

Melanoma Group

Summary

We are interested in identifying molecular mechanisms involved in melanoma progression and drug resistance. Specifically, our research focuses on stress response programmes (involving apoptosis, autophagy, senescence and endosome mobilisation) and how they are deregulated during tumour development. Our experimental systems include a combination of cell lines, mouse models and tissue biopsies isolated from benign and malignant melanocytic lesions. Our ultimate goal is to translate our results into a more rational approach to melanoma diagnosis and drug treatment.

Strategic Goals

- Identify mechanisms of suppression of melanoma initiation
- Define the contribution of stress response programmes (apoptosis, senescence and autophagy) to melanoma progression and metastasis
- Address mechanisms of melanoma chemoresistance using genetic and pharmacological approaches
- Develop new models of melanoma for a more physiological analysis and validation of targeted therapies

María S. Soengas *Group Leader*



María S. Soengas was born in Agolada, Pontevedra, Spain in 1968. She embarked upon her scientific career first as an undergraduate student at the *Universidad de La Coruña* and later at the *Universidad Autónoma de Madrid*, where she graduated in Molecular Biology. There she received her PhD with First Class Honours for her studies on molecular mechanisms of DNA replication at the laboratory of M. Salas, *Centro de Biología Molecular Severo Ochoa*.

In 1997 Soengas moved to S. Lowe's Group at the Cold Spring Harbor Laboratory, New York, USA, where she assessed the role of apoptosis as a tumour suppressor mechanism, with special emphasis on melanoma. She then joined the Department of Dermatology at the University of Michigan in 2002 to develop a basic research programme in Melanoma. Her group defined new molecular mechanisms underlying human melanoma initiation, progression and chemo-resistance.

The main objective of Soengas' Melanoma Group at the CNIO is to translate basic research in melanoma to the clinic by identifying novel markers of this disease and targets for drug development.

Soengas has been recipient of fellowships and awards from both the Human Frontiers in Science Programme and the Leukemia and Lymphoma Society of America. She has also received a Life Science Biomedical Scholar Award from the University of Michigan as well as Career Development Awards from the American Dermatology Foundation, the Elsa V. Pardee Foundation, the V Foundation for Cancer Research and the Diana Ashby Young Investigator Award from the Society for Melanoma Research. She has also been honoured with the *Premio María Josefa Wonenburger* from the *Xunta de Galicia*.



Post-doctoral fellows: Agnieszka Checinska, Lionel Larribere (until August), Erica Riveiro, David Sáenz (since July), Damiá Tormo. **Graduate students:** Direna Alonso, Eva Pérez. **Technicians:** Tonantzin G. Calvo, Estela Cañón.

Highlights

Mechanisms of suppression of melanoma initiation: senescence and alternative splicing

Current statistics indicate that 1 in 58 individuals will develop melanoma during his/her lifetime. This rate would be considerably higher if potent tumour suppressors were not in place. Fair skinned individuals bear an average of 10 to 40 nevi (moles) which are constituted by melanocytes containing pro-oncogenic mutations in the MAPK pathway, primarily in the BRAF kinase or the small GTP-ase NRAS. However, less than 1/1000 nevi develop into melanoma. Our research focuses on the identification of genetic and epigenetic factors that prevent the proliferation of nevus cells, and how these mechanisms of protection are disengaged to promote melanoma progression and chemoresistance.

In collaboration with D. Peeper, the Netherlands Cancer Institute (NKI) we have previously shown that premature senescence plays a key role in blocking the transformation of human melanocytes by the BRAF^{V600E} mutation. We have also reported a novel form of senescence driven by the Unfolded Protein Response (UPR) of the endoplasmic reticulum that specifically blocks HRAS^{G12V}-mediated, but not BRAF-mediated, melanocyte transformation. Importantly, we also demonstrated that the differential activation of stress programmes by the BRAF and RAS oncogenes can also extend to human melanomas. In recent studies,

integrating cDNA arrays with functional studies, we have identified significant differences in mRNA expression profiles driven by BRAF, NRAS and HRAS mutations. We are currently evaluating novel stress response factors and cell cycle regulators to define how selective changes in these oncogenes will give rise to histopathologically different human nevi.

Molecular mechanisms of melanoma maintenance: chromatin remodelling and autophagy

Melanoma cells accumulate a plethora of genetic and epigenetic defects in multiple signalling cascades. Treatments aimed at bypassing these alterations are currently being tested in preclinical and clinical settings. Nevertheless, no efficient antitumoural responses have thus far been demonstrated in advanced melanoma patients. We therefore hypothesised that melanoma cells possess additional, yet unknown mechanisms of resistance.

In our search for novel mediators of melanoma progression and drug resistance, we focused on genes mapping at loci that are frequently altered in melanoma. It was of particular interest to consider the small arm of chromosome 6, which is found to be amplified in most melanomas. Using comparative genomic hybridisation (GSK), spectral karyotyping (SKY) and histochemical analyses in tissue

demonstrate an efficient anti-melanoma activity of this compound in various animal models including those with highly immunosuppressed backgrounds (recapitulating immune defects in melanoma patients). These data provide proof-of-principle of new tractable crosstalk points between cytosolic dsRNA helicases, endo/lysosomes and apoptotic modulators that may be exploited therapeutically.

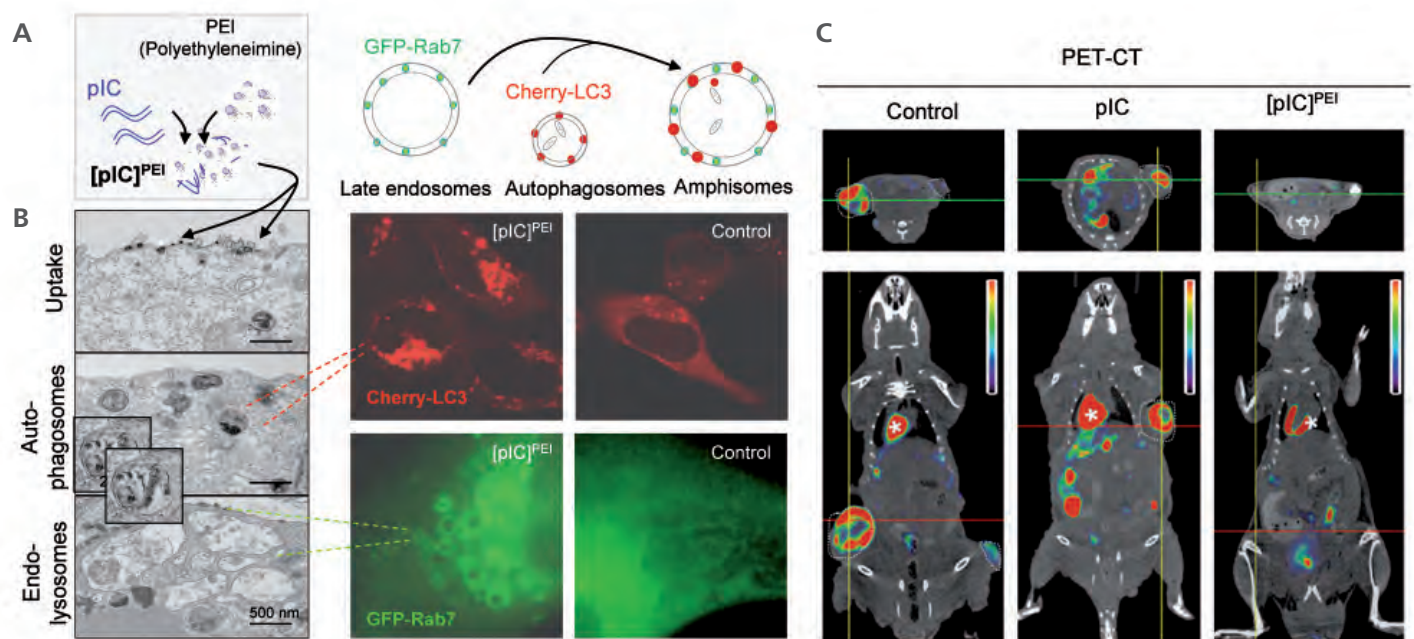


Figure 2: [pIC]PEI-driven antimelanoma activity *ex vivo* and *in vivo*. (A) Schematic of the reagents used to define the mode of action of this complex. (B) Mobilisation of the endo/lysosomal machinery determined by electron microscopy and fluorescence-based imaging of Rab7 and LC3 proteins. (C) Antitumour activity of [pIC]PEI monitored by PET-CT in Tyr:NRASQ61K; INK4a/ARF^{-/-} mice.

Publications

Tormo D, Checinska A, Alonso-Curbelo D, Pérez-Guijarro E, Cañón E, Riveiro-Falkenbach E, Calvo TG, Larribere L, Megías D, Mulero F, Piris MA, Dash R, Barral PM, Rodríguez-Peralto JL, Ortiz-Romero P, Tüting T, Fisher PB, Soengas MS (2009). Targeted activation of innate immunity for therapeutic induction of autophagy and apoptosis in melanoma cells. *Cancer Cell* 16, 103-114.

Jia L, Soengas MS, Sun Y (2009). ROC1/RBX1 E3 ubiquitin ligase silencing suppresses tumor cell growth via sequential induction of G2-M arrest, apoptosis, and senescence. *Cancer Res* 69, 4974-4982.

VanBrocklin MW, Verhaegen M, Soengas MS, Holmen SL (2009). Mitogen-activated protein kinase inhibition induces translocation of Bmf to promote apoptosis in melanoma. *Cancer Res* 69, 1985-1994.

Khodadoust MS, Verhaegen M, Kappes F, Riveiro-Falkenbach E, Cigudosa JC, Kim DS, Chinnaiyan AM, Markovitz DM, Soengas MS (2009). Melanoma proliferation and chemoresistance controlled by the DEK oncogene. *Cancer Res* 69, 6405-6413.

Tormo D, Alonso-Curbelo D, Soengas MS (2009). MDA5-mediated autonomous cell death in aggressive melanomas. *Clin Transl Oncol* 11, 39-42.

Awards and Recognition

Editorial Board Member, *Oncogene*

"Women in Science" Award from the *Instituto de la Mujer*, Spain

3rd *Josefa Wonenburger Prize*, Board of Galicia, Spain