Chronic myeloid leukaemia-derived exosomes promote tumour growth through an autocrine mechanism

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Objective
Cancer cells can generate their own signals in order to sustain their growth and survival and recent studies have revealed the role of cancer derived-exosomes in modulating cancer cell behaviour. The aim of the present work is to evaluate the autocrine role of exosomes derived from Chronic Myeloid Leukaemia (CML) cells.

Materials and Methods
Cell line used in experiments is LAMA84, a human CML cell line. MTT, Brdu and colony formation assays were performed after up to 1 week of exosomes treatment. NOD-SCID mice were subcutaneously injected with LAMA84 and exosomes. Western Blot and Real Time PCR analysis were performed in in vitro and in vivo samples to assess the expression of pro- and anti-apoptotic molecules, as well as the signal transduction pathways. TGF-β1 receptor inhibitor was used on exosomes-treated cells.

Results
CML cells exposed to CML exosomes, show a dose dependent increased proliferation compared with controls. Treatment of mice with exosomes caused a greater increase in tumour size compared with control (PBS-treated mice). Real time PCR and western blot analysis showed an increase of mRNA and protein levels of anti-apoptotic molecules and a reduction of the pro-apoptotic molecules both in in vitro and in vivo samples. Furthermore, we found that TGF- β1 was enriched in CML-exosomes and that exosomes- stimulated proliferation of leukaemia cells, as well as the exosome-mediated activation of the anti-apoptotic phenotype, could be abrogated by blocking TGF-D1 signalling.

Conclusion
CML derived-exosomes promote, through an autocrine mechanism, the proliferation and survival of tumour cells by activating anti-apoptotic pathways. This mechanism is dependent by a ligand-receptor interaction between TGF-β1, in CML exosomes, and TGF- β1 receptor in CML cells. Our data underline the importance of evaluating the role of leukaemia-derived exosomes for the development of combinatorial therapies that potentiate the effect of Imatinib treatment.