



# CXC chemokine ligand 12 (CXCL12) via its cognate receptor (CXCR4) controls the chemotaxis of multiple myeloma cell line (U266) via PI3K/AKT, PLC $\beta$ 3, RhoA, NF $\kappa$ B and ERK1/2

Gamal Badr

## Abstract:

In multiple myeloma (MM), malignant plasma cells reside in the bone marrow, where they accumulate in close contact with stromal cells. Chemotaxis of malignant plasma cells and stromal cells in the surrounding microenvironment is an essential component of tumour dissemination during progression and metastasis. The mechanisms responsible for the chemotaxis of malignant plasma cells in the bone marrow are still poorly understood. Thus, in the present study, we investigated the mechanisms involved in the chemotaxis of U266 MM cell line. U266 cells strongly expressed CCR9, CXCR3 and CXCR4 chemokine receptors, but only migrated toward CXCL12 (the sole ligand for CXCR4). To clarify the signaling pathways involved in the regulation of MM cell chemotaxis, we therefore analyzed the effect of various inhibitors targeting intracellular effector proteins on the CXCL12-mediated chemotaxis of U266 using flow cytometry and Western blot analysis. Using flow cytometry, we observed that the chemotaxis of U266 cell towards CXCL12 was completely abrogated by adding AMD (CXCR4 antagonist), PTX (G-protein coupled receptor inhibitor) and U73122 (Phospholipase C inhibitor). Moreover, CXCL12-mediated U266 chemotaxis was partially inhibited by 1  $\mu$ M wortmannin (WM, Class II PI3K inhibitor), SH5 (AKT inhibitor), Y27632 (RhoA inhibitor), SN50 (NF $\kappa$ B inhibitor) and PD98059 (ERK1/2 MAPK inhibitor). Similar results were obtained using Western blot analysis where we observed that triggering of CXCR4 by CXCL12 resulted in the activation of PLC $\beta$ 3, AKT, RhoA, NF $\kappa$ B and ERK1/2. Taken together, our results revealed that PLC $\beta$ 3, PI3K/AKT, RhoA, NF $\kappa$ B and ERK1/2 are crucial effectors for CXCL12-mediating MM cell chemotaxis.

## Keywords:

Western blot, CXCL12, chemotaxis, flow cytometry, multiple myeloma.

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