66 SURFACE NANOTOPOGRAPHY AND CELL SHAPE MODULATE TUMOR CELL SUSCEPTIBILITY TO NK CELL CYTOTOXICITY

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Background Natural killer (NK) cells are innate cytotoxic lymphocytes exerting cytotoxicity against virally infected cells and tumor cells.[1] NK cell cytotoxicity is primarily determined by biochemical signals received by ligands expressed on target cell surfaces. In addition to the biochemical signals, NK cell cytotoxicity could be regulated by biophysical environments of tumor cells such as nanoscale surface topography typically existing on extracellular matrixes (ECMs) or cell morphology determined by ECM or cell density. Matrixes.[2, 3] Engineered surfaces, including soft substrates with various rigidities, nanostructured surfaces, and micropatterned surfaces, may serve as alternative tools to further dissecting the roles of biophysical cues in tumor microenvironment in NK cell cytotoxicity.

Methods To test this possibility, we used engineered surfaces that allowed control of cell shape and surface nanotopography to investigate how NK cell cytotoxicity is regulated by tumor cell shape and surface nanotopography.[4, 5] Tumor cells were plated on flat vs. nanogrooved surfaces, or micropatterned into circular vs. elliptical geometries, and the effects of surface topography and tumor cell morphology on NK cell cytotoxicity were investigated. Cell morphology and cytotoxicity of NK cells were analyzed by live fluorescence imaging. For the filamentous actin intensity measurement, patterned cells were fixed and permeabilized and stained with fluorescence labeled phalloidin.

Results NK cells exhibited significantly higher cytotoxicity against tumor cells on nanogrooved surfaces than those on flat surfaces. However, it was not clear whether nanotopography underlying tumor cells itself was a major factor for enhanced NK cell cytotoxicity or not, as cells cultured on nanogrooved surfaces typically exhibit elongated morphologies. To directly test whether elongated morphology of tumor cells is sufficient for enhanced NK cell cytotoxicity, we manipulated tumor cell shape to circular and elliptical. NK cell exhibited significantly higher cytotoxicity against tumor cells on tumor cells in elliptical patterns than tumor cells in circular patterns. Both nanogrooved surfaces and elongated morphology of tumor cells induced stress fiber formation, which in turn increase cytoskeletal tension. Thus, we checked correlation between stress fiber formation and cytotoxicity, and found positive correlation between them.

Conclusions These results indicate that tumor cells in elliptical micropatterns or on nanogrooved surfaces are more susceptible for NK cell-mediated cytotoxicity due to increased cellular tension by stress fiber formation. These results suggest that biophysical microenvironments surround tumor cells influence NK cell cytotoxicity against tumor cells by cytoskeletal tension regulation.

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