Prostaglandins (PG) are detected in virtually all organs and cells, whereas their enhanced release follows inflammatory mechanisms. PG synthesis, especially of PGE$_2$, PGD$_2$ and PGF$_{2\alpha}$, also takes place in epidermal keratinocytes as a result of arachidonic acid (AA) metabolism (Kondoh et al., 1985; Pentland and Needleman, 1986) and is differentially supported by specific enzymatic systems, the constitutively expressed cyclooxygenase (COX)-1 and the inducible COX-2 (Holtzman et al., 1994). Several mediators, such as phorbol myristate acetate, calcium ionophore A23187, melittin, Bradykinin, epidermal growth factor, 1-oleoyl-2-acetyl glycerol platelet-activating factor (synthetic analog of diacylglycerol), cholecalciferol, interleukin-1, and tumor growth factor-$\alpha$ have been shown to activate this pathway (Kondoh et al., 1985; Fairley et al., 1986; Kvedar and Levine, 1987; Fisher et al., 1989; Pentland and Mahoney, 1990; Hanke et al., 1996; Kanekura et al., 1998). Exogenous PG regulate major keratinocyte functions, i.e., inhibit or stimulate proliferation in vitro under different culture conditions (Harper, 1976; Sugita et al., 1986), modify cyclic nucleotide levels (Wilkinson and Orenberg, 1979), and enhance calcium-induced cornification (Evans et al., 1993). Endogenous PG have been shown to enhance keratinocyte proliferation (Pentland and Needelman, 1986). On the other hand, fibroblasts are less responsive to PG pathway activators, whereas keratinocytes can activate fibroblasts to produce prostocyclin which is a paracrine prodifferentiating agent for keratinocytes (Baden et al., 1992).

Despite the abundant knowledge on the PG pathway in keratinocytes, little is known on its activity in sebaceous gland cells, which represent differentiated epithelial cells. PG synthesis, especially that of PGD$_2$ and PGE$_2$, has been detected in mouse sebaceous gland cells (Henke et al., 1986). In 1998, Ma et al reported a major finding: estrogen treatment, which induces peroxisome proliferation in the uropylgoid gland in the duck, also enhanced AA metabolism in this organ. Conversion of PGD$_2$ to the natural PGJ$_2$ metabolite, $\Delta^{12}$-PGJ$_2$, was induced by estradiol treatment preceding peroxisome proliferation. Exogenous $\Delta^{12}$-PGJ$_2$ and 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ activated the peroxisome proliferators-activated receptor (PPAR)-$\gamma$1, being, therefore, its natural ligands. However, in this organ, Neufang et al (2001) have shown that in a COX-2 overexpressing mouse, PG accumulation occurs, the skin exhibits a preneoplastic phenotype, and that sebaceous gland hyperplasia, increased sebum levels, sparse coat of greasy hair, and hyperplasia of scale epidermis due to a disturbed program of epidermal differentiation are present. These data confirmed previous results by Rosenfield et al (1998) that PPAR-$\gamma$1 ligands induce lipid accumulation in mouse preputial gland cells in vitro. In addition, the latter group has shown that exogenous carbaprostacyclin (cPGI$_2$), stable prostocyclin analogue and a natural PPAR-$\delta/-\alpha$ ligand, significantly induced lipid-forming colonies in mouse preputial gland cells in vitro and that retinoid X receptor agonists amplified the effect of cPGI$_2$ (Kim et al., 2001). Proliferation of the mouse preputial gland cells was also enhanced significantly by cPGI$_2$. Interestingly, AA induces accumulation of lipids in human sebaceous gland cells in vitro (Wröbel et al., 2003) and downregulation PPAR-$\gamma$ through selective ligands has currently been suggested to be involved in the development of seborrhea and acne (Zouboulis et al., 2003, 2005).

In this issue, lwata et al (2005) close the knowledge gap by providing evidence that 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ augments the formation of lipid droplets in hamster auricle sebaceous gland cells in vitro. This effect occurs due to a diacylglycerol acyltransferase-triggered increase of triacylglycerol synthesis, which indicates sebaceous gland cell differentiation, and is accompanied by an increase of the relative levels of 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ to PGF$_{2\alpha}$ and PGE$_2$. Hamster auricle sebaceous gland cells were found to constitutively produce COX-2 but not COX-1, whereas human facial sebaceous gland cells constitutively produce both COX-2 and COX-1 (Alestas et al, in press). Although COX inhibition by indomethacin, diclofenac or NS-398 led to an expected reduction of PGF$_{2\alpha}$ and PGE$_2$ production, synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ increased, and triacylglycerol synthesis was also enhanced. Triacylglycerol synthesis was also enhanced in the presence of the PPAR-$\gamma$1 ligand troglitazone. Similarly, topical administration of indomethacin to hamster auricles was found to cause the development of sebaceous glands with the augmentation of sebum deposition in vivo. The indomethacin and NS-398-augmented 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ production and triacylglycerol synthesis here suppressed by a nonselective cytochrome P-450 inhibitor, which did not affect the similar troglitazone effect.

This fascinating work provides a number of links in understanding the biological role of the PG pathway in sebaceous gland cells: a) COX-2 and a still unknown cytochrome P-450 enzyme—downstream to PGD synthase—exhibit opposite effects. Therefore, COX-2 inhibitors reduce PGF$_{2\alpha}$...
and PGE$_2$ levels but increase 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ production and triacylglycerol synthesis. The clinical consequence could be that COX-2 inhibition may lead to a downregulation of an existing inflammatory reaction but may also enhance seborrhoea; and b) both natural and synthetic PPAR-$\gamma$1 ligands enhance lipid synthesis in sebaceous gland cells following different modes of action, which for the natural PPAR-$\gamma$1 ligand 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ is the regulation of a cytochrome P-450 enzyme.

In addition, the results of this study combined with the results of the previous reports mentioned above give a partial explanation of the rather complex sebotropic effect of estrogens (Callens et al., 1996; Dieudonne et al., 2000). Estrogens seem to upregulate 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ synthesis and subsequently enhance PPAR-$\gamma$1 activity and sebaceous lipid synthesis (Ma et al., 1998; Iwata et al., 2005). This pathway of estrogen effectiveness is probably complementary to estrogen’s capacity to upregulate the insulin-like growth factor 1 pathway and, subsequently, production of sebaceous lipids (Makrantonaki et al., 2002; Mendez-Davila et al., 2004).

At last, the work of Iwata et al. (2005) provides indirect evidence that the inhibition of the lipoygenase pathway, which exhibits proinflammatory and sebotropic activities and a possible regulation of PPAR-$\alpha$ (Alestas et al., in press; Zouboulis et al., 2003, 2005) is likely to be more powerful than the inhibition of the PG pathway, including PPAR-$\gamma$1 regulation, for future treatments of seborrhoea and acne. On the other hand, manipulating the PG pathway may be of great interest in improving the activity of aging sebaceous glands by parallel downregulation of inflammatory signals, thus improving the quality of aging skin.

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