MedicalXpress

Study sheds new light on a crucial enzyme for the immune response

April 20 2015

A new study by immunology researchers at the IRCM led by Javier M. Di Noia, PhD, sheds light on a mechanism affecting AID, a crucial enzyme for the immune response. The scientific breakthrough, published in the latest issue of *The Journal of Experimental Medicine*, could eventually improve the way we treat the common flu, as well as lymphoma and leukemia.

The researchers study white blood cells, called B-lymphocytes, whose main function is to produce antibodies to fight against infections. More specifically, they focus on an enzyme found in B cells known as AID, or activation-induced deaminase.

"AID is crucial for an efficient antibody response," explains Dr. Di Noia, Director of the Mechanisms of Genetic Diversity research unit at the IRCM. "However, high levels of AID can also have harmful effects and lead to certain cancer-causing mutations. The objective is to find the perfect level of AID activity to maximise the protection it provides to the body while reducing the risk of damage it can cause to cells."

The research team previously found that Hsp90, one of the most abundant and vital proteins found in cells, maintains the levels of AID by stabilizing it while it is still immature. In fact, they realized that inhibiting Hsp90 significantly reduces the levels of AID in the cell.

"Through this new study, we identified another mechanism, controlled by the protein eEF1a, that has the opposite effect," says Stephen P.

Methot, PhD student in Dr. Di Noia's laboratory and first author of the article. "The protein eEF1a retains AID in the cell's cytoplasm, away from the genome. However, unlike Hsp90, it maintains AID in a ready-to-act state. We discovered that blocking the interaction between AID and eEF1a helps AID access the cell nucleus and thereby boosts AID activity. As a result, this could increase immune response and help fight infections, for instance."

"We found the eEF1a mechanism is necessary to restrict AID activity in the cell," adds Mr. Methot. "It acts as a buffer by allowing the cell to accumulate enough AID to be efficient, but limits its activity to prevent the oncogenic or toxic effects that could result if too much AID is in continuous contact with the genome."

The IRCM scientists identified two existing drugs that can act on the eEF1a mechanism to release AID into the cell. They could potentially be used to boost AID activity and, thus, immune responses.

"With this discovery, we now understand mechanisms that can both reduce and increase the activity of AID by targeting different proteins," concludes Dr. Di Noia. "This knowledge could eventually lead to new treatments to boost the immune system and help our aging population fight influenza, for example, as AID activity in our cells decreases with age. On the other hand, therapies could also be developed to lower toxic levels of AID in certain cancers such as B-cell lymphoma and leukemia."

More information: *Journal of Experimental Medicine*: jem.rupress.org/content/212/4/581

Provided by Institut de recherches cliniques de Montreal