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This study has been published in the prestigious journal PNAS

Benign skin tumours provide clues to the molecular mechanisms involved in cancer

- ***Analysing the genetic architecture of benign lesions can provide important information for discovering the mechanisms which prevent tumours from becoming malignant***

A study jointly led by researchers from the Hospital del Mar and the IMIM in Barcelona, Regensburg University (Germany) and the Epithelial Carcinogenesis group of the Molecular Pathology Programme at the National Centre for Cancer Research (CNIO, Centro Nacional de Investigaciones Oncológicas) has explained new aspects regarding the genetics of benign skin tumours which question how tumours develop and progress. The results have been published today in the PNS journal.

The study's starting point

This research group, which includes both experts from the CNIO and the IMIM, Hospital del Mar Research Institute, has worked extensively on bladder cancer. It is not uncommon to find mutations of the FGFR3 gene in this tumour. Previous studies had shown that by inducing mutations in this gene in animal models, mice developed skin lesions very similar to human seborrheic keratosis (a very common type of skin lesion which is completely benign and similar to warts). These findings set collaboration between molecular biologists and dermatologists in motion in a project part-financed by the Asociación Española Contra el Cáncer (Spanish Association Against Cancer) which has led the researchers to analyse these keratosis lesions. It was shown that 90% of these benign lesions have cancer mutations, which are often multiple, not just in the FGFR3 genes, but also in the PIK3CA and KRAS genes.

If benign and malignant lesions share the same mutations, what makes them malignant in some cases and not in others?

Seborrheic keratoses are very common among people of advanced age and often occur in tens or a few hundred. The easy accessibility of skin for performing biopsies enabled the (prospective) collection of between 5 and 10 lesions from each patient and the comparison of the genetic alterations of these benign lesions.

This research has led to important conclusions:

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- ✓ Despite the fact that these skin lesions are benign, they often contain multiple cancer mutations, that is, mutations in genes involved in the main cell pathways activated in cancer, such as those of the tyrosine kinase-RAS-MAP kinase and the PI3 kinase-AKT receptors.

- ✓ In addition, the mutations do not lead to the senescence of the seborrheic keratoses being activated. Senescence is the ability of the cell to leave the cell cycle. It is a genetic protection mechanism which keeps tumour or pre-tumour cells from dividing, thus stopping the tumour from progressing. Therefore, the failure of these seborrheic keratoses to become malignant would not be explained by the senescence phenomenon.

"Despite the fact that cancer mutations do exist in seborrheic keratoses, there are inhibition or negative feedback systems which prevent the cancer pathways from being activated in these lesions", explains Dr. Agustí Toll, dermatologist at the Hospital del Mar and co-author of the article.

An additional important finding of this study is that lesions which appear to be independent, located on the skin a few centimetres away from each other, probably have a common phylogenetic origin. The hypothesis is that these are not acquired mutations but genetic alterations which are clones and "from birth".

Most of what we know about how genetic alterations contribute in the development of cancer comes from the study of malignant tumours. This study emphasises the fact that analysing the genetic architecture of benign tumours can provide important information for discovering the mechanisms which prevent tumours from becoming malignant.

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