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PROGRESSI E PROSPETTIVE DELLE TERAPIE CELLULARI

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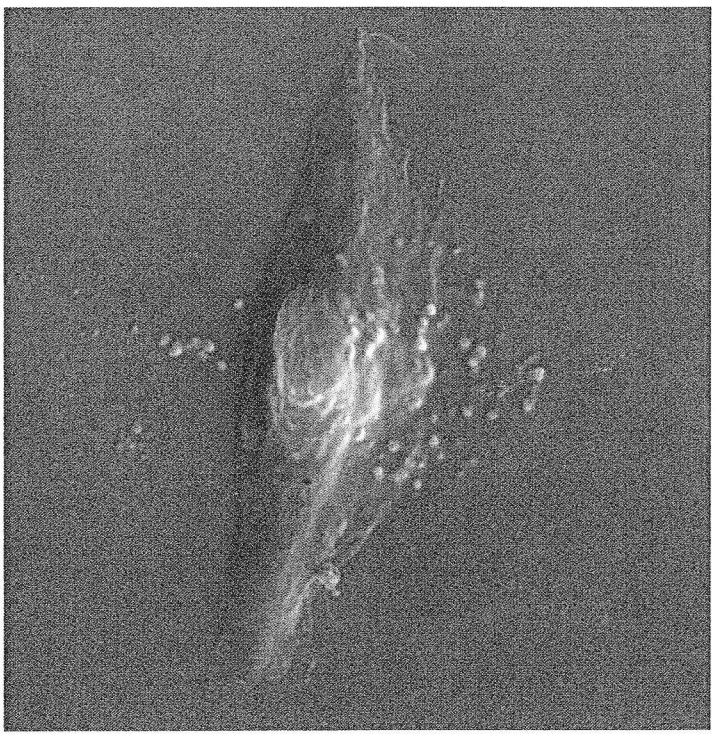
MESENCHYMAL STROMAL CELLS ADVANCES



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Exosomes mediate a paracrine interplay between Chronic Myelogenous Leukaemia and stromal cells: a role for interleukin 8

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Chronic myeloid leukaemia (CML) is a clonal hematopoietic stem cell disorder in which leukemic cells display a reciprocal t(9:22) translocation that results in the formation of the chimeric Bcr-Abl oncoprotein with a constitutive tyrosine kinase activity. As a consequence, Bcr-Abl causes increased proliferation, inhibition of apoptosis and altered adhesion of leukemic blasts to bone marrow (BM) microenvironment. Exosomes are small vesicles of 40-100 nm diameters that are initially formed within the endosomal compartment and are secreted when a multivesicular body (MVB) fuses with the plasma membrane. These vesicles are released by many cell types including cancer cells and are considered messengers in intercellular communication. Recently, a considerable interest in the cancer field has focused on tumour microenvironment and how the interaction between malignant cells and normal host cells affects cancer progression. Several data indicate that during cancer progression, tumour stroma has not only a supportive role, but is also a leading player in the modulation of carcinoma development. A stimulating aspect in the field of CML biology is the role of the microenvironment in regulating the growth, survival and drug-resistance of leukemic cells. Bone marrow (BM) stromal cells are the source of signals such as cytokines, growth factors and ECM molecules that can modulate leukaemia cell growth and response to drug. Exosomes released by cancer cells constitute an important part of the tumour microenvironment as they can transfer various messages to target cells thus affecting disease, pointing out the role of vesicles as new actors in the crosstalk between cancer and normal cells in the tumour microenvironment. Data concerning the effect of exosomes in CML-stromal cell interactions are up to now missing. Our proposal is to better investigate if the release of exosomes from CML cells can modulate the tumour microenvironment (the secretion of both soluble and insoluble molecules) through a paracrine interplay among leukaemia cells and stromal cells. Our results showed that treatment of stromal cells, HS5, with CML-derived Exo induced a significant increase of IL8 as well as LAMA84 cell adhesion to stromal monolayer. Addition of recombinant IL8 to LAMA84 cells activated survival pathways and increased the adhesion of leukemic cells to stroma. The inhibition of IL8 receptors, CXCR1 and CXCR2, on LAMA84 cells, reverted the previously described effects. In conclusion, we show that leukemic and stromal cells establish a bi-directional crosstalk: CML-derived exosomes induce the production of the IL8 in stromal cells thus sustaining the growth and survival of CML cells in a paracrine way.