PRESS RELEASE

CIC bioGUNE researchers uncover the structural complexity of the archaeal DNA replication machinery and of the interaction of the foot-and-mouth disease virus with its cellular receptor

Both studies, co-directed by the Ikerbasque Research Professor Nicola G.A. Abrescia, have been published in the prestigious journal Nature Communications

The study on the interaction of the foot-and-mouth disease virus with its cellular receptor, the integrin alphaVbeta6, will enable the design of virus entry inhibitors

In both studies, the use of electron microscopy has been pivotal to the understanding of cellular mechanisms, including virus entry into cells

(Bilbao, 25 May 2017). Researchers from CIC bioGUNE and from Indiana University have revealed the architecture of the assembly of archaeal DNA replication machinery, a group of single-cell microorganisms capable of surviving in extreme conditions and which possibly represent the oldest forms of life on Earth.

Nicola G.A. Abrescia, an Ikerbasque Research Professor and Group Leader at CIC bioGUNE, explains: "Over 30 years after its first characterization, we have shown that Sulfolobus PolB1 DNA polymerase is not a single-subunit enzyme as was previously believed, but rather is a heterotrimeric holoenzyme. DNA polymerase holoenzyme assemblies are thus found in all three domains of life: Eukarya, Bacteria and Archaea. Our work demonstrates how association with accessory subunits can dramatically impact on the core activity of a replicative DNA polymerase in a manner that enhances the efficiency of the resultant assembly during genome duplication, a fundamental cellular process across the three domains of life".

The relevance of this discovery, published in the prestigious journal Nature Communications, lies in understanding the cellular DNA replication mechanism, using Archaea as a simplified model system of the far more complex eukaryotic processes.

One important outcome of this study is the potential use of this holoenzyme for biotechnological applications. Several biotech companies are very much interested in the use of highly stable enzymes that can perform in a wide range of conditions, including temperature and/or pH.

The project was launched in 2013 and is the result of a collaboration between the laboratory of Professor Abrescia in CIC bioGUNE and that of Professor Stephen Bell at Indiana University. In recent years, this collaboration has led to significant contributions in the field of cellular transcription and genome replication.

In addition to biochemical and X-ray crystallography techniques, the use of electron microscopy methodology has played a pivotal role in this study. Nowadays, electron microscopy (EM), and specifically cryo-EM, is hugely impacting in several areas of basic and translation research, including biomedicine.

Research into the foot-and-mouth disease virus

Cryo-electron microscopy (cryo-EM) has also been the technique used in another research study contributed by the CIC bioGUNE team and which has also been published in the journal Nature Communications. Through this study, the architecture and the underlying interactions between the foot-and-mouth disease virus (FMDV) and its cellular receptor, the integrin alphaVbeta6, have been unravelled.

FMDV is a highly dangerous animal pathogen that has caused enormous animal and economic losses worldwide. “The understanding of the recognition process between FMDV and the integrin receptor will pave the way for the design of virus entry inhibitors to avoid or mitigate the spread of FMDV”, Prof. Abrescia explains.

As three-way collaboration together with CIC bioGUNE, the laboratories headed by Profs. David I. Stuart and Juha Huiskonen at Oxford University (U.K.) and by Prof. Timothy Springer at Harvard University (U.S.) have led this research.

The study on the FMDV-alphaVbeta6 interaction started back in 2005 with the collaboration between David I. Stuart and Nicola G.A. Abrescia. However, breakthrough progresses made in the field of electron microscopy have finally enabled us to determine the full structure of the FMDV-alphaVbeta6 complex and to decipher the interactions that lead to the virus attaching to the receptor of the host cell.

About CIC bioGUNE

The Centre for Cooperative Research in Biosciences (CIC bioGUNE), located in the Bizkaia Technology Park, is a biomedical research organisation conducting cutting-edge research at the interface between structural, molecular and cell biology, with a particular focus on the study of the molecular bases of disease, for use in the development of new diagnostic methods and advanced therapies.

1) Identification and characterization of a heterotrimeric archaeal DNA polymerase holoenzyme

Yan J, Beattie T, Rojas AL, Schermerhorn K, Gristwood T, Trinidad J, Albers SV, Roversi P, Gardner A, Abrescia* NG, and Bell* SD. Nature Communications.

2) Rules of engagement between alphaVbeta6 integrin and the RGD-loop of foot-and-mouth disease virus

Kotecha A, Wang Q, Dong X, Ilca SL, Ondiviela M, Zihe R, Seago J, Charleston B, Fry EE, Abrescia* NG, Springer* TA, Huiskonen* JT and Stuart* DI. Nature Communications.