The Therapeutic Potential of Suppressing Chemokine Receptor CXCR4 Pathway Components in Small Cell Lung Cancer (SCLC) Through First-Generation Potent Inhibitors

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Characterized as recalcitrant cancer, small cell lung cancer (SCLC) is a rare neuroendocrine-type lung cancer with growing resistance to immune checkpoint inhibitors, leading to rapid metastatic relapses and acquired drug resistance. Using chemical signaling, tumor cells can communicate with their tumor microenvironment and other cells, but the autocrine and paracrine effects of signaling secreted by SCLC are unclear. The expression of CXCR4 and CXCL12 in a wide range of malignancies (~85%) suggests that inhibitors targeting this axis may have therapeutic interventions beyond SCLC. Moreover, data reveals that MIF and CXCL12 are SCLC's most highly secreted cytokines. To identify the therapeutic potential of suppressing chemokine receptor CXCR4 pathway components, two SCLC cell lines were drugged with three inhibitors (Grk6-IN-1, ISO-1, Plerixafor) through drug assays. Results indicated that inhibiting CXCR4 and other CXCR4-axis components significantly affects the pathway and the ability of metastasis. Western blots showed homozygous knockouts of CXCR4, resulting in reduced expression of GRK6, CXCL12, and MIF in cell viability. Similarly, ISO-1 and Plerixafor were shown to prevent colony formation at low drug and cell uM while displaying some cytotoxic activity at higher concentrations as a regimen designed to prevent metastasis. Grk6-IN-1 demonstrated cytotoxic activity (as seen in MTS assays) at ~1 uM while preventing colony formation at lower drug and cell uM. Although Grk6-IN-1 is a first-generation kinase inhibitor previously used in one MM clinical trial, results suggest that GRK6 may be a promising drug target in SCLC and that developing next-generation drugs for GRK6 should be pursued.

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