

CXCR4-SDF-1 AXIS IN METASTASIS OF RHABDOMYOSARCOMAS

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We hypothesized that the CXC chemokine receptor-4 (CXCR4) –stromal-derived factor-1 (SDF-1) axis may be involved in the metastasis of CXCR4-positive tumor cells into the bone marrow and lymph nodes, which secrete the chemokine SDF-1. To explore this hypothesis further, we phenotyped various human tumor cell lines for expression of CXCR4, and found that it was not detectable (as assessed by FACS) in human melanoma (8), breast (5) and lung cancer (5) cell lines, but was highly expressed on the cell surface in 7 out of 7 rhabdomyosarcoma (RMS) cell lines (as determined by FACS). We also found that cell lines derived from alveolar RMS, which is associated with a poor prognosis, expressed higher levels of CXCR4 than the lines derived from embryonal RMS. Since RMS frequently metastasizes to the bone marrow and lymph nodes, we postulated that the CXCR4–SDF-1 axis could play an important role in this process. We tested the various biological responses of CXCR4⁺ RMS cell lines to stimulation by SDF-1, such as phosphorylation of signaling proteins, proliferation, survival, migration and adhesion, as well as the expression of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs). We found that although SDF-1 did not affect the proliferation or survival of these cell lines, in several of them, it induced: i) phosphorylation of MAPK p42/44; ii) locomotion; iii) chemotaxis across membranes covered by laminin or fibronectin; and iv) adhesion to laminin and fibronectin as well as increasing MMP-2 and diminishing TIMP secretion. Based on these observations, we suggest that the CXCR4–SDF-1 axis may play an important role in tumor spread and the metastasis of RMS cells to bone, and that molecular strategies aimed at inhibiting this axis could thus prove to be useful therapeutic measures.