COMMENTARY

# Dropping Lipids for Epidermal Defense

See related article on page 337

Matthias Schmuth

Department of Dermatology, University of Innsbruck, Austria

A major task of the epidermis is to defend the organism against outside harm which can be of biological, physical or chemical nature. Today's lifestyle involves frequent exposure to chemicals with irritating properties, making irritant contact dermatitis a common dermatologic problem. Irritant contact dermatitis is an inflammatory skin condition with a (per year) prevalence of up to 10% of the population. It represents the prototype of a cutaneous reaction that is triggered by danger signals from injured cells (Elias *et al*, 1999; Matzinger, 2002). Its inflammatory reaction is initiated by external damage to the stratum corneum, resulting in disruption of the epidermal permeability barrier and a release of cytokines, which in turn rapidly puts the innate immune system on alert to prevent invasion of microbes through the weakened barrier.

Additional, nonimmunologic aspects of irritant contact dermatitis are reported in this issue of the JID (p. 337). The hypothesis of Corsini and coworkers (2003) is that in irritant contact dermatitis, intracellular lipid droplets, containing adipose differentiation related protein (ADRP), protect from cytotoxity. Corsini *et al* report that lipid droplets occur in keratinocytes after sodium dodecyl sulfate (SDS) exposure. These droplets mainly consist of triacylglycerols, derived from re-distribution rather than synthesis or uptake of lipids. SDS exposure concurrently induces ADRP expression, both *in vitro*, in cultured keratinocyte, and *in vivo*, in mouse skin. Notably, blockage of ADRP exacerbates SDS-induced cytotoxicity.

What is the role of epidermal lipid droplets in irritant contact dermatitis? In the epidermis, lipids are compartmentalized: (i) in the extracellular space as multilamellar lipid sheets, mediating permeability barrier function; (ii) in cell membranes, either as structural components or as part of the cellular signaling machinery; or (iii) in the cytoplasm, preferentially in a specialized cell organelle, the lamellar body, from where they are secreted into the extracellular space of the suprabasal epidermis (Grubauer *et al*, 1987). Yet, in pathological situations, cytoplasmic lipids can also aggregate in cytoplasmic droplets lacking lamellar features. Such droplets have previously been described in states of disturbed epidermal lipid metabolism and after exposure of the epidermis to irritants such as dithranol and retinoids. Here, Corsini *et al* not only describe formation of lipid droplets after SDS exposure, but also, for the first time, report on the expression of ADRP in keratinocytes which is increased with SDS treatment. Although much is known about lamellar body content and function, there is little information on cytoplasmic lipid droplets and their associated proteins in keratinocytes.

Many cell types can package accumulating neutral lipids in cyto-plasmic droplets, consisting of a core of neutral lipids surrounded by a phospholipid layer, in which proteins are embedded. ADRP is one such protein that colocalizes to the surface of the droplets together with a number of other proteins, including caveolins, vimentin and the family of lipid droplet associating proteins (LDAP), including perilipin, tail interacting protein of 47 kDa (TIP-47) and S3-12. ADRP, by sequence homology, is the fourth member of the LDAP family and is located not only on the outside of lipid droplets, but also in the vicinity of the plasma membrane (Brasaemle *et al*, 1997).

By its localization, ADRP would be suited to serve as a docking protein for lipolytic or lipogenic enzymes. As of yet, there is no information whether ADRP is involved in lipid hydrolyzation by cytosolic lipases or in lipogenesis. However, forced expression of ADRP promotes uptake of long chain fatty acids across cell membranes, suggesting that it might function as a shuttling protein of lipid substrates from the plasma membrane to the lipid droplet surface (Gao and Serrero, 1999). Alternatively, ADRP could play a role in maintaining droplet integrity, modulating coalescence of small droplets into larger droplets, or facilitating droplet movement and secretion (Targett-Adams *et al*, 2003).

There is evidence cholesterol, fatty acids, peroxisome proliferator activated receptor (PPAR) ligands, ibuprofen and indomethacin induce ADRP expression in adipocytes. There is evidence that ADRP has functions beyond a passive repository of accumulating intracellular neutral lipids derived from chemical damage of plasma membranes. While in keratinocytes, PPAR ligands increase ADRP expression (Schmuth *et al*, unpublished observation); they also ameliorate the inflammatory reaction in irritant contact dermatitis (Sheu *et al*, 2002). Conversely, as reported by Corsini, *et al* absence of ADRP exacerbates SDS-induced cytotoxicity. Furthermore, calcium chelation modulates ADRP expression and lipid droplet formation, raising the question of how calcium signaling (changes in epidermal calcium gradients are known to regulate lipid secretion from lamellar bodies) could be involved in this process. How these findings relate to each other remains unanswered. Whatever the answer, ADRP, thus far mainly described in adipocytes, seems to play an unexpected role in the epidermis. Further characterization of its function in keratinocytes could open new perspectives on epidermal lipid metabolism and its role in irritant contact dermatitis.

## REFERENCES

Brasaemle DL, Barber T, Wolins NE, Serrero G, Blanchette-Mackie EJ, Londos C: Adipose differentiation-related protein is an ubiquitously expressed lipid storage droplet-associated protein. *J Lipid Res* 38:2249–2263, 1997

Corsini E, Viviani B, Zancanellao, *et al*: Induction of Adipose differentiation related protein and neutral lipid droplet accumulation in keratinocytes by skin irritants. *J Invest Dermatol* 121:337–344, 2003

Elias PM, Wood LC, Feingold KR: Epidermal pathogenesis of inflammatory dermatoses. *Am J Contact Dermat* 10:119–126, 1999

Gao J, Serrero G: Adipose differentiation related protein (ADRP) expressed in transfected COS-7 cells selectively stimulates long chain fatty acid uptake. *J Biol Chem* 11:16825–16830, 1999

Grubauer G, Feingold KR, Elias PM: Relationship of epidermal lipogenesis to cutaneous barrier function. *J Lipid Res* 28:746–752, 1987

Matzinger P: The danger model. A renewed sense of self. *Science* 296:301–305, 2002

Sheu MY, Fowler AJ, Kao J, *et al*: Topical peroxisome proliferators activated receptor-alpha activators reduce inflammation in irritant and allergic contact dermatitis. *J Invest Dermatol* 118:94–101, 2002

Targett-Adams P, Chambers D, Gledhill S, Hope RG, Coy JF, Girod A, McLauchlan J: Live cell analysis and targeting of the lipid droplet-binding adipocyte differentiation-related protein. *J Biol Chem* 278:15998–16007, 2003