CXC chemokine receptor 4 is essential for maintenance of renal cell carcinoma-initiating cells and predicts metastasis.

Abstract:
In many solid tumors, cancer stem cells (CSC) represent a population with tumor-initiating, self-renewal, and differentiation potential, which can be identified by surface protein markers. No generally applicable markers are yet known for renal cell carcinoma (RCC). Two RCC cell lines (RCC-26, RCC-53) were found to differ widely in their capacity to form spheres in vitro and to establish tumors in mice, potentially reflecting differences in CSC content. A subpopulation expressing the CXC chemokine receptor 4 (CXCR4) was present only in the more tumorigenic cell line RCC-53. When grown as spheres, most of the RCC-53 cells were CXCR4-positive, expressed stem cell-associated transcription factor genes at elevated levels, and were more resistant toward the tyrosine kinase inhibitors sunitinib, sorafenib, and pazopanib. Sorted CXCR4-positive cells exhibited greater capacity for sphere formation and tumor growth-inducing potential in vivo than CXCR4-negative cells. Significantly, higher CXCR4 mRNA levels in primary RCC tumors from patients with localized but not disseminated disease predicted shorter survival. Downregulation of CXCR4 expression by small interfering RNA (siRNA) or pharmacological inhibition by AMD3100 compromised tumor sphere
formation, viability of CXCR4-positive cells, and increased their responsiveness toward tyrosine kinase inhibitors. In conclusion, CXCR4 identifies a subpopulation of tumor-initiating cells in RCC cell lines and plays a role in their maintenance. The relative insensitivity of such cells to tyrosine kinase inhibitors might contribute to the development of therapy resistance in RCC patients. Future therapies therefore could combine blockade of the CXCR4 signaling pathway with standard therapies for more effective treatments of metastatic RCC.

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