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Platelet-activating factor induces proliferation in differentiated keratinocytes

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Abstract Increased levels of platelet-activating factor (PAF; 1-*O*-alkyl-2-acetyl-sn-glycero-3-phosphocholine) are found in several inflammatory dermatoses, but PAF's exact role in epidermis is uncertain. In order to better understand the physiological consequences of excess PAF production in epidermis, we examined the gene regulatory effects of PAF short-term stimulation in differentiated HaCaT keratinocytes by transcriptional profiling. Even though PAF induces COX2 expression, we found that PAF regulates only few genes associated with inflammation in differentiated keratinocytes. Rather, we show that natural PAF rapidly regulates genes involved in proliferation, (anti)-apoptosis and migration, all sub-processes of re-epithelialization and wound healing. Moreover, profiling of phosphorylated kinases, cellular wound-scratch experiments, resazurin assay and flow cytometry cell cycle phase analysis all support a role for PAF in keratinocyte proliferation and epidermal re-epithelialization. In conclusion, these results suggest that PAF acts as an activator of proliferation and may, therefore, function as a connector between inflammation and proliferation in differentiated keratinocytes.

Keywords HaCaT · Transcriptional profiling · Inflammation · Wound healing · Psoriasis

Abbreviations

EGF	Epidermal growth factor
EGFR	EGF receptor
MAPK	Mitogen-activated protein kinase
MIAME	Minimum information about microarray experiment
PAF	Platelet-activating factor
PAFR	Platelet-activating factor receptor
PLA2	Phospholipase A2

Introduction

PAF (1-*O*-alkyl-2-acetyl-sn-glycero-3-phosphocholine) is a potent phospholipid-derived regulator of a variety of physiological and pathological processes, including inflammation and allergy [1, 2]. Cells synthesize PAF in response to several cellular stressors [3, 4] and elevated levels of PAF are found in various inflammatory dermatoses such as urticaria, immunobullous diseases, and psoriasis [5–7]. Inflammatory exudates such as blister fluid [8] and corneal wound fluid [9, 10] are reported to contain elevated levels of PAF, suggesting a PAF–inflammation association. Improved precision in spectroscopic measurements of PAF show that physiological levels in serum may be 100 times higher than previously thought [11]. PAF and PAF-like ligands function predominantly through their

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