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Analysis of the effect of SI-CLP on tumor growth and on the composition of tumor microenvironment

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SI-CLP belongs to the family of chitinase-like proteins that combine properties of cytokines and growth factors. SI-CLP was identified as an intracellular ligand for the multifunctional receptor stabilin-1, expressed on tumor-associated macrophages (TAM). YKL-40, a homologue of SI-CLP, has tumor-promoting activities in animal models for glioblastoma, colorectal carcinoma and breast adenocarcinoma, and elevated levels of YKL-40 in human serum correlate with poor prognosis in various types of cancer. In contrast, previous data obtained in our laboratory demonstrated that SI-CLP has an inhibitory effect on tumor growth in mouse model for breast adenocarcinoma correlating with decreased amount of stabilin-1+TAM. However, the mechanisms of SI-CLP-mediated suppression of tumor growth remain to be unknown. The aims of the present study were to identify the functional role and possible mechanism of SI-CLP effects in cancer development using mouse model for breast adenocarcinoma. The effects of SI-CLP on the biology of cancer cells, tumor angiogenesis, and phenotype and amounts of immune cells in tumor microenvironment were analyzed. To examine whether expression of stabilin-1 on TAM is critical for the tumor-suppressive effect of SI-CLP, TS/A cells stably transfected with SI-CLP (TS/A-SI-CLP) and the control empty vector (control TS/A-EV) were injected subcutaneously into BALB/c wt and stabilin-1 knockout (ko) mice. The suppressive effects of SI-CLP on tumor growth in the stabilin-1 ko mice were similar to wt mice at all time points analyzed (from day 7 until day 21), indicating that SI-CLP does not require stabilin-1 expression on TAM for its intratumoral effects. In vitro analysis of TS/A-SI-CLP and TS/A-EV demonstrated that SI-CLP does not suppress TS/A cell proliferation or migration. Quantitative immunohistochemistry demonstrated that the presence of SI-CLP does not affect tumor angiogenesis and infiltration of neutrophils and eosinophils in vivo. However, SI-CLP significantly inhibited infiltration of TAM in tumor mass without changing their tumor-supporting phenotype. The direct inhibitory effect of SI-CLP on the CCL2 induced recruitment of mouse bone-marrow derived macrophages and human monocytes was demonstrated in vitro. Reduced amount of TAM in TS/A tumor tissue correlated with the decreased amount of FoxP3+ cells, while SI-CLP had no direct effect on T-cell migration in vitro. In summary, the results of the study demonstrated that SI-CLP suppresses growth on breast adenocarcinoma primarily by inhibiting the infiltration of tumor-associated macrophages and reducing tumor-supportive activities of tumor microenvironment.