Relationship Between c-Abl and ADAM Proteins in the Progression of Chronic Myeloid Leukemia (CML)

Ferretti, G. D. S. 1, Oliveira, G.A.P. 1, Carvalho, C.A.M. 1, Gomes, A.M.O. 1 and Silva, J.L. 1

1 Laboratório de Termodinâmica de Proteínas e Estruturas Virais Gregorio Weber, IBqM, UFRJ, Río de Janeiro, RJ, Brasil.

Post-translationally modifications have effects on the location and activity of proteins. In cancer, this issue is becoming increasingly important, as key oncoproteins require this type of modification. The c-Abl protein, directly involved in the CML development, is expressed in two spliced forms: 1a (non-myristoylated) and 1b (myristoylated). In CML-cells, the resulting Bcr-Abl protein leads to an altered adhesion of progenitor cells to the bone marrow stroma, which fails to differentiate, and consequently populate the bloodstream as naive cells. ADAM proteins, also known as sheddases, are transmembrane polypeptides that cut off or shed extracellular portions of transmembrane proteins, being directly involved in cell-cell and cell-extracellular matrix (ECM) interactions. Once both proteins play a role in different cancer phenotypes, the main goal of this work is to investigate the relationship between them in the CML context. Confocal Microscopy from transfected HEK293T cells showed that c-Abl-1b variant was present in the cell cytosol and also in membrane region, while c-Abl-1a was entrapped in a condensed region. Decreased expression of ADAM-10 mRNA was observed by reverse-transcriptase polymerase chain reaction (RT-PCR) when c-Abl-1b protein was overexpressed in HEK293T cells as compared to the non-myristoylated protein. In contrast with transcript results, increased levels of ADAM-10 were observed by western blotting data. ADAM-15 and -17 were not affected. These set of results suggest an involvement of c-Abl in the regulation of ADAM-10 protein through the myristoyl tether. Understanding how these proteins regulate each other could help to elucidate its mechanism of action and the progression of CML.