A discovery could be important for the therapy of lymphoma and leukemia

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A recent scientific discovery made by researchers at the Institut de recherches cliniques de Montréal (IRCM) led by Dr. Javier Marcelo Di Noia, Director of the Mechanisms and Genetic Diversity research unit, was published online today by The *Journal of Experimental Medicine*. The team identified a mechanism regulating activation-induced deaminase (AID), which could be important for the therapy of some types of lymphoma and leukemia.

AID is a B-lymphocyte enzyme that creates deliberate mutations in the DNA encoding antibodies, which helps produce an appropriate immune response. However, inappropriate expression of AID can also have harmful effects and lead to certain oncogenic (cancer-causing) mutations. When found in a tumour, uncontrolled levels of AID could increase the rate of gene mutation and, in turn, accelerate the progression of the disease.

"In studying the regulation of AID, we attempted to understand what restricts its access to the cell's nucleus," explains Alexandre Orthwein, doctoral student in Dr. Di Noia's research unit and first author of this study. "If we could control that aspect, we could prevent AID's negative mutating effects. We then discovered that Hsp90, one of the most abundant and vital proteins found in cells, stabilizes AID in the cytoplasm. Cytoplasmic AID is in fact in a dynamic equilibrium regulated by Hsp90."

By stabilizing AID, Hsp90 determines the enzyme's overall expression

levels, which correlate with the extent of its physiological functions. Hence, Hsp90 assists AID-mediated antibody diversification. A number of Hsp90 inhibitors being commercially available, the researchers found that Hsp90 inhibition destabilizes AID, thus resulting in a proportional reduction in antibody gene diversification. Moreover, since AID levels also correlate with its pathological side effects, Hsp90 inhibition prevents uncontrolled off-target mutation by AID.

"We showed that inhibiting Hsp90 with known drugs, which are also currently used in clinical trials for the treatment of certain cancers, significantly reduces the amount of AID and, consequently, prevents this enzyme's undesired activity on DNA," adds Dr. Di Noia. "This regulatory mechanism determines the functional levels of AID in normal B cells and B cell lymphoma lines. So, Hsp90 inhibition provides the first pharmacological means to regulate AID expression and activity, which could be relevant for the therapy of some types of lymphoma and leukemia."

Dr. Di Noia, along with the IRCM's Technology Transfer Office, is currently taking the necessary steps to patent the proposed application of the Hsp90 inhibitors with the Canadian Intellectual Property Office (CIPO) and the United States Patent and Trademark Office (USPTO). These patent applications, promoted and commercialized by Univalor, cover the use of the AID biomarker in the selection of a cancer-fighting therapy. In the context of this technology, the treatment using an Hsp90 inhibitor targets tumours expressing AID, and consists of the administration of predetermined doses of the inhibitor in accordance with the expression levels of AID in the tumours.

According to The Leukemia & Lymphoma Society of Canada, one person is diagnosed with a blood cancer every four minutes and someone dies from a blood cancer every 10 minutes. This statistic represents over 54,000 people per year. In 2010, about 628,415 people are living with

lymphoma or are in remission.

More information: For more information, please refer to the online article published by *The Journal of Experimental Medicine*. The print publication will be available on November 22, 2010.

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