PRESS RELEASE

Revealing the mode of binding between the DNA repair machinery and a carcinogenic protein

- *A team from CIC bioGUNE led by Francisco J. Blanco has determined the structure of the complex formed by the p15 protein, present in several kinds of cancer and part of the cellular DNA repair machinery.*

- *The structure reveals "a novel and unexpected mode of binding" that opens up the opportunity for designing selective inhibitors with anticancer therapeutic potential.*

- *The study, published in Nature Communications, involved researchers from the CNIO and the universities of Copenhagen, Granada and Montpellier.*

(Bilbao, 12 March 2015).- A scientific project led by the Ikerbasque researcher at CIC bioGUNE Francisco J Blanco reveals the 3D structure of a molecular complex comprised of the cancer-related protein p15, the DNA double helix and the PCNA protein. The finding opens a new opportunity for the design selective inhibitors with therapeutic potential. The study was published in the scientific journal *Nature Communications.*

Cancer is currently the second cause of death and its incidence increases with age. Thanks to progress in early diagnosis and in drug control of tumour growth survival rates have significantly increased.

The protein p15 is found in high amounts in several kinds of cancer and in a direct relationship with the seriousness of the disease prognosis, and the PCNA protein is a well known target to develop drugs with anticancer properties. However, researchers are facing an added obstacle, which is the presence of several proteins all bound to the aforementioned PCNA molecule in a similar way, whereby it is difficult to design selective inhibitors.

"Up to now it was known that the p15 protein is associated with PCNA and regulates the machinery that repairs the DNA damage caused by ultraviolet radiation, but the

specific way this process took place was not known", assures the project leader, Dr Blanco.

The main finding of the study by the Center for Cooperative Research in Biosciences CIC bioGUNE, with headquarters in Bilbao, reveals that p15 binds to PCNA in a novel way: crossing the PCNA ring and also making contact with the DNA itself.

"This mode of binding is an unexpected result, because other proteins that regulate the activity of PCNA also bind to the ring but without passing through its central channel", states Blanco.

Knowledge of the binding of p15 to the inside walls of the PCNA ring opens the possibility for designing small molecules that selectively interfere with p15 without affecting the binding of other proteins, whereby there is potential to develop therapies with as little disturbance as possible to the operation of the cell machinery.

A highly complex project

The research group responsible for the study published its conclusions on 12 March in the prestigious scientific journal *Nature Communications* after having invested several years of intense multidisciplinary work and thanks to the integrated use of various structural biology tools.

The p15 protein by itself is highly disordered, andacquires a partially organised structure only when it interacts with PCNA. For the analysis of p15 and its interaction the use of Nuclear Magnetic Resonance (NMR) and computational simulations has been fundamental. However, the size of the PCNA ring and the complex with p15 exceeds the NMR capacity to provide high resolution information, whereby this information has been obtained by means of crystallographic techniques.

Moreover, to observe the DNA double helix and its location in the centre of the ring it was necessary to use electron microscopy; other tools enabled quantifying the strength of interactions between the three components of this macromolecular complex.

"This research reveals how the complementary nature and synergy of the different techniques used is crucial to tackle the increasingly challenging goals put forth in structural biology and how CIC bioGUNE offers the services of specialised technological platforms that greatly facilitate addressing these goals in a comprehensive way", adds Blanco, Ikerbasque researcher in the Basque centre.

The project also involved the participation of researchers from the Spanish National Cancer Research Centre (CNIO in Spanish) and the Universities of Copenhagen, Granada and Montpellier.

About CIC bioGUNE

The Centre for Cooperative Research in Biosciences CIC bioGUNE, with headquarters in the Bizkaia Science and Technology Park, is a biomedical research organisation that conducts innovative research at the interface between structural, molecular and cell

biology, focusing especially on the study of the molecular basis of disease, to be used in the development of new diagnostic methods and advanced therapies.

Study references

Structure of the p15PAF–PCNA complex and implications for clamp sliding during DNA replication and repair.
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