


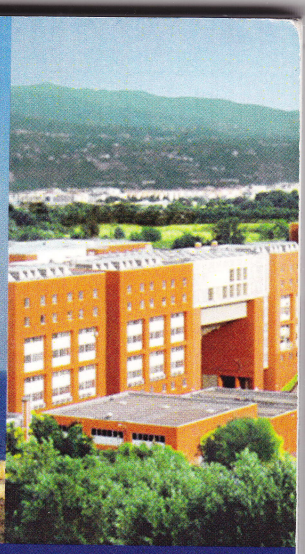

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Programma & Abstracts

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Sessione IV
Meccanismi molecolari in sistemi complessi

Crosstalk between chronic myelogenous leukemia (CML) and bone marrow stromal cells: role of interleukin 8 and CML derived- exosomes

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Chronic myelogenous leukemia (CML) is a myeloproliferative disorder characterized by the t(9:22)(q34:q11) reciprocal translocation, resulting in the expression of the chimeric Bcr–Abl oncoprotein with constitutive tyrosine kinase activity. Exosomes (Exo) are small vesicles of endosomal origin and of 40-100 nm diameter released by many cell types including cancer cells. Several data indicate that Exo play an important role in cell-to-cell communication and tumor-stroma interaction, thus potentially affecting cancer progression. It is well known that stromal microenvironment contributes to disease progression through the establishment of a bi-directional crosstalk with cancer cells. In the bone marrow (BM), stromal cells are able to sustain the growth and survival of leukemic cells by protecting malignant cells from chemotherapy- induced death; on the other hand, leukaemia cells induce changes in the bone marrow stroma composition. Our hypothesis is that CML exosomes could have a functional role in this crosstalk. We demonstrate that treatment of BM-derived-HS5 cells with LAMA84-released Exo induced a significant increase of Interleukin 8 (IL8), as well as an augmented LAMA84 cell adhesion to stromal monolayer and LAMA84 migration towards HS5 conditioned medium. To better investigate the possible role of IL8 in the modulation of leukemia phenotype, we treated CML cells with recombinant IL8 (rIL8). Addition of rIL8 to LAMA84 cells increases the adhesion of leukemic cells to stromal cells and triggers survival pathways, as demonstrated by colony formation assay in methocult and activation of signal transduction pathways by western blot. Inhibition of IL8 receptors, CXCR1 and CXCR2, with SB225002 on LAMA84 cells reverts the effects described previously, confirming a role of IL8 in this crosstalk. In conclusions our data show that LAMA84-derived Exo modulate bone marrow microenvironment, increasing the production of the IL8 by stromal cells; moreover IL8 is able to affect leukemia cell proliferation and survival in a paracrine fashion.