Clinical Implications

- Robinson et al. report a population-based case-control study that found an increased risk of basal cell carcinoma with tetracycline use and of squamous cell carcinoma with diuretic use.
- It seems reasonable that patients prescribed these medications should be counseled regarding sunlight protection.
- Taking a history of photosensitizing medication use should be part of screening for skin cancer risk.

REFERENCES


See related article on pg 1998

Phacomatosis Pigmentokeratotica Is a “Pseudodidymosis”
Rudolf Happle

In phacomatosis pigmentokeratotica, papular nevus spilus coexists with nevus sebaceous. The disorder was thought to be a didymosis with early postzygotic recombination. In this issue, however, Groesser and co-workers provide a new concept. Both nevi originate from a single heterozygous HRAS mutation in a pluripotential progenitor cell. This new understanding has implications for other proposed examples of didymosis in humans.


Phacomatosis pigmentokeratotica (PPK) is characterized by the coexistence of nevus sebaceous and papular nevus spilus (Figure 1). The disorder has so far been considered to represent an example of twin spotting or didymosis, which is why it has also been called “didymosis spilo-sebacea” (Happle, 2010). These binary nevi are often associated with various extracutaneous defects. Seventeen years ago, we proposed the hypothesis that the disorder represents a nonallelic twin-spot phenomenon (Happle et al., 1996). Accordingly, the two nevi would have originated from an early event of postzygotic recombination, resulting in a loss of heterozygosity and, thus, being homozygous at either of the two loci that were situated in different regions on a pair of homologous chromosomes (Happle, 1999). Thus far, this etiological concept had been accepted widely (Boente et al., 2000; Martínez-Menchon et al., 2005; Bouthors et al., 2006; Gruson et al., 2006; Oh et al., 2012), although molecular proof was lacking.

In the present issue, however, Groesser et al. (2013) present molecular findings that disprove the twin-spot hypothesis. From an analysis of six patients affected with PPK, they provide convincing evidence that both the sebaceous nevus and the papular nevus spilus originate from the same postzygotic HRAS mutation, being present in a heterozygous state. Hence,
Clinical Implications

- For phacomatosis pigmentokeratotica, the hypothesis of nonallelic twin spotting is now untenable.
- Molecular analysis of other binary genodermatoses, such as phacomatosis cesioflammaea and phacomatosis spilorosea, may show that the concept of nonallelic didymosis is similarly untenable.
- In the proposed dermatological examples of allelic didymosis, such as cutis tricolor, and the paired occurrence of nevus flammeus and nevus anemicus, having common origin from one heterozygous progenitor cell is far less likely.

in this complex disorder, the concept of nonallelic didymosis is untenable.

The discovery that PPK is caused by a postzygotic-activating HRAS mutation present in a multipotent progenitor cell has important implications for future research on binary mosaic genodermatoses. This is especially true for some of the other proposed examples of nonallelic twin spotting, such as phacomatosis cesioflammaea and phacomatosis spilorosea (Happle, 2005). I fully agree with Dr. Groesser and his co-workers that such binary skin disorders may likewise turn out to be caused by a single pleiotropic mutation present in a heterozygous state. In contrast, we should bear in mind that in Drosophila melanogaster several examples of nonallelic didymosis have been thoroughly studied (Stern, 1936; Graf et al., 1984; Spanó et al., 2001). Therefore, it seems reasonable to assume that nonallelic didymosis may occur sometimes in mammals, including humans.

Moreover, it seems still likely that the concept of allelic didymosis as proposed for the paired occurrence of nevus flammeus and nevus anemicus (Happle, 1999), mixed vascular nevus syndrome (Ruggieri et al., 2012), and cutis tricolor (Lionetti et al., 2010) will be corroborated by molecular studies. This view is supported by the fact that allelic didymosis is a well-established phenomenon in both plants and animals (Harrison and Carpenter, 1977; Vig et al., 1982; Griffin et al., 2009).

Groesser et al. (2013) infer that in isolated Schimmelpenning syndrome, the underlying mosaic HRAS mutation is lost in the melanocytic progenitor cells. Conversely, in isolated papular nevus spilus syndrome (Happle, 2010), the mosaic HRAS mutation would be lost in the epithelial progenitor cells. As the two syndromes occur together rather often in the form of PPK, this binary disorder may today be categorized as a “pseudodidymosis.”

Accordingly, PPK can now be taken as a clinical variant of the Schimmelpenning syndrome (Groesser et al., 2012), but with the same justification that it may also be categorized as a variation of papular nevus spilus syndrome. Apparently, the extracutaneous abnormalities associated with either of the two nevi show remarkable differences. The neurological defects of the Schimmelpenning syndrome include mental deficiency, seizures, and hemiparesis, whereas papular nevus spilus syndrome tends to be associated with segmental hyperhidrosis and dysesthesia. Future studies may show whether the presence of such dichotomous nosological relations can be documented in more patients affected with PPK or with one of its melanocytic or epithelial components.

CONFLICT OF INTEREST
The author states no conflict of interest.

REFERENCES
A key function of the skin is to provide a permeability barrier to restrict the movement of water, electrolytes, and other small molecules between the outside environment and the internal milieu. Following disruption of the permeability barrier, there is a rapid restoration of barrier function, and one of the key signals initiating this repair response is a decrease in the concentration of calcium in the outer epidermis. In this issue, Borkowski et al. present evidence showing that activation of Toll receptor 3 by double-stranded RNA may be another pathway for activation of permeability barrier repair. These results provide further evidence for a link between innate immunity and the permeability barrier.


An important function of the skin is to form a barrier between an outside hostile environment and the internal milieu. One key barrier function is to restrict the movement of water, electrolytes, and other small compounds, that is, the permeability barrier. Without a competent permeability barrier, life outside of the sea would be impossible. Recent studies have linked abnormalities in permeability barrier function to the development and progression of common skin disorders, including atopic dermatitis and psoriasis (Wolf and Wolf, 2012; Wolf et al., 2012).

The permeability barrier is mediated by lipid-enriched lamellar membranes located in the extracellular spaces of the stratum corneum (Feingold, 2007). The membranes contain ceramides, cholesterol, and free fatty acids predominantly. These lipids are delivered to the stratum corneum through the exocytosis of lamellar bodies from stratum granulosum cells (Feingold, 2007). In turn, the lamellar bodies contain glucosylceramides, sphingomyelin, phospholipids, and cholesterol. To form functional lamellar membranes, the glucosylceramides and sphingomyelin are converted to ceramides, a process catalyzed by the enzymes beta-glucocerebrosidase and acid sphingomyelinase, and the phospholipids are converted to free fatty acids, a process catalyzed by PLA2 (Feingold, 2007). The synthesis of lamellar bodies by keratinocytes requires a sufficient pool of cholesterol, sphingolipids, and phospholipids. Fatty acids are required for the synthesis of phospholipids and sphingolipids, and they are derived from either de novo synthesis by keratinocytes and/or uptake of exogenous fatty acids by keratinocytes (Feingold, 2007). Cholesterol may also be synthesized in keratinocytes and/or transported into keratinocytes by several uptake pathways (Feingold, 2007). The mechanism by which phospholipids and cholesterol are incorporated into lamellar bodies is not known, but recent studies have demonstrated that the transport of glucosylceramides into lamellar bodies is mediated by ABCA12 (Feingold, 2007).

Following disruption of the permeability barrier, there is a rapid restoration of barrier function (Feingold, 2007). A number of responses occur in the underlying epidermis that facilitate this repair process, including: (1) an almost immediate secretion of a pre-formed pool of lamellar bodies, (2) increased lipid synthesis, (3) an increase in lipoprotein receptors and fatty acid transport proteins that facilitate the

**Innate Immunity Stimulates Permeability Barrier Homeostasis**

Kenneth R. Feingold1

A key function of the skin is to provide a permeability barrier to restrict the movement of water, electrolytes, and other small molecules between the outside environment and the internal milieu. Following disruption of the permeability barrier, there is a rapid restoration of barrier function, and one of the key signals initiating this repair response is a decrease in the concentration of calcium in the outer epidermis. In this issue, Borkowski et al. present evidence showing that activation of Toll receptor 3 by double-stranded RNA may be another pathway for activation of permeability barrier repair. These results provide further evidence for a link between innate immunity and the permeability barrier.


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