

Genomic Instability *Junior Group*

Summary

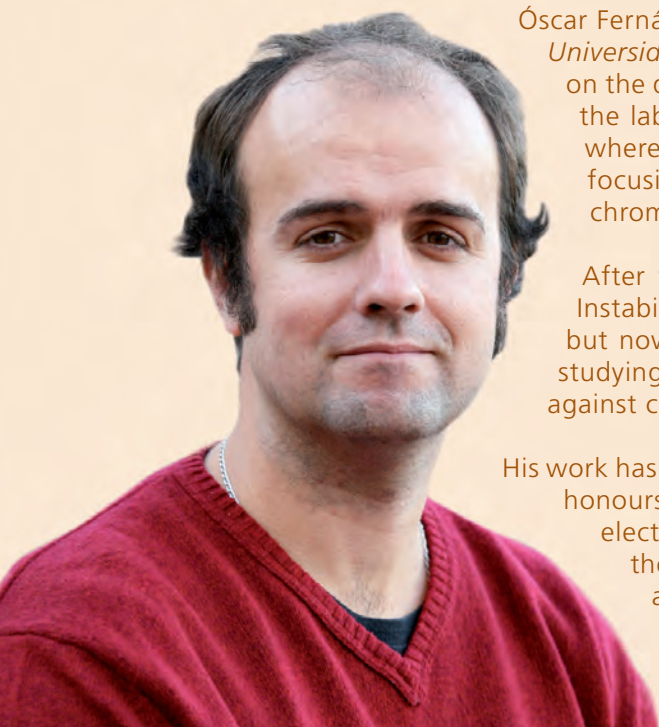
DNA damage is a common initiator of cancer and ageing. We aim to understand the mechanisms by which mammalian cells detect, signal and repair DNA breaks. We are currently focusing on two main lines of research: firstly, we are trying to elucidate the influence that chromatin has on DNA repair, and secondly, we are evaluating whether the transduction cascades that are activated by DNA damage are important tumour suppressors *in vivo*.

We have now generated a battery of cellular and animal models that should help us understand the actual physiological relevance of a defective DNA damage response.

Strategic Goals

- Evaluate the potential of the DNA damage response as a tumour suppressive barrier
- Explore the potential therapeutic value of the activation of DNA damage response (DDR) in the absence of DNA damage
- Understand how DDR is assembled in the context of chromatin
- Develop murine models of Genomic Instability Syndromes
- Discover new synthetic lethal effects that might facilitate the specific elimination of tumours harbouring loss of tumour suppressors

Óscar Fernández-Capetillo *Junior Group Leader*



Óscar Fernández-Capetillo (born in Bilbao in 1974) obtained his PhD from the *Universidad del País Vasco* working on the role of E2F transcription factors on the development of the immune system with A. Zubiaga. He then joined the laboratory of A. Nussenzweig at the National Cancer Institute, USA, where he started to work on the cellular response to DNA damage (DDR), focusing particularly on the role of the histone variant H2AX and other chromatin-related aspects.

After three years at the NCI he joined the CNIO to lead the Genomic Instability Group where his work has continued to focus on chromatin but now mainly concentrates on developing cellular and animal tools for studying the role of the ATR/Chk1 signalling cascade in the protection against cancer and ageing.

His work has been recognised through several national and international awards/honours including the Eppendorf Award for Young Investigators (2009), elected EMBO Young Investigator (2008), an ERC Starting Grant (2007), the membership to the EPIGENOME Network of Excellence (2006), and the Swiss Bridge Award (2005).



Staff scientists: Alexandra Bras, Matilde Murga. **Post-doctoral fellows:** Ariana Jacome, Andres J. López, M. Fernanda Montaña. **Graduate students:** Paula Gutiérrez, Bárbara Martínez, Ángela Monasor (since April), Juan L. Rodríguez, Luis I. Toledo, Enrico Tenaglia (since October). **Technicians:** M. del Mar de Miguel (until May), Rebeca Soria, Rafal Zur (since October).

Highlights

ATM is dispensable for the response to oncogenes

One of the current models of cancer proposes that oncogenes activate DNA damage response (DDR), which would limit the growth of the tumour in its earliest stages. Correlating with this model, *in vitro* studies revealed that ATM depletion could bypass oncogene-induced senescence and promote tumorigenesis. However, given that the nature of the oncogene-induced-DDR is thought to be 'replicative stress' (RS), ATR – rather than ATM – should be the main responder to oncogenes. In order to genetically test this model we took advantage of a murine model where the oncogenic *K-ras*^{V12} mutation can be activated with tamoxifen, leading to the formation of lung tumours. Our data showed there was no effect of ATM-deficiency on the amount of senescence initiated by oncogenic Ras *in vivo*. Whether limiting the ATR response may on the contrary have an effect, remains to be seen.

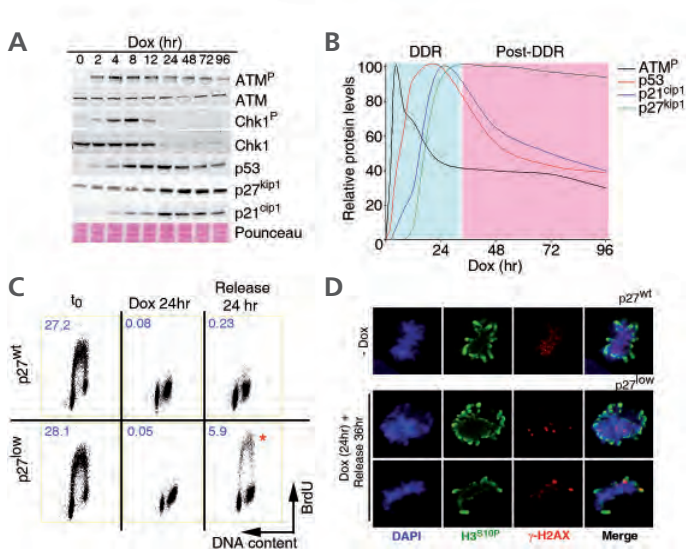


Figure: p27 stabilisation is essential to maintain cell cycle arrest in response to DNA damage. In response to adriamycin, p27 levels rise only after a prolonged exposure to the drug, and concomitant to a dampening of the ATM/ATR response (A, B). p27 depleted cells fail to maintain the checkpoints initiated by DNA damage (C), and progress into mitosis with DNA breaks (D).

A two step DNA damage response

If oncogenes contribute to DNA damage then it is likely that they do so for a significant amount of time. With this in mind we explored whether there were novel mechanisms responsible for keeping cells arrested in response to a prolonged exposure to DNA damage. We now have evidence that a secondary p27/Rb-dependent but ATM/ATR-independent pathway plays a key role in such response (Figure). These results demonstrate that ATM/ATR-independent signalling mechanisms might become essential to protect the genome when the source of DNA damage remains persistent. Our results might help reconcile the oncogene-induced DNA damage model with clinical evidence that points to non-DDR members (such as p27 or Rb) as the most important tumour suppressors in human cancer.

Publications

Marión RM, et al. (2009). A p53-mediated DNA damage response limits reprogramming to ensure iPS cell genomic integrity. *Nature* 460, 1149-1153.

Murga M, et al. (2009). A mouse model of the ATR-Seckel Syndrome reveals that replicative stress during embryogenesis limits mammalian lifespan. *Nat Genet* 41, 891-898.

Martínez P, et al. (2009). Increased telomere fragility and fusions resulting from *TRF1* deficiency lead to degenerative pathologies and increased cancer in mice. *Genes Dev* 23, 2060-2075.

Cerqueira A, et al. (2009). Overall Cdk activity modulates the DNA damage response in mammalian cells. *J Cell Biol* 187, 773-780.

Cuadrado M, et al. (2009). p27Kip1 stabilization is essential for the maintenance of cell cycle arrest in response to DNA damage. *Cancer Res* 69, 8726-8732.

Lafarga V, et al. (2009). p38 Mitogen-activated protein kinase- and HuR-dependent stabilization of p21(Cip1) mRNA mediates the G(1)/S checkpoint. *Mol Cell Biol* 29, 4341-4351.

Efeyan A, et al. (2009). Limited role of murine ATM in oncogene-induced senescence and p53-dependent tumor suppression. *PLoS ONE* 4, e5475.

Awards and Recognition

Eppendorf Award for Young European Investigators, Germany

Fundación Pfizer Award for the best manuscript in basic research, Spain

Miguel Catalán Research Award from the Comunidad de Madrid, Spain