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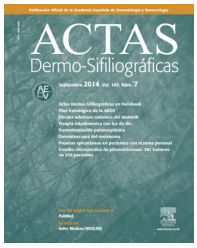

REVIEW

New Experimental Models of Skin Homeostasis and Diseases☆

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Podoplanin;
Genetically modified mice;
Three-dimensional skin equivalents;
Skin-humanized mice;
Photodynamic therapy

Abstract Homeostasis, whose regulation at the molecular level is still poorly understood, is intimately related to the functions of epidermal stem cells. Five research groups have been brought together to work on new in vitro and in vivo skin models through the SkinModel-CM program, under the auspices of the Spanish Autonomous Community of Madrid. This project aims to analyze the functions of DNA methyltransferase 1, endoglin, and podoplanin in epidermal stem cell activity, homeostasis, and skin cancer. These new models include 3-dimensional organotypic cultures, immunodeficient skin-humanized mice, and genetically modified mice. Another aim of the program is to use skin-humanized mice to model dermatoses such as Gorlin syndrome and xeroderma pigmentosum in order to optimize new protocols for photodynamic therapy.

PALABRAS CLAVE
Programa SkinModel-CM;

Nuevos modelos experimentales para el estudio de la homeostasis y la enfermedad cutánea

Resumen La homeostasis de la piel, cuya regulación molecular es aún bastante desconocida, está íntimamente relacionada con la función de las células madre epidérmicas. El programa

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Células madre epidérmicas;
ADN metil transferasa 1;
Endoglina;
Podoplanina;
Ratones modificados genéticamente;
Equivalentes cutáneos 3D;
Ratones con piel humanizada;
Terapia fotodinámica

SkinModel-CM, auspiciado por la Comunidad de Madrid, reúne 5 grupos de investigación con el propósito de desarrollar nuevos modelos experimentales *in vitro* e *in vivo* para analizar la función de ADN metiltransferasa 1, la endoglina y la podoplanina en la actividad de las células madre epidérmicas y en la homeostasis y el cáncer cutáneos. Estos nuevos modelos comprenden tanto cultivos organotípicos 3 D, como ratones inmunodeficientes con la piel humanizada y ratones modificados genéticamente. Otro objetivo del programa es el uso de ratones con la piel humanizada como modelo para reconstruir enfermedades cutáneas, tales como el síndrome de Gorlin y el xeroderma pigmentoso, con el objeto de optimizar nuevos protocolos de intervención mediante la terapia fotodinámica.

Introduction

The Skin: Its Function and Biological Utility

Although the skin is the most extensive and accessible organ in our body, the biological processes that regulate its homeostasis are still not well understood. The skin is not just a simple barrier to protect us from harmful external agents and prevent water loss but rather one of the most complex and dynamic tissues in our body. It would not be an exaggeration to say that the skin is as complex as the nervous system but with one essential difference: the brain cannot replace damaged neurons whereas skin is constantly renewed and can repair a wound, repopulating skin tissue with new cells. Knowledge of the biological and molecular basis governing the architecture, differentiation, and regeneration of the skin is crucial for understanding skin diseases and developing appropriate treatments. Basic research encompassing efforts to move both from the laboratory to the clinic and from the clinic to the laboratory (what is known as translational research) have given a strong impulse to our knowledge of skin diseases. An example is the recent identification by several international research consortia of 15 new susceptibility loci for psoriasis in individuals in the European population, increasing the number of genes associated with this disease to 36.[1] Many of these genes are associated with innate immunity and are shared by other autoimmune diseases, thus highlighting the importance of the skin in innate and acquired immune defense.

Molecular oncology studies have enabled the identification of key intracellular signaling pathways in skin cancer. An example is the frequent activation of the mitogen-activated protein kinases in malignant melanoma as a result of mutations in *braf* (the mammalian homolog of the *v-raf* oncogene of murine sarcoma virus identified in the brain) or *nras* (the mammalian homolog of rat sarcoma virus identified in neuroblastoma).[2] The finding that *hedgehog* signaling is responsible for the formation of basal cell carcinomas (BCC) was also a major breakthrough.[3] These advances have enabled the identification of new pharmacological targets and the incorporation into clinical oncology of more selective and individualized treatments for skin cancers, such as vemurafenib, a $BRAF^{V600E}$ mutant protein inhibitor (the *braf* mutation is the main one in $BRAF^{V600E}$-positive cancers) in melanoma[4] and vismodegib, an antagonist of the Smo (*Smoothened*) membrane protein implicated in the activation of the *hedgehog* pathway for the treatment of advanced BCC.[5]

Skin disease accounts for almost 20% of the caseload in primary care, and skin cancer is the most highly incident cancer in the general population. In addition to the most common noncancer diseases, such as dermatitis, acne, and psoriasis, there are more than 400 hereditary diseases of low prevalence, known as genodermatosis, which overall account for a significant percentage of the caseload in dermatology departments. The etiology of many of these diseases is well known, but in other cases, the causes are complex and we are still a long way from an in-depth understanding. Despite advances in diagnosis and improved knowledge of the molecular biology of many pathological skin processes, corresponding progress in treatment has not been made. For example, in skin cancer, surgical excision, accompanied by chemotherapy and/or radiotherapy, is still the most widespread approach. This is partly because appropriate experimental models are not available for testing of new drugs and new therapies before embarking on costly and often fruitless clinical trials.

The skin is a fascinating biological model for basic science and one that transcends the confines of dermatology. The epidermis was the first organ in which stem cells were identified in situ through a label retention technique (see below) and, along with the hematopoietic system, is the tissue where stem cells are best characterized. In addition, a close relationship has been demonstrated between stem cells and cancer, on the one hand, and between stem cells and ageing, on the other. Biomedical engineering and tissue engineering in particular have revolutionized dermatology research, providing new in vitro and in vivo experimental models for studying the majority of genodermatoses and for testing new therapies. The development of skin-humanized mouse models has enabled human skin diseases to be reproduced in mice.

SkinModel is the name given to a platform that has brought together 5 research groups in the Spanish