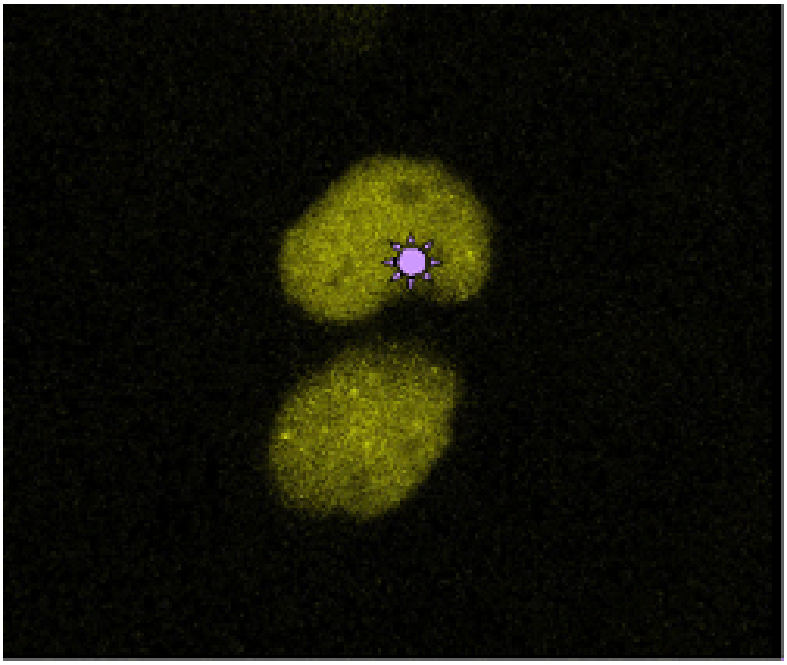
UABDIVULGA
BARCELONA RECERCA I INNOVACIÓ

03/2007

# Researchers find the mechanism by which cells resist chemotherapy



A team of researchers from the UAB's Mutagenesis Group, led by Dr Jordi Surrallés, has identified one of the mechanisms used by cancer cells to resist chemotherapy. In his paper, published in *The EMBO Journal*, Dr Surrallés describes how proteins of the Fanconi/BRCA pathway recognise the presence of genetic mutations in order to repair them. The researchers also found that alteration of this mechanism makes tumour cells much more sensitive to certain drugs. This discovery will make it possible to develop strategies to make tumours more vulnerable to chemotherapy.

One of the main mechanisms responsible for repairing mutations in humans is the cancer-suppressing Fanconi anaemia/BRCA pathway. This mechanism makes it possible for the cells to identify genetic mutations in order to correct them.

If this mechanism does not function correctly, it leads to Fanconi anaemia, a rare genetic disorder characterised by progressive bone-marrow failure, various congenital malformations and a very high risk of cancer.

Furthermore, the proteins of this pathway are largely responsible for the resistance of tumours to many antitumour agents such as cisplatin and other chemotherapeutic agents that kill tumour cells by producing DNA interstrand crosslinks. That is, they identify cellular alterations induced by chemotherapy and correct them, "accidentally" helping the tumour.

Many tumours have molecular anomalies in this pathway. These defects mean the tumours can be treated efficiently using certain antitumour agents. There are at least 13 genes involved in the pathway. Three of these (BRCA2, BRIP1 and PALB2) are responsible for the high proportion of hereditary breast cancers (between 5 and 10% of all breast cancers).

Understanding how this DNA repair pathway works is of great interest to biomedicine, not only for Fanconi anaemia patients, but also for the general cancer population, since it determines the the efficacy of chemotherapy in treating many tumours. However, the involvement of 13 genes in the same pathway makes the study more complexed.

A team of researchers from the UAB's Mutagenesis Group, led by Doctor Jordi Surralés, has identified one of the important unresolved questions regarding this pathway: how the Fanconi anaemia proteins detect the presence of mutations so they can repair them.

The researchers have found that the mutations block the DNA replication process, a process that is necessary, especially in tumour tissues, for the cells to be able to divide and proliferate. By blocking the replication process, the mutations activate a type of enzyme, the ATR kinase, which phosphorylates (introduces phosphate groups into) histone H2AX, a protein present in the chromatin that surrounds the damaged DNA. The phosphorylated histone H2AX indicates the location of the genetic damage to the Fanconi proteins and places them in exactly the right place to repair the DNA.

The researchers have shown that one of the 13 Fanconi proteins, the FANCD2, binds directly to the phosphorylated histone H2AX. The BRCA1 protein also plays a part in this process and, alongside the BRCA2, it is involved in most hereditary breast cancers. So these proteins cooperate in repairing the genetic damage, preserving the stability of the chromosomes and preventing the onset of tumours.

This research will have many implications on biomedicine. The increase in knowledge on this pathway will make it possible to design strategies for the chemosensitisation of tumour cells. Dr Jordi Surallés's team has also observed that many breast cancer cell lines are between two to three times more sensitive to chemotherapy if they have partially inhibited the Fanconi FANCD2 gene expression.

The results of this study, carried out entirely within the UAB Department Of Genetics and Microbiology, will be published in The EMBO Journal. Most of the work was carried out by the post-doctoral researchers Massimo Bogliolo and Alex Lyakhovich. The group directed by Dr Jordi Surallés is funded by the EU commission, the FEDER fund, the Spanish Ministry of

Education and Science, the Spanish Ministry of Health and Consumption, Fundación La Caixa, Genoma España and the Centro de Investigación Biomédica en Red en Enfermedades Raras.

**Jordi Surralles**
Universitat Autònoma de Barcelona
Jordi.Surralles@uab.cat

View low-bandwidth version