

Chronic Myelogenous Leukemia: Approaches to Pharmacological Resistance

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Editorial

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder characterized by the reciprocal t (9:22) chromosomal translocation. This rearrangement produces the so-called Philadelphia chromosome carrying the chimeric Bcr-Abl oncoprotein, p210, responsible of disease progression [1].

Because of its critical role in pathogenesis, the scientific community had focused on targeting Bcr-Abl for treatment of CML. For many years Imatinib (IM), as selective inhibitor of the Tyr-Kinase activity of the oncoprotein, was used to treat CML patients [2].

From 2000 some data relative to IM resistance were available. There are many mechanisms responsible of IM resistance, more often point mutations that cause the progression to blast crisis and death in few months. To circumvent them, more potent TKIs have been subsequently approved [3]. However, another problem arise: these compounds don't work on all patients because of the different IM-resistant mutants of BCR-ABL[4].

Therefore, there is a continuous need for new drugs and combinations that could improve responses and survival rates for CML. Moreover, because of the complexity of signalling pathways and the overexpression of many of them on tumour cells, the simultaneous use of different drugs to target alternative signalling may produce an higher therapeutic success accompanied by less toxicity.

After a comparative functional and proteomic analysis of CML cell lines [5], we worked many years trying to overcome IM-resistance with new compounds and we studied the effects of Carboxyamidotriazole (CAI) and later of Carboxyamidotriazole Orotate (CTO) on CML cell lines IM-resistant. Calcium is a well-known second messenger involved in regulation of cell proliferation and apoptosis. Many data indicate that Ca²⁺ regulates signalling transduction pathways involved in malignant phenotype and tumor progression [6]; furthermore, Ca²⁺ homeostasis can affect development and progression of CML [7].

CAI, an inhibitor of calcium-mediated signal transduction pathways, is one of the first cytostatic signal inhibitor proposed as anti-cancer drugs. It has been tested in solid tumor patients in Phase I and II clinical trials at the National Cancer Institute [8,9]. CTO is the orotate salt form of CAI, developed at Tactical Therapeutics. INC (New York, NY, USA). CTO shows a reduced toxicity, increased oral bioavailability and achieves higher plasma concentrations and stronger efficacy when compared to the parental compound [10].

We demonstrated that CAI reduces cell proliferation, increases cell death and it is able to inhibit both bcr-abl dependent and independent signalling pathways on IM-resistant CML cell lines [11]. In light of this results, we keep working to better clarify the molecular mechanisms of CAI on our CML model. For this reason, we used three myeloid murine cell lines (32D) encoding for BCR/ABL-p210 (full

length), BCR/ABL-T315I and BCR/ABL-E255K mutants. T315I and E255K are two mutations frequently observed in CML patients; in presence of these mutations IM cannot bind to the kinase or cannot recognize it because the kinase maintain an inactive conformation. We demonstrated that CAI exert its effects through an increase of reactive-oxygen species that in turn modulate total amount and activity of the oncoprotein Bcr-Abl, downstream signalling and apoptosis [12]. Because of the higher solubility and efficacy of CTO with respect to the parental compound (CAI), we also tested the effects of CTO on IM-resistant CML cell lines, demonstrating its inhibitor effects on cell proliferation and on CML tumor xenografts growth; moreover CTO modulates angiogenesis in vitro and in vivo [13].

Many advances have been made in understanding the biology of tumor and the scientific community begin to take care of the bone marrow microenvironment that play a prominent role for the progression of malignant cells through the pre-metastatic niche formation.

In particular, importance has been made on the role of cytokines, growth factors, adhesion molecules released by both tumor and non-tumor cells into the microenvironment that provide a suitable niche for cancer cell growth and survival. In this context, a number of studies investigated the role played by microvesicles released by cells as cargos of cytokines or nucleic acids (e.g. mRNAs or miRNAs) and in the modulation of tumour progression [14,15]. Between microvesicles, exosomes are classified according to their endosomal origin and their size (40-100 nm). Recent publications describe exosomes as new players in modulating the tumor microenvironment, promoting angiogenesis and tumor development [16]. Trying to clarify the role of CML-derived exosomes in the pre-metastatic niche formation, we studied the crosstalk between CML and bone marrow stromal cells. First of all we demonstrated that CML survival and resistance to chemotherapy are affected by bone marrow stromal cells and that CML cells release exosomes that are able to influence in vitro and in vivo angiogenesis [17,18]. Later we clarify the mechanism demonstrating that addition of CML-derived exosomes to vascular endothelial cells as well as to bone marrow stromal cells is able to induce both in vitro and in vivo tumor progression, through the stimulation of interleukin 8-mediated paracrine and autocrine loops [19,21].

The EGFR is a signal transducer highly conserved during evolution. It plays an important role in different physiological processes, as well as in cancer progression. Recent evidences describe an extracrine (exosomal targeted receptor activation) signalling involving the exosomes-mediated packaging and release of EGFR ligands [22]. AREG is an EGFR ligand highly expressed in different tumors; importantly, tumor exosomes carrying AREG are rapidly internalized leading to cancer cell invasion [23].

We demonstrated a new extracrine signalling where CML derived exosomes, carrying AREG, modulate bone marrow microenvironment through activation of EGFR signalling on stromal cells and subsequent release of IL8. Importantly, exosomes isolated from serum of CML patients carry AREG, thus confirming the role of AREG-EGFR axis mediated by CML exosomes, also *in vivo* [24].

Conclusion

In the bone marrow microenvironment, 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.

Briefly, we have demonstrated a possible mechanism through which, in the context of this bidirectional crosstalk, CML exosomes exert their effect on tumor microenvironment: CML exosomes, through activation of EGFR in stromal cells, induce the production and release of IL8; IL8 supports the growth and survival of CML cells both *in vitro* and *in vivo*. These results contribute to better understand the role of exosomes in the crosstalk between bone marrow derived cells and CML cells and may suggest new therapeutic approaches involving exosomes and their content for early diagnosis and treatment of chronic myelogenous leukemia.

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