

Cell Competition *Junior Group*

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Scientific Report 2010 *crío*



Eduardo Moreno

Junior Group Leader

Eduardo Moreno, born in Madrid in 1970, carried out his PhD in the laboratory of G. Morata, at the *Centro de Biología Molecular (CBM)* of the *Universidad Autónoma de Madrid*. As a Postdoctoral Fellow, he worked at the laboratory of K. Basler at the University of Zurich (Switzerland) and has been a Principal Investigator at the CNIO since 2005.

Eduardo Moreno, together with G. Morata, identified the caudal gene and demonstrated that it is responsible for identity formation of the last segment in *Drosophila*. Studying the phenomenon of cell competition, in collaboration with G. Morata and K. Basler, he discovered that proliferating cells compete for the internalisation of extracellular factors that promote growth and survival. Basler and Moreno also showed that the protooncogene *myc* is a potent inducer of cell competition and established a connection of cell competition to early steps of cancer formation.

Since 2005, his laboratory at the CNIO has identified several crucial factors that distinguish winners from losers during cell competition, including the "Flower code". This has consequently established his laboratory as a leader within the cell competition field. His group has also shown that non-apoptotic cell competition aids adult stem cells to induce the differentiation of their daughter cells.

In recognition of his work, Eduardo Moreno received the Extraordinary Award from the *Universidad Autónoma de Madrid*, the Young Scientists Award Innogenetics from the *Sociedad Española de Biología Molecular y Bioquímica (SEBBM)*, the Young Investigator Award from the Brupbacher Foundation Against Cancer in Zurich, as well as a European Research Council (ERC) starting grant in 2008. Moreno was recently awarded the Josef Steiner Cancer Research Award 2011.

Summary

In our lab we have studied how *Drosophila* wing imaginal discs distinguish winners from losers during cell competition. We have described the function of several crucial factors in this process, including Flower and dSparc. *Drosophila* Flower forms an extracellular code that reveals the fitness of a cell to its neighbours and is subsequently required to label cells as "winners" or "losers".

The second gene described in detail is the *Drosophila* homologue of SPARC/Osteonectin which acts as a self-protective signal expressed by loser cells during cell competition. The intriguing role of SPARC in cancer and metastasis is better understood in the context of its role in cell competition. Both genes belong to different pathways. We are currently focused on establishing how neighbouring cells interpret the "Flower code" and which molecules interact with Flower. We are also studying other genes involved in cell competition in *Drosophila* and mice.

Strategic Goals

- Understand how cells of differing fitness interact within a tissue
- Explore the implications of the "Flower code" during development, cancer and ageing
- Elucidate how stable "cell societies" are formed and maintained over time





Post-doctoral fellows: Sergio Casas, Francisco A. Martín and Christa Rhiner. **Graduate students:** Fidel N. Lolo, Jesús M. López-Gay, Evgeniya S. Petrova and Marta Portela. **Technician:** Ismael Fernández.

Highlights

Projects completed in 2010 include the discovery of the "Flower code". We have shown that Flower forms an extracellular code that reveals the fitness of a cell to its neighbours in *Drosophila* and which is subsequently required to label cells as "winners" or "losers". In *Drosophila*, the *fwe* locus produces three isoforms: *fwe^{ubi}*, *fwe^{Lose-A}* and *fwe^{Lose-B}*. Basal levels of *fwe^{ubi}* are constantly produced in wing imaginal discs but, during cell competition, loser cells downregulate *fwe^{ubi}* and upregulate the two *fwe^{Lose}* isoforms. The expression of *fwe^{Lose}* transcripts ultimately leads to caspase activation in the loser cells. Our results in *Drosophila* suggest that the *flower* gene is required to distinguish losers from winners during cell competition for resources and survival factors. The different Flower isoforms tag cells as "losers" (expressing the Lose-A and/or Lose-B isoforms) or "winners" (cells expressing the ubi isoform) but the eventual death of the loser cells largely depends on the balance between the levels of two opposing secreted signals: 1) a protective signal encoded by *dSPARC* (see below) and 2) an unknown killing signal.

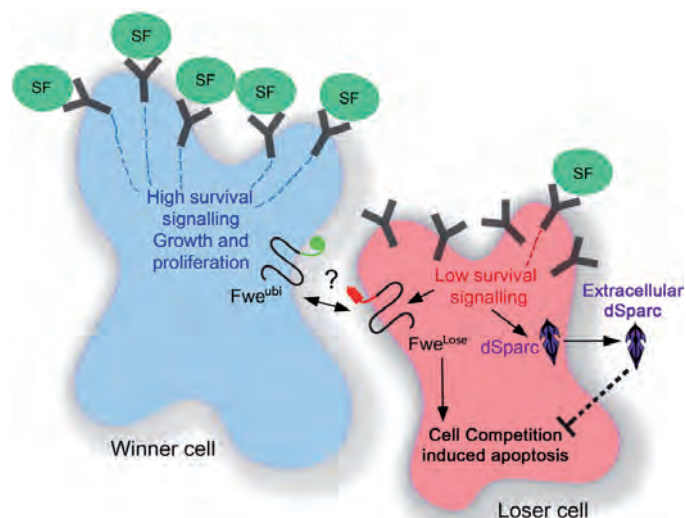


Figure: The "Flower code" distinguishes winners and losers during cell competition, whereas dSparc acts as a self-protective signal for loser cells.

We also identified the *Drosophila* homologue of SPARC/Osteonectin as a self-protective signal expressed by loser cells during cell competition. We further showed that dSPARC is not a general inhibitor of apoptosis, despite its potent inhibition of cell competition-induced cell death. dSPARC may allow useful cells to recover from transient and limited damage before being unnecessarily eliminated by their neighbours. Our results show that dSPARC and Fwe function in parallel and opposing pathways during cell competition – with dSPARC providing transient protection, and the "Flower code" promoting cell elimination. However, if the differences in cellular fitness persist and/or are too great, cell competition-induced apoptosis is nevertheless triggered. The role of SPARC specifically repressing cell competition may have important consequences in our understanding of mammalian development, homeostasis, stem cell replacement and cancer. Specifically, deregulation of this mechanism is likely to be important in cancer, for example by allowing metastatic cells to survive in a new environment or during the expansion of cancerisation fields.

Publications

Portela M, Casas-Tinto S, Rhiner C, López-Gay JM, Domínguez O, Soldini D, Moreno E (2010). *Drosophila* SPARC is a self-protective signal expressed by loser cells during cell competition. *Dev Cell* 19, 562-573.

Rhiner C, López-Gay J, Soldini D, Casas-Tinto S, Martín F, Lombardía L, Moreno E (2010). Flower forms an extracellular code that reveals the fitness of a cell to its neighbors in *Drosophila*. *Dev Cell* 18, 985-998.