Important advance in the fight against skin cancer

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Researchers from the Hospital del Mar Medical Research Institute (IMIM), lead by Lluís Espinosa, have identified a new function of the IB protein that is key in the development of squamous-cell carcinoma, a type of skin cancer. The study has been published in the prestigious journal *Cancer Cell* and provides a new tool for the diagnosis of the disease and, in the future, will enable the identification of novel therapeutic targets to treat this type of cancer.

"In this study we identified a new function of a protein that directly regulates the activity of the genes involved in cell differentiation and in the development of cancer" explains Lluís Espinosa, a researcher of the Stem Cells and Cancer group at IMIM, and the coordinator of the study, which also involved the participation of researchers from Hospital del Mar, Centre for Genomic Regulation and from national and international universities.

Until now, the only known function of the protein IB was in the cytoplasm where it inhibits the NF-B factor, a protein complex that is involved in the immune response. Now we have discovered that in the nucleus of keratinocytes, the typical skin cells, and also in the nucleus of fibroblasts, there is a different form of IB that results from its binding to another molecule called Sumo (leading to the Sumo-IB protein) that had been previously observed by other groups, but no function had been adscribed.

During the study, the authors analyzed a cohort of 112 patient samples with urogenital skin squamous-cell carcinoma at different stages of tumour progression. Results showed that in samples with invasive tumours or that had developed metastasis, IB disappeared from the nucleus. This indicated that during the tumour progression process, nuclear IB was lost and accumulated in the cytoplasm.

The finding of this new function of IB in the cell nucleus represents a change in the paradigm of this field and could even entail a re-interpretation of some previously published studies.

Every year, over 250,000 new cases of squamous-cell skin cancer are diagnosed. This is the second most common type of skin cancer and it develops in the squamous cells that form the upper layers of the skin. Squamous-cell carcinoma can develop in any part of the body but it is most common in areas exposed to the sun. Until now, there were no good clinical or histological markers to predict metastasis in this type of tumour.

"Although it still has to be validated in a sufficient number of patients, the detection of this protein in skin lesions could serve as a diagnosis tool and to predict the prognosis of squamous-cell carcinoma" explains Agustí Toll, dermatologist at the Hospital del Mar and researcher at the IMIM, and one of the authors of this article. Besides being a possible biomarker for squamous-cell carcinoma prognosis, the identification of the mechanisms regulating the aggressive behaviour of skin tumours could have a therapeutic use. When metastasis occurs, the prognosis of patients with these tumours is generally poor and current treatments (surgery, radiotherapy and chemotherapy) are linked to severe side effects, especially among elderly patients. "This discovery could have a very significant impact on the treatment of this type of cancer when we identify drugs that revert the loss of nuclear IB that is observed in squamous-cell carcinoma" says Espinosa.

The aim of the researchers is to discover the mechanisms regulating the loss of nuclear IB to identify therapeutic targets that could be used in the future to fight against skin cancer. The researchers also believe that the new mechanism could be relevant for other types of cancers.

More information: "Chromatin-bound IkBa regulates a subset of Polycombtarget genes in

differentiation and cancer". María Carmen Mulero, Dolors Ferres-Marco, Abul Islam, Pol Margalef, Matteo Pecoraro, Agustí Toll, Nils Drechsel, Cristina Charneco, Shelly Davis, Nicolás Bellora, Fernando Gallardo, Erika López-Arribillaga, Elena Asensio-Juan, Verónica Rodilla, Jessica González, Mar Iglesias, Vincent Shih, M. Mar Albà, Luciano Di Croce, Alexander Hoffmann, Shigeki Miyamoto, Jordi Villà-Freixa, Nuria López-Bigas, William M. Keyes, María Domínguez, Anna Bigas and Lluís Espinosa. *Cancer Cell*.

Provided by Hospital del Mar Medical Research Institute