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About

Paloma Garcia is a Senior Researcher under the Science City Research Alliance (SCRA) initiative.

Qualifications

- PhD Biology 1997
- BSc Biology 1994

Biography

Paloma Garcia qualified with a BSc in Biology (Biochemistry and Molecular Biology) from the University Autonoma of Madrid in 1994. She went on to study her PhD in Biology before being awarded with a Marie Curie fellowship to work at the Weatherall Institute of Molecular Medicine (WIMM) in Oxford in 1998. In 2002, Paloma moved to the Medical School in Birmingham as part of Professor Frampton´s group.

In 2009, Paloma was awarded with a Science City Research fellowship to study the role of the transcription factor B-Myb in the maintenance of genome integrity in ESCs and iPS cells.

Teaching

Teaching Programmes

- Laboratory supervision of **BMedSc** and **MRes** projects and summer internship students
- Research "Taster" sessions for Year 1 **MBChB**

Postgraduate supervision

Paloma supervises MRes, PhD and postdoctoral researchers. She is interested in supervising doctoral research students in the following areas:

- The role of transcription factor B-Myb in the maintenance of genome stability in embryonic stem cells and (ESCs) and induced pluripotent stem cells (iPSCs).
- The implication of B-Myb haploinsuficiency in the development of haematological disorders.

Research

Research themes

DNA damage response, Pluripotency, Reprogramming, haematological disorders, leukaemia, conditional knock out, bone marrow transplants, derivation of ESCs.

Research activity

B-Myb and genome stability in mESCs

B-Myb is a ubiquitously expressed member of the myb proto-oncogene family known to be amplified in several types of tumours such as neuroblastoma, breast cancer and ovarian cancer. It has also been shown that reduced levels can lead to chromosome instability, a hallmark of cancer. These findings point at a dual role of B-Myb as an oncogene and also as a tumour suppressor. We have recently demonstrated using single DNA-fibre techniques that B-Myb ablation leads to chromosome instability by affecting replication dynamics in somatic and embryonic stem cells. Also, there is a significant accumulation in dsDNA breaks during the normal replication cycle in the absence of DNA damage as well as 24h after irradiation. DNA lesions are a normal occurrence during the replication of the genome, but failing to repair those results in mutations, genome instability and cell death. Our data indicates that cells lacking B-Myb are inefficient in repairing their DNA, leading to accumulation of lesions and genome instability.

We hypothesise that B-Myb acts as a key protein safeguarding chromosome stability. Our research focuses on elucidating how B-Myb influences DNA replication, particularly in relation to its roles at the intra S-phase checkpoint, and in replication fork-progression, DNA repair and telomere maintenance.

B-Myb in haematological disorders during ageing

Paloma is also interested in studying the role of the transcription factor B-Myb in the development of haematological disorders such as leukaemia, myelodysplasia and myeloproliferative disorders

myeloproliferative disorders.

Blood disorders are a common feature of ageing. Statistics show that more than 62% of people diagnosed with myeloid dysplastic syndrome (MDS), myeloid proliferative disorder (MPD) and leukaemia fall within the age group over 60 years. One theory suggests that during the life of an individual, DNA mutations accumulate in the genome during the cell replicative process due to failure in repair mechanisms, leading to either activation of oncogenes or silencing of tumour suppressors, hence establishing the onset of the disease.

A percentage of patients with MDS, MPD and myeloid leukaemia present cytogenetic abnormalities that include deletion of the long arm of chromosome 20 (del20q), which includes the region encoding B-Myb. It has been proposed that one or more genes from this region could be acting as tumour suppressors, and that deletion of the gene(s) will favour the onset or progression of the disease. The identity of the gene(s) responsible for the disease association is unknown.

Using genetic engineering, Paloma has generated a mouse model of B-Myb haploinsufficiency in which one allele of the B-Myb gene is deleted (B-Myb+/D). We have kept a cohort of 24 mice (11 wt and 13 B-Myb+/D) for 22 months, after which time 12 out of 13 B-Myb+/D mice (92%) developed blood disorders (leukaemia, MPD and MDS), compared to 1 out of 11 wt littermates (9%). We have also demonstrated that under replicative stress conditions, animals transplanted with B-Myb+/D cells developed haematological disorders more rapidly (after 8 months).

This novel data indicates that B-Myb is a strong candidate for the gene responsible for the pathological consequences of del20q.

Derivation of embryonic stem cells and iPScs generation

Paloma has been the first researcher in Birmingham University to derive embryonic stem cells from blastocysts of genetically modified mice. Her expertise in ESCs culture maintenance and derivation as well as conditional knock-out generation has resulted in her being the person of reference for other groups wishing to generate ESCs from knock out models. Also, Paloma has been instrumental in setting up the generation of induced pluripotent stem cells from mouse fibroblasts, and advices research from other groups aiming to generate human iPSCs.

Other activities

- Member of the BUSCC steering committee
- Member of the UK national Stem Cell Network

Publications

- Clarke, M.L., Dumon, S., Ward, C., Jager, R., Freeman, S., Dawood, B., Sheriff, L., Lorvellec, M., Kralovics, R., Frampton, J and García, P*. (2012) MybL2 haploinsufficiency increases susceptibility to age-related haemopoietic neoplasia. Leukaemia 2012 Aug 22. doi: 10.1038/leu.2012.241. [Epub ahead of print].
- Jones, R.M., Mortusewicz,O., Afzal, I., Lorvellec, M., García, P., Helleday, T and Petermann, E. Oncogene-induced replication stress by increased replication initiation resulting in conflicts with transcription. Oncogene. 2012 Sep 3. doi: 10.1038/onc.2012.387. [Epub ahead of print].
- Haining, E.J., Yang, J., Bailey,R. L., Khan, K., Collier, R., Tsai, S., Watson,S.P., Frampton, J., García, P., Tomlinson M. (2012) The TspanC8 Subgroup of Tetraspanins Interacts with A Disintegrin and Metalloprotease 10 (ADAM10) and Regulates Its Maturation and Cell Surface Expression. J Biol Chem, 287(47): 39753-65.
- García, P*., Berlanga, O., Vegiopoulos, A., Vyas, P and Frampton, J. (2011). c-Myb and GATA-1 alternate dominant roles during megakaryocyte differentiation. J Thromb Haemost, 9(8):1572-1581.
- Lorvellec, M., Dumon, S., Maya-Mendoza, A., Jackson, D., Frampton, J., and García, P*. (2010). B-Myb is Critical for Proper DNA Duplication during an Unperturbed S phase in Mouse Embryonic Stem Cells. Stem Cells, 28: 1751-1759.
- García, P. Clarke, M.L., Vegiopoulos, A., Berlanga, O., Camelo, A., Lorvellec, M. and Frampton, J. (2009) Reduced c-Myb activity compromises HSCs and leads to a myeloproliferation with a novel stem cell basis. EMBO J, 28: 1492-1504.
- García P., and Frampton, J. (2008) Hematopoietic lineage commitment: miRNAs add specificity to a widely expressed transcription factor. Dev Cell. 14: 815-6.
- García, P., and Frampton J. (2006). The transcription factor B-Myb is a key regulator of DNA replication in both diploid and polyploidy megakaryocytes. J Cell Sci, 119: 1483-93.
- Vegiopoulos, A., García, P., Emambokus, N. and Frampton, J. (2006) Coordination of erythropoiesis by the transcription factor c-Myb. Blood, 107: 4703-10.
- García, P., Berlanga, O., Watson, R., and Frampton J. (2005) Generation of a conditional allele of the B-Myb gene. Genesis, 43: 189-95.

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