-four passages, breast normal tissue-associated fibroblasts (NAFs) obtained persistent activity for expressing high levels of proinflammatory factors, including IL-1α, IL-1β, IL-6 and IL-8. IL-1α and IL-1β were respectively reported to play a role in induction of IL-6 and IL-8, so we tested the hypothesis that breast cancer cells might induce IL-6 and IL-8 expression in NAFs via an IL-1α or IL-1β signaling pathway. By using an IL-1α neutralizing antibody, we found that abolishment of IL-1α activity completely repressed the enhanced IL-8 expression and partially reduced the enhanced IL-1β and IL-6 expression in NAFs that were pre-cocultured with breast cancer MDA-MB-468 cells. However, an IL-1β neutralizing antibody had no effect on the expression of these cytokines. Furthermore, the treatment of an IL-1α neutralizing antibody also reduced the enhanced IL-1β, IL-6 and IL-8 expression in CAFs. These results suggested that IL-1α may mediate induction of IL-1β, IL-6 and IL-8 expression in cancer-associated fibroblasts. An IL-1α signaling pathway in stromal cells may be a target for prevention of breast cancer development and progression.

Key words: breast cancer cell, fibroblast, IL-1α, proinflammatory cytokine