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Anchoring ABL for a better fate

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Chronic Myelogenous Leukemia (CML) is a cancer of the white blood cells that is most commonly found in adults and in the elderly. Its incidence has been estimated to be 1 to 2 in 100,000 people. CML was the first cancer to be associated with a genetic abnormality, known as the Philadelphia Chromosome, which 95% of all CML patients carry in their cells.

The Philadelphia Chromosome is formed by exchanges of material belonging to two distinct chromosomes, number 9 and number 22. To form the Philadelphia Chromosome, these two chromosomes break at very specific places, disrupting the BCR (in chromosome 22) and the ABL (in chromosome 9) genes that were otherwise normal. Juxtaposition of these two genes in the Philadelphia Chromosome creates an abnormal kinase tyrosine known as BCR/ABL, which is an enzyme associated with cell regulation. The Philadelphia Chromosome is associated with loss of cell control and presence of immortal cells, which leads to cancer.

In the 1990s, ST1-571 (known as imatinib or Gleevec), a new inhibitor of kinase tyrosine, was developed and tested against CML cells. Since then, the drug has been used as the first line of treatment in many patients, increasing survival rates and improving patients' quality of life. However, some patients develop resistance to the drug, which has fostered development of novel drugs that act on alternative sites on the BCR/ABL enzyme.

Aiming to gain in-depth knowledge about the mechanisms involved in ABL control in normal cells, a group led by Dr. Jerson Silva at the

Federal University of Rio de Janeiro, Brazil used small angle X-ray scattering, nuclear magnetic resonance, and confocal microscopy to investigate the dynamics of the entire ABL regulatory unit. The study shows that activation of the protein releases intramolecular interactions between a regulatory unit found in the N-terminal region of the ABL, the so-called N Cap, and a number of molecular modules, and pushes ABL to anchor on the cell membrane. The whole complex undergoes motions lasting micro- to milliseconds that ultimately result in the death of the cell.

The study also reveals that changes in the N-terminal region, or its absence, are associated with the entire cell escaping apoptosis, the mechanism responsible for cell death. With no apoptosis, cells become immortal and cancer strikes.

The finding has major implications for CML research as it has been known for some time that CML cells are resistant to apoptosis and that, unlike their normal counterparts, they are not found anchored to the cell membrane but loose in the cell cytoplasm. According to Guilherme A. P. de Oliveira, the first author of the study, "our findings indicate that the ABL regulatory unit is involved with the right localization of the enzyme in the cell, dictating the fate of the cell."

The results also gain further importance in the light of recent studies showing that ABL kinases have enhanced expression and activity in some solid tumors.

More information: "Intramolecular dynamics within the N-Cap-SH3-SH2 regulatory unit of the c-Abl tyrosine kinase reveal targeting to the cellular membrane" *Journal of Biological Chemistry*, www.jbc.org/content/early/2013 … jbc.M113.500926.long