The USP15 biological thermostat: A promising novel therapeutic target in cancer

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After years studying the molecular bases of glioblastoma - the most common brain tumor and one of the most aggressive of all cancers, the group led by Dr. Joan Seoane , Director of Translational Research at the Vall d'Hebron Institute of Oncology (VHIO) and ICREA Research Professor has today published a study in *Nature Medicine* identifying USP15 as a critical protein in cancer which, thanks to its molecular characteristics, shows enormous therapeutic promise.

USP15 promotes tumor progression by activating the TGFβ pathway. Playing a highly significant oncogenic role in glioblastoma, TGFß is a powerful immunosuppressant allowing the tumor to escape the host immune system. It also acts as an angiogenic factor inducing blood vessels, promotes tumoral invasion, activates cancer stem cells, and in some tumors, induces metastases.

USP15 as a "Biological Thermostat" at the core of a TGFβ chain reaction

Dr. Seoane's team has unmasked the USP15 enzyme as activator of the TGFβ chain reaction. In tumors the USP15-TGFß axis is deregulated due to USP15 gene amplification leading to an aberrant TGFß activation.

USP15 acts by controlling and correcting the TGFβ activity in the same way that a thermostat regulates temperature. If the TGFβ activity is high,

it reduces; and if it is low, it increases the TGFβ activity. USP15 therefore achieves optimal TGFβ activity.

Protein stability is regulated through the elimination or aggregation of ubiquitins, small proteins that establish which molecules need to be eliminated. This process is finely regulated by deubiquitinating enzymes (DUBs) such as USP15 which determine the correct level of a protein under certain physiological conditions. In this orchestrated manner, USP15 controls and adapts the TGFβ receptor stability and, therefore, the activity of the pathway.

The problem arises when, in some tumors, the USP15 gene is amplified due to genetic mutations and the enzyme is over produced. The thermostat breaks down and is therefore only sensing the "cold" resulting in the overactivation of the TGFβ pathway. Remarkably, this is not only a phenomenum of glioblastomas since the USP15 gene has also been found activated in other types of cancer such as breast or ovarian cancer.

Dr. Joan Seoane explained "When we inhibited USP15 in a real model of human glioblastoma, TGFβ activity decreased and the tumor did not develop. USP15 regulates tumor progression and is critical in cancer."

DUBs (deubiquitinating enzymes): a novel avenue in therapeutic targets

Sometimes potentially powerful therapeutic targets are found but are not pharmacologically accessible due to their biochemical characteristics. "Enzymes in general - particularly deubiquitinating enzymes (DUBs) such as USP15, can easily be deactivated and are therefore good therapeutic targets", Seoane commented, "our results, generated thanks to the funding received from the Spanish Association Against Cancer (AECC), show exciting new promise in improved treatment of cancer

patients.".

Provided by Vall d'Hebron Institute of Oncology