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Lab Team

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Scientific Background

The class *Nr3c* of the steroid hormone receptors belongs to the nuclear receptor superfamily and includes the glucocorticoid (GC) receptor (GR), the mineralocorticoid receptor (MR), and the sex steroid receptors for progesterone and androgens. All nuclear receptor family members are ligand-dependent transcription factors, whose ability to integrate cellular processes explains that these receptors are the most targeted molecules for the treatment of skin diseases in the clinical practice.

Our group has studied the role of GR in skin development and disease through genetically modified mouse models with GR gain- and loss-of-function (see publications). We have demonstrated that both the ubiquitous ablation as well as epidermal-specific overexpression of GR leads to major defects in mouse skin development. The epidermal loss of GR (GR epidermal knock out or GR^{EKO} mice) provoked skin barrier defects and cutaneous inflammation. Remarkably, many of the genes misexpressed in GR^{EKO} skin were also dysregulated in inflammatory skin diseases such as atopic dermatitis and psoriasis. Moreover, GR^{EKO} adult mice were more susceptible to perturbation of skin homeostasis and also showed increased susceptibility to several skin carcinogenesis protocols. Collectively, our data demonstrated that GR exerts a potent anti-proliferative, anti-inflammatory and anti-tumor role in the epidermis, by functionaly interfering with diverse signaling pathways including IKK/NF-kappaB, MAPK/AP-1 and PI3K/AKT.

Given the complex interaction of hormone signaling, we have recently expanded our interests to analyze the function of the closely related the mineralocorticoid receptor (MR) in cutaneous biology. This line of research is supported by several evidences, including that GCs can bind MR with high affinity, both MR and GR bind the same response element, and transgenic mice with epidermal-specific overexpression of either MR or GR exhibited high phenotypic resemblance.

Research Interests

Our specific objectives are:

1. Analyze the impact of keratinocyte-restricted inactivation of the MR in the epidermis (development and disease)

1.1. - Generation and characterization of mice with epidermal loss of MR (MR epidermal knock out or MR^{EKO} mice)
1.2. - Investigate the responses of MR^{EKO} mice to glucocorticoids (GC), GC-induced delayed wound healing, and inflammation
1.3. - Generation and characterization of keratinocyte cell lines with MR inactivation

2. Identification and validation of gene targets of GR and MR in keratinocytes: Therapeutical perspectives.

2.1.- Identification of novel MR target genes in skin by transcriptomic and ChIP-seq approaches

2.2.- Signaling pathways involved in MR-mediated signaling. Common and distinct pathways triggered by MR and GR

RELEVANT PUBLICATIONS (last 5 years)

Latorre V*, Sevilla LM*, Sanchis A and Pérez P (*equal contribution) 2013 Selective ablation of glucocorticoid receptor in mouse keratinocytes increases susceptibility to skin tumorigenesis. *Journal of Investigative Dermatology* 33(12):2771- 2779.

Sevilla LM*, Latorre V*, Sanchis A, and Pérez P (*equal contribution) 2013 Epidermal inactivation of the glucocorticoid receptor triggers skin barrier defects and cutaneous inflammation. *Journal of Investigative Dermatology* 33(2):361-70. doi: 10.1038/jid.2012.281.

Pérez P 2011 Glucocorticoid receptors, epidermal homeostasis and hair follicle differentiation *Dermato-Endocrinology* REVIEW for the special issue of the Journal *Nuclear Hormone Receptors* 3(3), 1-9.

Sevilla L*, Bayo P*, Latorre V, Sanchis A, and Pérez P (*equal contribution) 2010 Glucocorticoid receptor regulates overlapping and differential gene subsets in developing and adult skin. *Mol Endocrinology* 24(11), 2166-2178.

Page A, Navarro M, Garín M, Pérez P, Casanova ML, Moreno R, Jorcano JL, Cascallana JL, Bravo A, and Ramírez A 2010 IKKbeta leads to an inflammatory skin disease resembling interface dermatitis *Journal of Investigative Dermatology* 130(6), 1598-1610.

Bayo P, Sanchis A, Bravo A, Cascallana JL, Buder K, Tuckermann J, Schütz G, and Pérez P 2008 Glucocorticoid receptor is required for skin barrier competence. *Endocrinology* 149(3), 1377-1388.

Donet E, Bosch P, Sanchis A, Bayo P, Ramírez A, Cascallana JL, Bravo A, and Pérez P 2008 Transrepression function of the glucocorticoid receptor regulates eyelid development and keratinocyte proliferation but is not sufficient to prevent skin chronic inflammation. *Mol Endocrinology* 22(4), 799-812.