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## On the role of the endogenous opioid system in regulating epidermal homeostasis

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### Abstract

The presence of functional opioid receptors on epidermal keratinocytes, with attendant regulation of keratinocyte proliferation and differentiation, indicate their novel role in maintaining epidermal homeostasis. Expression of proenkephalin precursors and neuropeptide products in the same compartment opens an opportunity to study the role of this endogenous opioid circuitry, with its regulators, in modulating epidermal barrier function.

### Keywords

skin; opioids; opioid receptors; homeostasis; pathology

### Expression of functional $\delta$ -opioid receptors (DOR) in the epidermis

In this issue of *JID*, Dr. Bigliardi's team presents evidence that DORs are expressed in the suprabasal layers of the epidermis and that they are phenotypically active (Neumann *et al.*, 2014). Specifically, ligand activation of DORs can stimulate the ERK 1/2 MAPK pathway with attendant effects on keratinocyte proliferation and differentiation programs. The authors conclude that DORs activity in human keratinocytes can profoundly affect epidermal morphogenesis and homeostasis with implications in skin physiology and pathology.

### An endogenous opioid signaling system in the epidermis

Interestingly, DORs are expressed predominantly in the suprabasal differentiated layers of human epidermis, with expression patterns that are almost identical to those of proenkephalin (PENK) and Met- and Leu-enkephalin antigens (Slominski *et al.*, 2011). Because enkephalins serve as ligands for DORs, both findings (Neumann *et al.*, 2014;

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### Conflict of Interest

The author states no conflict.

Slominski *et al.*, 2011) identify a novel opioid system composed of endogenously produced enkephalins that would act in para- or autocrine fashion to regulate epidermal homeostasis.

Because the epidermis, serving as a physical and biological barrier (Feingold and Elias, 2014), senses and reacts to environmental factors to regulate epidermal and skin homeostasis (Slominski and Wortsman, 2000; Slominski *et al.*, 2012), the local endogenous opioidogenic system should also be regulated by environmental factors in order to play a significant role in the regulation of local homeostasis. In agreement with this concept, expression of PENK and PENK-derived neuropeptides is regulated by TLR4 (LPS) and TLR2 (PAM3CSK4) agonists as well as by ultraviolet B (UVB) radiation (Slominski *et al.*, 2011), indicating that production of PENK-derived neuropeptides can be stimulated by biological and physical insults. However, it still remains to be determined whether similar biological and physical insults regulate DOR expression in a fashion similar to the regulation of melanocortin receptors, which are widely expressed in human skin (Bohm *et al.*, 2006; Slominski *et al.*, 2012). In addition, the proposed role of DORs in wound healing (Neumann *et al.*, 2014) would require determining whether physical disruption of the skin barrier also enhances the expression of PENK as a part of skin wound healing processes; this could be similar to the mechanisms of skin responses to stress that rely on complex neuropeptides action (McLaughlin and Zagon, 2012; Slominski *et al.*, 2000; Slominski *et al.*, 2013).

### Potential functions of the cutaneous opioid system

As indicated by Neumann *et al.* (Neumann *et al.*, 2014), in conjunction with regulated production of PENK-derived peptides (Slominski *et al.*, 2011) and the complex role of opioids in regulating cell proliferation and the function of epithelia (McLaughlin and Zagon, 2012), the local opioid system would include opioid growth factor (OGF) – OGF receptors (OGFr) axis, acting as a homeostatic regulator of the epidermis as proposed by (McLaughlin and Zagon, 2012).

Additional functions of local opioid activity would be secondary to a well-documented immunomodulatory role of PENK-derived peptides that include stimulation of innate immunity, which is conserved across many species (Metz-Boutigue *et al.*, 2003; Tasiemski *et al.*, 2000). These functions were discussed previously in the context of regulating local skin immunity and antimicrobial activities (Slominski *et al.*, 2011). The stimulation of the innate immune activity by opioids could be crucial in regulating wound healing and restoration of epidermal integrity, in particular when the latter is disrupted by UVB radiation (Slominski *et al.*, 2012; Slominski *et al.*, 2011).

Consistent with the above is deregulated expression of PENK antigens in pathological skin, including psoriasis, inflammatory dermatoses and neoplastic processes (Slominski *et al.*, 2011). The above pattern of PENK expression nicely complements the hypothesis that DOR's activity is spatially and temporally controlled in human skin, affecting skin physiology and pathology (Neumann *et al.*, 2014), with implications in dermatopharmacology, as also proposed by (McLaughlin and Zagon, 2012; Slominski *et al.*, 2012; Slominski *et al.*, 2011)

## Integration of local opioid activity with the skin neuroendocrine system

It must be noted that skin cells and cutaneous nerve endings also express: 1) other opioid receptors, including  $\mu$ - and  $\kappa$ -OR (McLaughlin and Zagon, 2012; Neumann *et al.*, 2014; Slominski *et al.*, 2012), 2) proopiomelanocortin (POMC) together with a molecular system regulating its processing towards  $\beta$ -endorphins, 3) melanocortin peptides that include PC1 and PC2 convertases, and 4) a CRH signalling system regulating POMC processing in a context dependent manner (Slominski *et al.*, 2000; Slominski *et al.*, 2013). PC1 and PC2 convertases process both PENK and POMC precursors towards final regulatory neuropeptides in a regulated fashion. Thus, the extended local opioid system (McLaughlin and Zagon, 2012; Neumann *et al.*, 2014; Slominski *et al.*, 2000; Slominski *et al.*, 2011) can be integrated into the function of the broader skin neuroendocrine system regulating homeostasis on local and systemic levels, including sending signals to the brain (Slominski and Wortsman, 2000; Slominski *et al.*, 2012).

In this context, the extended opioid cutaneous system is highly organized, encoding mediators and receptors coupled differentially to signal transduction systems and endowed with stress-neutralizing activities. This system helps to maintain skin integrity and to restrict stress-dependent disruptions of internal homeostasis. From the evolutionary point of view, such a system could develop in the integument, as proposed for the HPA axis (Slominski, 2007), in order to protect the integrity of the integument. During evolution the DOR system would adapt as an efficient regulator of central and systemic homeostasis. Thus, the paper by Neumann *et al.* (Neumann *et al.*, 2014) opens new areas of dermatological exploration.

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