

Role of direct intercellular exchange of vesicles and proteins in modulating biological functions of chronic myeloid leukemia cells by stromal cells

Over the recent years there has been growing interest in cell-cell interactions as well as the intercellular exchange of cellular cargo (e.g. proteins) between cells. On one hand cell-cell interactions relying on the direct contact-dependent intercellular exchange of cargo seem to call into question the cell theory which claims that each cell is an autonomous unit. On the other hand this is a phenomenon of great significance both in physiological and pathological conditions as it allows us to explain multiple phenomena driven by mechanisms that remained unknown until now. Moreover, it is likely to play an important role in cancer development.

We have decided to investigate the process of direct intercellular exchange of cellular cargo in chronic myeloid leukemia (CML). CML is driven by the expression of fusion oncogene BCR-ABL with constitutive tyrosine kinase activity. In the first (chronic) phase patients are likely to respond to treatment with tyrosine kinase inhibitors (TKIs, e.g. imatinib, dasatinib). However, after some time there is a relapse of the disease and its progression to blast crisis phase when the majority of patients turn out to be resistant to the currently applied therapies. Interactions between CML cells and bone marrow stromal cells are known to be significantly responsible for progression of the disease and the fact of acquiring resistance to treatment.

Tunneling nanotubes (TnTs) are the mainly proposed structures that facilitate the above-mentioned direct intercellular exchange of cargo. They are thin and long membranous channels interconnecting cells. As they contain some types of cytoskeletal components, organelles and molecules can be transported within them directly from one cell to the other. Our preliminary data has shown that TnTs interconnect leukemic and stromal cells. What is more, we have demonstrated that the intercellular exchange of vesicular cargo between these cells depends on the direct contact between them and is regulated by the currently used anti-CML drug – imatinib.

Therefore we have formulated a hypothesis that the direct contact-dependent intercellular exchange of vesicles and proteins has a significant functional meaning for CML cells functioning. In the proposed studies we are going to focus on the identification and analysis of proteins transferred in a TnT-mediated manner within vesicles towards leukemic cells. Also, we are going to verify whether vesicular cargo transferred from stromal to leukemic cells can modulate their biological functions, relevant to CML progression. These data will broaden our understanding of direct intercellular communication of CML cells with their microenvironment and its impact on leukemia development. In further perspective, our results can possibly indicate novel processes regulated by CML microenvironment which may be targeted in future therapies.