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Tocilizumab Suppresses the Pro-carcinogenic Effects of Breast Cancer-associated Fibroblasts Through Inhibition of the STAT3/AUF1 Pathway

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Abstract : Active breast cancer-associated fibroblasts (CAFs), the most influential cells in breast tumor microenvironment, express/secrete high levels of the proinvasive/metastatic interleukin-6 (IL-6). Therefore, we have tested here the effect of the IL-6 receptor (IL-6R) inhibitor tocilizumab (TCZ; Actemra) on different active breast CAFs. We have shown that TCZ potently and persistently suppresses the expression of various CAF biomarkers, namely α-SMA, SDF-1 as well as the STAT3 pathway and its downstream target AUF1. TCZ also inhibited the proliferation, migration and invasion abilities of active breast CAF cells. Additionally, TCZ repressed the ability of CAF cells in promoting epithelial-to-mesenchymal transition, and enhancing the migratory/invasive and proliferative capacities of breast cancer cells in vitro. Importantly, these findings were confirmed in orthotopic humanized breast tumors in mice. Furthermore, TCZ suppressed the expression of the pro-angiogenic factor VEGF-A and its transactivator HIF-1α in CAF cells, and consequently inhibited the angiogenic-promoting effect of active CAFs both in vitro and in orthotopic tumor xenografts. These results indicate that inhibition of the IL-6/STAT3/AUF1 pathway by TCZ can normalize active breast CAFs and suppress their paracrine pro-carcinogenic effects, which paves the way toward development of specific CAF-targeting therapy, badly needed for more efficient breast cancer treatments.

Keywords : angiogenesis, interleukin-6, paracrine, cancer-associated fibroblasts
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