A potential new therapeutic target for Ewing sarcoma

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The sarcoma research group of the Bellvitge Biomedical Research Institute (IDIBELL), led by Dr. Òscar Martínez-Tirado, has identified a potential new therapeutic target for Ewing sarcoma, the second most frequent bone cancer in children and adolescents, and a tumor known for its aggressiveness and tendency to metastasize. The research is published in the *International Journal of Cancer*.

For years, the main line of research of the Ewing sarcoma group focused on the caveolin 1 protein (CAV1), which is associated with treatment resistance and metastasis, among other issues. However, the location of this protein in the cell makes its use as a therapeutic target virtually impossible. "That is why we were looking for a CAV1 cofactor with an equally relevant role, but a more accessible location," says Dr. Martínez-Tirado, "and the EphA2 membrane receptor, already described in previous studies, meets these requirements."

In their latest work, researchers not only demonstrate the connection between the EphA2 receptor and caveolin 1, but also establish a correlation between the phosphorylation of EphA2 and the aggressiveness of tumors in Ewing sarcoma. "In several in vitro and in vivo tests, we observed that this membrane receptor plays a key role in the migration of tumor cells."

Regarding in vivo studies, the research team used two different models. The artificial model of metastasis, more experimental, allows researchers to assess the ability of cells to adhere to the pulmonary

epithelium in adverse conditions. On the other hand, the new orthotopic model developed by the same group a few months ago induces a spontaneous metastasis, similar to what can be observed in a clinical setting.

"In the lab, we have shown that the lack of EphA2 receptor significantly decreases the incidence and number of metastases," says Dr. Martínez-Tirado, "and thanks to our collaboration with Hospital Virgen del Rocío, we also saw that 90 percent of Ewing sarcoma patients express this receptor (mimicking caveolin 1), a fundamental fact when it comes to selecting EphA2 as a therapeutic target. At the same time, working with patient samples also allowed us to correlate EphA2 ligand-independent activity, associated with its phosphorylation, with lower survival. "

Thanks to the stable financial support of the Alba Pérez Foundation, IDIBELL researchers will keep on working on the development of treatments based on blocking the activity of this receptor. "Through drug nanoengineering techniques, we aim to develop a molecule with a double effect, capable of blocking EphA2 in tumor cells and delivering other targeted drugs at the same time," concludes the IDIBELL researcher.

More information: Silvia Garcia-Monclús et al, EphA2 receptor is a key player in the metastatic onset of Ewing sarcoma, *International Journal of Cancer* (2018). DOI: 10.1002/ijc.31405

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