MedicalXpress

Researchers uncover a new function for an important player in the immune response

March 27 2014

IRCM researchers led by Javier M. Di Noia, PhD, uncovered a new function of AID, a crucial enzyme for the immune response. The discovery, recently published by the scientific journal *Proceedings of the National Academy of Sciences* (*PNAS*), helps explain a rare genetic disorder that causes an immunodeficiency syndrome.

The Montréal research team studies the enzyme AID, or activation-induced deaminase, that can be found in B lymphocytes (the group of white blood cells whose main function is to produce antibodies to fight against infections). AID creates deliberate mutations in DNA to modify the antibody genes, which is necessary to produce an appropriate immune response. However, inappropriate functioning of AID can also have harmful effects and lead to certain oncogenic (cancer-causing) mutations.

"One of AID's roles is to trigger antibody class switching, a critical mechanism for immune responses," explains Dr. Di Noia, Director of the Mechanisms of Genetic Diversity research unit at the IRCM. "Class switching is the process that allows a B cell to produce different classes of antibodies, so the immune system can respond to and eliminate a wide variety of antigens."

AID initiates a mechanism whereby a break occurs in the DNA, within the antibody genes, and a segment is removed. The free ends on either side of the removed fragment must be rejoined to repair the DNA strand and, thus, produce a new class of antibody.

"Not only is AID responsible for triggering class switching, but we also discovered that it facilitates DNA repair during this process," says Astrid Zahn, PhD, research associate in Dr. Di Noia's laboratory and first author of the study. "In addition, we identified which domain of the enzyme controls this novel activity. These findings show that AID provides a link between the DNA damage and repair steps during class switching."

"Our study also helps explain a rare disease known as hyper-IgM syndrome type 2 (HIGM2) that is caused by mutations affecting AID," adds Dr. Zahn. "The disease is part of a family of genetic disorders in which patients only produce Immunoglobin M (the default class of antibody produced by B lymphocytes), but none of the other classes of antibodies elicited during infections. This dramatically compromises the immune system's ability to fight infectious diseases."

In the human genome, two copies (or alleles) of a gene exist for every protein, one coming from each parent. HIGM2 is usually caused by a total AID deficiency because both alleles of the gene are inactivated. However, in about 10 per cent of HIGM2 patients, only one allele of AID is mutated. This mutated enzyme is therefore dominant, as it causes the disease despite the simultaneous presence of normal AID in the B cell. The researchers found that all mutated AID variants were specifically lacking the domain identified in their study as being important for DNA repair.

"In HIGM2 patients, the absence of this region makes AID exceptionally efficient at producing DNA damage but without the ability to initiate the necessary repair mechanisms," concludes Dr. Di Noia. "As a result, the mutated AID interferes with the normal mechanism of class switching and becomes toxic for B cells, thus causing the immunodeficiency syndrome."

More information: www.pnas.org/content/111/11/E988.abstract