The significance of water in a promising biomarker against cancer

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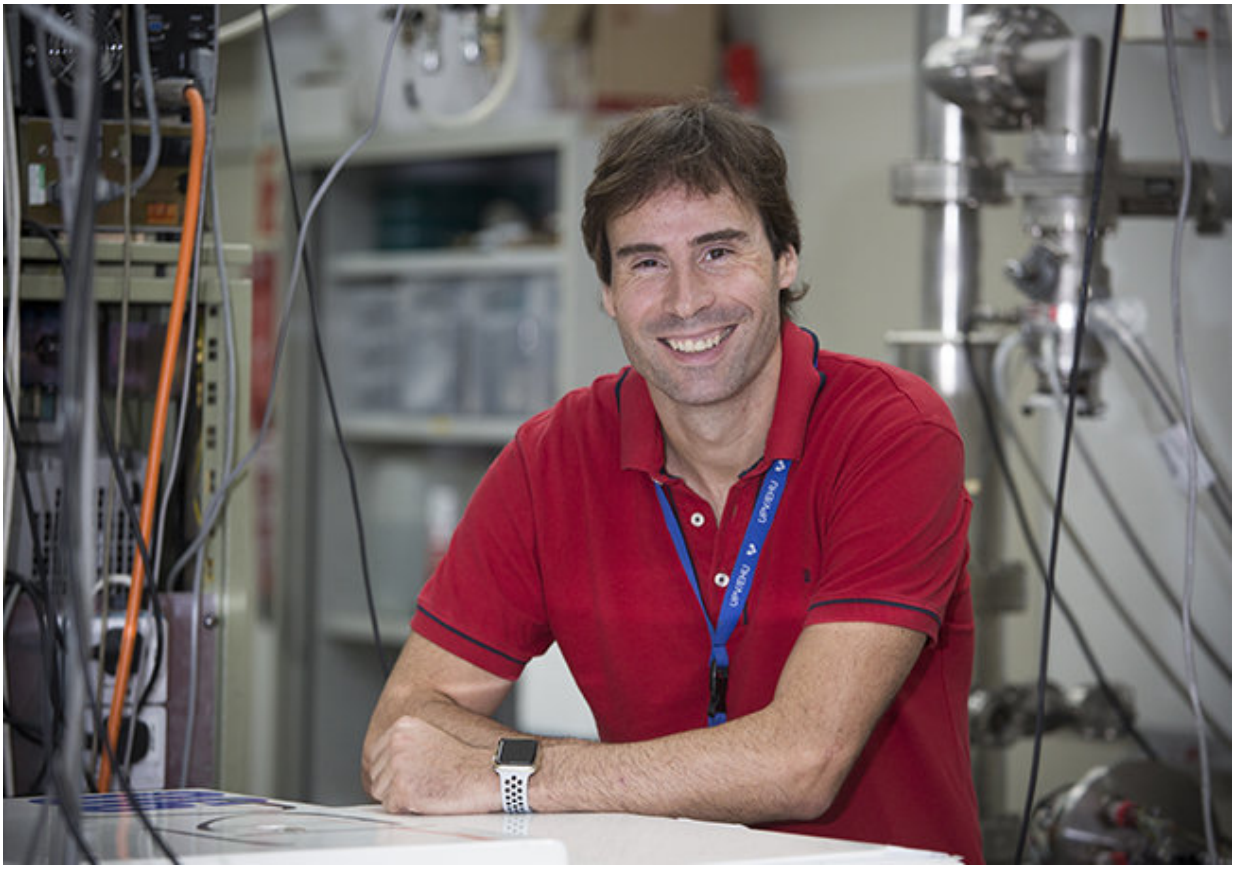

Emilio J. Cocinero, member of the UPV/EHU's Department of Physical Chemistry and the Biofisika Institute has collaborated with Francisco Corzana of the University of La Rioja, and Ramón Hurtado of the ARAID Foundation. Credit: Egoi Markaida. UPV/EHU

The Tn antigen appears in 90 percent of cancers and is associated with metastasis. Thus, it is a promising biomarker for identifying cancer cells and has become a very attractive target in therapies to fight cancer, according to Emilio José Cocinero, member of the UPV/EHU's Department of Physical Chemistry and the Biofísika Institute, and one of the lead authors of the work. Antigens are molecules recognized by the immune system as a threat, which induce the formation of antibodies.

The researchers studied two apparently similar variants of Tn antigens that differ only in one serine or threonine amino acid. "We have seen that they behave very differently in water," said Cocinero. "By using an approach that is both experimental and computational, we have shown that the Tn antigen bonded with threonine adopts a rigid shape in solution thanks to a water molecule that helps to stabilise the structure. By contrast, the Tn antigen bonded with serine lacks the structural component and is flexible in solution. These differences are not observed in the gas phase studies, and both molecules behave in exactly the same way, which has made it possible to unequivocally discover, for the first time, the role of water in the three-dimensional structure of these molecules," he added.

The researchers sought to understand the active role of water in this process. "We have been adding water molecules one by one to see how the Tn antigen behaved. We have seen that adding just one water molecule was enough to change the structure of both antigens, and in fact, water became located in various parts of the molecule," said Cocinero. "It is likely that the various shapes of the Tn antigen give rise to different interactions with cell receptors and antibodies, and the compression of these structures could facilitate the design of more effective detection tools and anticancer drugs. This work is, in fact, part of a long-term project that aims to try to produce potential vaccines against cancer.

"The major problem with this molecule, the Tn antigen, is that it is naturally present in the body, which means that the body's immune response is very low because our body does not perceive it as a foreign body. What we have seen is that if the concentration of this molecule increases, it means that cancer has developed. We can follow the evolution of this molecule to see the degree to which the cancer has developed. The ideal scenario in the future would involve the potential creation of synthetic molecules that are not present in the body and which would have the same structure as the Tn antigen; the body would thus perceive them as foreign bodies, and therefore unleash a greater immune response against cancer cells."

More information: Iris A. Bermejo et al, Water Sculpts the Distinctive Shapes and Dynamics of the Tumor-Associated Carbohydrate Tn Antigens: Implications for Their Molecular Recognition, *Journal of the American Chemical Society* (2018). DOI: 10.1021/jacs.8b04801

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