

The CXCL12-CXCR4 chemotactic pathways as a target of adjuvant breast cancer Therapies

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In this review, Epstein discusses the potential role of the CXCL12 chemokine and its receptor, CXCR4, in the mechanisms for tumour micrometastasis and for hormonal and cytotoxic anti-cancer therapies.

Epstein suggests that the increase in circulating granulocyte colony stimulation factor (G-CSF) in response to moderate neutropenia and dose-dense chemotherapy could exert beneficial effects through CXCL12-CXCR4 regulation. Moderate neutropenia induces a compensatory increase in G-CSF due to secretion from bone-marrow stromal cells, and dose-dense chemotherapy is facilitated by exogenous G-CSF support, as well as by release of endogenous G-CSF from damaged stromal and endothelial cells. As well as inducing neutrophil proliferation, G-CSF induces neutrophil mobilisation into the bloodstream through the action of the serine protease DPPIV on CXCL12. Cleavage of this chemokine prevents its interaction with the CXCR4 receptor on the surface of neutrophils and permits their release from the bone marrow into the blood stream. Reduced concentration gradients of active CXCL12 are then no longer able to retain neutrophils in the bone marrow.

CXCR4 is not only expressed on the surface of neutrophils but is also frequently overexpressed in breast cancer cells. Furthermore, tissues to which breast cancer cells metastasize express CXCL12. Therefore the increase in G-CSF in response to either moderate neutropenia or administered with dose-dense chemotherapy could help prevent the micrometastasis of breast cancer cells. Since oestradiol induces the expression of CXCL12 in breast cells, irrespective of ER status, Epstein suggests that anti-hormonal treatments may also be successful in patients with ER-poor, CXCR4-positive disease.

<http://www.ncbi.nlm.nih.gov/pubmed/15516962?dopt=Citation>

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