

EXPRESSION OF CXCR4 AND SDF1/CXCL12 IN HUMAN NORMAL PITUITARY AND PITUITARY ADENOMA TISSUES: ROLE IN CELL PROLIFERATION

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Introduction: Pituitary adenomas represent up to 15% of primary intracranial tumors and are associated with significant morbidity due to local mass-related effects and/or hormone hypersecretion. Growth factors and cytokines are involved in development, functioning and cell division in the pituitary. Chemokines are now recognized as mediators in several physiologic and pathologic processes in both the central nervous and the endocrine systems. The chemokine stromal cell-derived factor 1 (SDF1/CXCL12) and its receptor, CXCR4, was reported to play a relevant role in cell proliferation and migration, tumor angiogenesis and progression in many tumor histotypes. **Objective:** To study the expression of the chemokine SDF1 and its receptor CXCR4 in normal human pituitary and pituitary adenomas, as well as their possible role in adenoma cell proliferation. **Methods:** The expression of SDF1 and CXCR4 in 56 human pituitary adenomas (25 GH-secreting adenomas, GHomas, and 31 non functioning pituitary adenomas, NFPAs) and in normal pituitary was evaluated by RT-PCR and immunohistochemistry (IHC). The functional role of CXCR4 was analyzed by [³H]-thymidine uptake assays in 7 fibroblast-free primary pituitary adenoma cell cultures (1 GHoma, 1 ACTH secreting adenoma and 5 NFPAs). **Results:** Twenty-three out of 25 (92%) GHomas express CXCR4 and 15 out of 25 (58%) SDF1 mRNAs. Among NFPAs 24/31 (77%) express CXCR4 and SDF1 mRNAs, and 18/31 (58%) of cases co-express the receptor and its ligand. IHC displayed a marked staining for CXCR4 and SDF1 in the adenomatous cells of both GHomas and NFPAs, confirming the RT-PCR data. Interestingly, in normal pituitary tissues CXCR4 was expressed only in a subset of cells and SDF1 labeling was almost absent. SDF1 (25nM) increased the *in vitro* proliferation of primary cell cultures of both GHomas and NFPAs, inducing a statistically significant increase (up to 60%, $P < 0.05$) in DNA synthesis in 5/7 cultures. Moreover, adenoma cells released SDF1 *in vitro*. The CXCR4 antagonist AMD3100, as well as somatostatin, the main physiological inhibitor of endocrine cell proliferation, significantly inhibited SDF1-induced mitogenic signals. **Conclusions:** These findings report, for the first time, that CXCR4 and SDF1 are overexpressed in human pituitary adenomas and that their concomitant expression may sustain tumor growth *via* an autocrine/paracrine pathway. Moreover, the results from *in vitro* assays demonstrate the presence of a functional CXCR4/SDF1 signalling in pituitary adenoma controlling cell proliferation and possibly contributing to the development of adenomas in humans.