

# Epithelial Cell Biology *Junior Group*

## Summary

In our laboratory we study the function of cadherin-catenin adhesion complexes in skin. In particular we are focusing on the role of p120-catenin (p120) in coordinating structural cues and integrating signals from epithelial cells and the tissue microenvironment that preserve skin homeostasis. We are also investigating how – when perturbed – they instigate tumour formation. We use mouse models and *in vitro* systems to analyse the contribution of this protein during skin physiology and disease.

## Strategic Goals

- Analyse the contribution of p120 to cell division, epithelial cell polarity, and tissue architecture
- Understand the role of inflammation in promoting genetic instability and skin cancer
- Study the function of p120 in the resolution of inflammation and how this contributes to tissue repair and hair follicle regeneration

## Mirna Pérez-Moreno *Junior Group Leader*

Mirna Pérez-Moreno, born in Acapulco, Guerrero, Mexico, obtained her PhD degree in Physiology in 1999 at the laboratory of L. Gonzalez-Mariscal, *Centro de Investigación y Estudios Avanzados* (CINVESTAV), Mexico City, Mexico.

During the final year of her graduate studies she completed a rotation with A. Cano at the *Instituto de Investigaciones Biomedicas* in Madrid and then stayed as a Postdoctoral Fellow to complete her work on the regulation of the tumour suppressor gene *E-cadherin*. She then joined B. Gumbiner in 2001 for a short postdoctoral training at the Memorial Sloan-Kettering Cancer Center (MSKCC), New York, USA.

In 2002 she joined E. Fuchs' Laboratory at the Howard Hughes Medical Institute, Rockefeller University, New York, USA, as a Postdoctoral Fellow. She was a recipient of the Breast Cancer Research Programme Fellowship of the U.S. Department of Defense. During this time she carried out fundamental research in skin biology, development and cancer, and continued to focus on the molecular mechanisms underlying the regulation of intercellular adhesion.

She joined the BBVA Foundation - CNIO Cancer Cell Biology Programme as Junior Group Leader in May 2008. Her Group is studying the functions of intercellular adhesion proteins in controlling growth and differentiation of skin epithelial progenitor cells and their crosstalk with signals arising from inflammatory cells during skin physiology and disease.



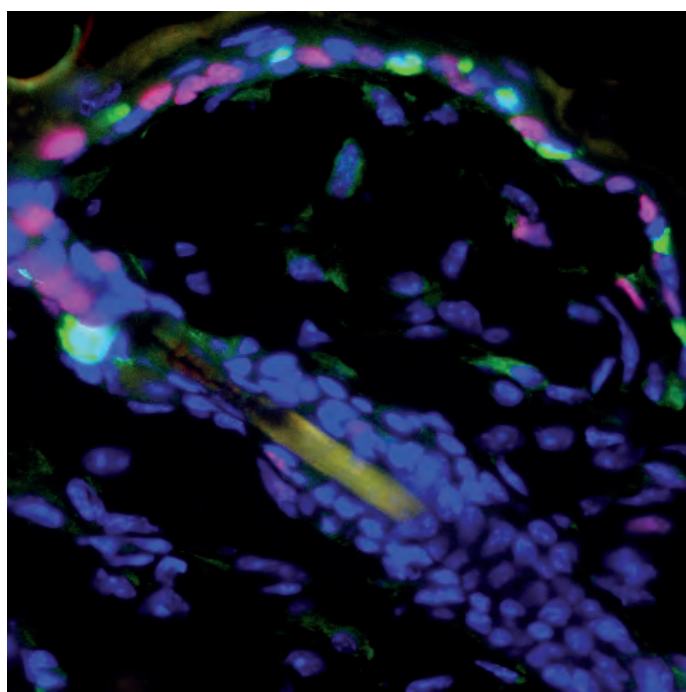


Post-doctoral fellow: Carolina Epifano. Graduate students: Ljiljana Dukanovic (since September), Marta N. Shahbazi. Technician: Luis Guillermo F. Leiva.

## Highlights

Alterations in the distribution/downregulation of p120 are frequently found in essentially all major carcinomas. However, the mechanisms underlying the contribution of these events to cancer are not yet clearly understood.

Using conditional targeting in mouse skin epithelia we observed that loss of p120 led to reductions in cadherin-catenin complexes without perturbation of epidermal architecture. This loss did however promote the activation of RhoA GTPase/NFκB signalling in epithelial cells instigating inflammation, which caused hair loss, epithelial proliferation and alterations in differentiation, resulting in the development of skin carcinomas.



**Figure:** Skin section showing the presence of lymphocytes (green) in epidermis, dermis and hair follicles. The distribution and number of these cells fluctuates during tissue repair and hair regeneration, where epithelial cells actively grow (cells positive for the proliferation marker Ki67 are shown in red).

Since not every inflammatory skin disease leads to cancer we are now analysing three major aspects:

- Intrinsic alterations in p120 null keratinocytes. These cells display cytokinesis defects, mitotic spindle alterations and extra centrosomes, which result in mitotic arrest. This is, at least in part, a consequence of the activation of RhoA GTPase, but it may also be due to the loss of interactions with microtubule-associated proteins. Using a yeast-two hybrid screen we found that p120 interacts with the microtubule-associated protein CLASP2, which is involved in cell polarity and mitotic spindle organisation. We are currently analysing the physiological relevance of this interaction.
- To study whether chronic inflammatory responses are sufficient to initiate new divisions in mitotically-arrested cells. Additionally, we would like to determine if these are causal events in promoting genetic instability and tumour progression.
- Dissect aberrant mechanisms in promoting the resolution of inflammation and how inflammation controls hair follicle remodelling. The final outcome of the interplay between immune system and the evolving cancer may depend on the interactions between genetically altered cells and the unique tissue microenvironment. This may favour a desirable tumour-suppression or an undesirable tumour-promotion. Inadequate resolution of inflammatory responses may explain the observed hair loss and skin tumourigenesis.

## Publications

Pérez-Moreno M (2009). When neighbourhood matters: tumour microenvironment. *Clin Transl Oncol* 11, 70-74.