In this Issue

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One Person: Two Skinss

The intellectual core of dermatology is to explain the biologic basis for the patterns rashes make. In some instances the reason for a particular order is quite clear; the external insult that leads to contact allergic eczema, or the photo-distribution of the rash triggered by ultraviolet radiation. Perhaps the most enigmatic of all have been the patterns first described by Blaschko over a century ago. Initially confused with dermatomal patterns, and hence a neurologic basis, we can now think of these rashes as highlighting the natural patterns of keratinocyte migration. The somatic mutation merely acting as a tracer – Nature's own green fluorescent protein so to speak – that reveals and records the developmental path cells have taken.

Ever since the molecular basis for some of the keratin disorders was elucidated and the keratin mutations identified by Elaine Fuchs in mosaic epidermolytic hyperkeratoses, a sensible research maxim has been that all generalized rashes will exist in mosaic forms. Sakuntabhai and colleagues (p. 1144) now add Darier's disease to the ever increasing list. Darier's disease we now know to be secondary to mutations in a sarco/endoplasmic reticulum Ca2+ ATPase. The authors now show that patients with segmental or focal nevi with the clinical and pathologic features of Darier's disease show somatic mutations in the same gene. Such patients are therefore genetic mosaics. The clinical lesson being that if the mosaicism affects the germs cells then germline transmission is possible.

The presence of such diseases should alert us to an even more interesting hypothesis. Many germline mutations will be embryonically lethal; we will never see the full cutaneous phenotype. On the other hand, as postzygotic events, confined to the skin, such mutations may have a phenotype. Focal rashes, or rashes following Blaschko's lines, with no obvious generalized equivalent, may provide an insight into the action of such embryonically lethal genes: Nature's own Cre-Lox constructs!

One Individual: Four Cancers

That carcinogenesis is a multistage process involving many genetic events is so much part of the mainstream and rolls so easily off the tongue that we often forget how great is the paucity of evidence linking each genetic change with the various behaviors we see in the clinic. Indeed, following on from the pioneering work of Bert Vogelstein on colorectal cancer, despite the large number of studies describing correlations between genetic change and morphology or tumor behavior in *groups* of patients, a persistent criticism is that such studies fail to take into account the limitations of cross-sectional analyzes in *different* persons with *different* genetic backgrounds (of both person and tumor).

The present study from Popp *et al* (p. 1095) addresses this issue in a singular way. The authors have managed to sample tumors and establish cell lines from the *same* individual with squamous tumors at various clinico-pathologic stages. They present thorough molecular analyzes using FISH and comparative genomic hybridization as well as sequencing and RT-PCR studies. An additional bonus to this landmark study is that, unusually for skin malignancies, the lines are wild-type for p53. This makes the described cells lines all the more interesting and valuable for studying what turns a normal keratinocyte into a malignant one. I predict the lines will be much sought after and may become as well known as the correspondence's earlier (jointly with Norbert Fusenig) HaCaT cell line!

One Agent: How Many Pathways?

Imagine how many fewer scientists would be gainfully employed if ultraviolet radiation (UVR) acted through one receptor and one simple signaling pathway. The paper from Scholzen and colleagues (p. 1021) reminds us how far from the truth we are in cataloguing, let alone understanding the myriad pathways that UVR exerts on skin. And what galls most is the way that Nature seems to have placed false trails all around and uses the same molecules in completely different physiologic pathways. In this study the authors show that the human melanocortin 1 receptor (MC1R), the receptor for the tridecapeptide α-melanocyte stimulating hormone (α-MSH), better thought of as a rate limiting step in melanogenesis, may serve a broader physiologic purpose. They confirm that MC1R is present on endothelial cells in culture and argue that these cells possess the necessary machinery including expression of POMC and the relevant proconvertases to generate POMC peptides. Irradiation with UVR leads to increased proconvertase expression (as do Il-1β and α-MSH itself) and the authors argue that in turn the resulting generation of α-MSH may play a role in the modulation of skin inflammation. Can anybody now imagine thinking of UVR as a designer drug?

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One Symptom; Two New Technologies

Technology seems to drive biology, perhaps even more than ideas. Two papers in the present *Journal* use new techniques to study old problems.

Itch is the major symptom of skin disease and consequently – one is tempted to add facetiously – ignored by all serious researchers. The problem is how to get a handle on this complaint, how to turn this most ubiquitous of symptoms into a tractable scientific problem. The papers by Darsow and colleagues (p. 1029) and Weidner and colleagues (p. 1015) offer potential insights.

Darsow *et al* take advantage of advances in imaging and use PET scanning to study the correlates of experimentally induced itching. The brain areas highlighted (by activation) include as one would expect some motor and sensory areas, but as the authors conclude are perhaps more complex and widespread than many might have at first thought. Although the study by Darsow is not the first to use this approach (see *J Neuroscience* 1997; 17:8003–8008) it is a welcome addition.

Also related to itch, but more to the point the absence of itch, in the this issue Schmelz and coworkers have used microdialysis to study the acute effects of substance P and CGRP in skin. Microdialysis, after much use by neuroscientists, is increasingly becoming a powerful technique in understanding skin physiology. It offers the real opportunity to measure the genuine physiologic levels of key mediators *in vivo* and of course to apply pharmacologic agents experimentally in a controlled way with the minimum (as the authors point out) of experimental artefact due to trauma. These authors report that despite causing vasodilation, neither substance P nor CGRP activate nocioreceptors (i.e., they failed to produce itch or pain). The authors suggest that delivery via microdialysis catheter may avoid previous problems associated with pain from intradermal injections confounding studies of neuropeptide action. If the authors' conclusions are correct then some of the present neuropeptide antagonist drugs may turn out to be less useful than many think, and yet again, the textbooks need revision.