Proteolysis in close vicinity of tumor cells is a hallmark of cancer invasion and metastasis. We show here that mouse mammary tumor virus-polyoma middle T antigen (PyMT) transgenic mice deficient for the cysteine protease cathepsin B (CTSB) exhibited a significantly delayed onset and reduced growth rate of mammary cancers compared with wild-type PyMT mice. Lung metastasis volumes were significantly reduced in PyMT; ctsb(+/-), an effect that was not further enhanced in PyMT; ctsb(-/-) mice. Furthermore, lung colonization studies of PyMT cells with different CTSB genotypes injected into congenic wild-type mice and in vitro Matrigel invasion assays confirmed a specific role for tumor-derived CTSB in invasion and metastasis. Interestingly, cell surface labeling of cysteine cathepsins by the active site probe DCG-04 detected up-regulation of cathepsin X on PyMT; ctsb(-/-) cells. Treatment of cells with a neutralizing anti-cathepsin X antibody significantly reduced Matrigel invasion of PyMT; ctsb(-/-) cells but did not affect invasion of PyMT; ctsb(+/-) or PyMT; ctsb(+/+) cells, indicating a compensatory function of cathepsin X in CTSB-deficient tumor cells. Finally, an adoptive transfer model, in which ctsb(+/-), ctsb(+/-), and ctsb(-/-) recipient mice were challenged with PyMT; ctsb(+/-) cells, was used to address the role of stroma-derived...
CTSB in lung metastasis formation. Notably, ctsb(-/-) mice showed reduced number and volume of lung colonies, and infiltrating macrophages showed a strongly up-regulated expression of CTSB within metastatic cell populations. These results indicate that both cancer cell-derived and stroma cell-derived (i.e., macrophages) CTSB plays an important role in tumor progression and metastasis.