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Modulation of invasive properties of CD133(+) glioblastoma stem cells: A role for MT1-MMP in bioactive lysophospholipid signaling.

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Future breakthroughs in cancer therapy must accompany targeted agents that will neutralize cancer stem cells response to circulating growth factors. Since the brain tissue microenvironmental niche is a prerequisite for expression of the stem cell marker CD133 antigen in brain tumors, we investigated the invasion mechanisms specific to CD133(+) U87 glioblastoma cells in response to lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P), two circulating bioactive lysophospholipids and potent inducers of cancer. A CD133(+) U87 glioma cell population was isolated from parental U87 glioblastoma cells using magnetic cell sorting technology. The CD133(+)-enriched cell population grew as neurospheres and showed enhanced maximal response to both LPA (approximately 5.0-fold) and S1P (approximately 2.5-fold) at 1 microM when compared to parental U87 cells. The increased response to LPA in CD133(+) cells, reflected by increased levels of phosphorylated ERK, was found independent of the cooperative functions of the membrane-type-1 matrix metalloproteinase (MT1-MMP), while this cooperativity was essential to the S1P response. Quantitative RT-PCR was performed and we found higher gene expression levels of the S1P receptors S1P1 and S1P2, and of the LPA receptor LPA1 in CD133(+) cells than in their parental U87 cells. These increased levels reflected those observed from in vivo experimental U87 tumor implants. Our data suggest that the CD133(+) cell subpopulation evokes most of the lysophospholipid response within brain tumors through a combined regulation of S1P/LPA cell surface receptors signaling and by MT1-MMP. The emergence of lead compounds targeting the stem cell niche and S1P/LPA signaling in CD133(+) cancer cells is warranted. (c) 2009 Wiley-Liss, Inc.

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