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A new target for squamous cell skin cancer?

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Prostaglandins (PGs) derived from arachidonic acid of cell membrane are synthesized by PG G/H synthase (cyclooxygenase; COX-1/-2) and signal as autocrine/paracrine lipids (1, 2). Similar to other tissues, COX-1 is constitutively expressed in keratinocytes of normal epidermis, whereas COX-2 expression is more variable and regulated (3, 4). COX-2 is induced for example by cytokines and growth factors; accumulated prostaglandins from COX-2 regulate pain, inflammation, and cancers (2, 3). In the case of cancer, increased levels of PGs disrupt differentiation and thus contribute to the sensitization of cells to carcinogens and ensuing hyperplasia (5, 6). Therefore, the inhibition of COX-2 activity with aspirin like compounds has been suggested as a potent chemo-preventive therapy to suppress tumor development, not just in skin but particularly for gastrointestinal cancers (2, 7).

While in most cases COX-2 appears to support oncogenesis, opposite evidence that constitutive expression of COX-2 prevents the development of skin tumor has been reported suggesting that distinct downstream PGs mediated by COX-2 in vivo might have opposing effects and thus explain these variable results (8). This is quite classic for this pathway; despite the plethora of physiologic systems were COX-2 appears active, aspirin has a very limited side effect profile. This is likely because in most cases of inhibition of COX-2, the simultaneous inhibition of both positive and negative individual downstream prostaglandin players has a net zero physiologic effect. The most classic opposing prostaglandins are PGE_2 and PGD_2. PGE_2 has been shown to correlate with the oncogenic effects of COX-2, but less work has been done on PGD_2. To better understand the functions of PGD_2 and its metabolites in skin tumors, Mantel et al. evaluated the role of Aldo-keto reductase 1C3 (AKR1C3) expression in proliferation of SCC cell lines.

AKR1C3 is a family of AKR1C isozymes with oxidoreductase activity and can shunt PGD_2 away from its receptors and metabolites through its conversion to F_2 series prostaglandins, although it has many distinct functions. One of those is controlling steroid homeostasis (9) and consistent with this, deregulation of AKR1C3 expression is detected in cancers from

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Conflict of interest
All authors have no conflict of interest to declare.

steroid hormone-related tissues including breast and prostate (10). Although the localization of AKR1C family has been already described in skin cells including keratinocytes, fibroblasts, and melanocytes (11–13), its function and regulation still remain unclear. Previously, Mantel et al. reported that AKR1C3 is significantly expressed in supra basal layers of human epidermis and is associated with differentiation of keratinocytes (14). In a recent issue (15), the authors demonstrate that PGD_2 and 15d-PGJ_2, its non-enzymatic metabolite, inhibit the proliferation of SCC cells possibly through PPARγ activation. Overexpression of AKR1C3 presumably decreases PGD_2 levels by metabolizing it to detectably higher levels of 9α11β-PGF_2. Although knockdown or overexpression of AKR1C3 had no effect on SCC proliferation, the authors could detect decreased sensitivity to PGD_2 in overexpressing cells.

AKR1C3 is one of four major types (AKR1C1-4) found in human and has stronger catalytic activity and higher affinity for PGD_2 than AKR1C1 and 2 (16, 17). Supporting the authors arguments, the AKR1C3-mediated product PGF_2, binds to its prostanoid receptor and induces MAPK signaling, thereby inactivating PPARγ (17, 18). These results support a role of AKR1C3 to inhibit the effects of PPARγ and might explain the decreased sensitivity to PGD_2 in AKR1C3 expressing cells.

Previous research on PGD_2 has detailed on its role in hair biology. PGD_2 is likely involved in the pathogenesis of androgenetic alopecia (AGA). Also, our group has reported that PGD_2 inhibits hair follicle neogenesis after wounding through the PGD_2 receptor 2 (DP-2/GPR-44). We demonstrated that *GPR-44* null mice had increased levels of wound induced hair neogenesis for example (19, 20). In the course of these studies, we tested the effect of PGD_2 on normal human keratinocyte proliferation and were surprised to find that, in contrast to the effects of PGD_2 in SCC cells, the PGD_2 promotes the proliferation of normal keratinocytes (19). This suggests contextual differences between cancer and normal cells. However, more robust dissection of this pathway including PGD_2 and 15d-PGJ_2 treatments of both normal and SCC keratinocytes after siRNA knockdown of PGD_2 receptors (DP-1/DP-2) and PPARγ should clarify these issues. Despite these questions, the anti-proliferative effects of 15d-PGJ_2 via the activation of PPARγ in SCC cells are consistent with the results from previous studies in different cancer cells (21, 22).

Although 15d-PGJ_2 has been known as an endogenous ligand for PPARγ, there exist some skepticism about whether 15d-PGJ_2 is an agonist in vivo for PPARγ. First, there are several PPAR-independent pathways mediated by 15d-PGJ_2 including nuclear factor kB, ROS, and SUMOylation (21, 23, 24). Second, the concentrations of 15d-PGJ_2 to activate PPARγ reported in previous studies (μM range) (25) are greatly higher compared to those of endogenous prostaglandins (pM range) (26, 27) associated with the physiological activity. Finally, the high concentration of 15d-PGJ_2 required for the inhibition of cell proliferation might be due to its strongly electrophilic and oxidative properties. To this end, it may be worth measuring the physiological amounts of PGD_2, 9α11β-PGF_2 and 15d-PGJ_2 in normal and SCC human skin using mass spectrometry (28). Afterwards, further research may be investigated to establish the regulatory mechanisms in the production of these two downstream metabolites from PGD_2 in vivo.

One unresolved paradox for this paper is the context of AKR1C3 expression. In normal tissues, AKR1C3 is expressed in terminally differentiated keratinocytes. However, in this article ARK1C3 is noted to be more highly expressed in SCC cell lines than normal keratinocytes. Also, it is proposed to enhance proliferation in SCC which would not be the case in keratinocytes of the upper layers of the epidermis. Future experiments described above might help clarify some of these questions.

There are many interesting experiments that the present report might suggest. For example, interesting questions are raised by our recent report that PGD_2 might promote AGA, and the present findings that PGD_2 increases the levels of AKR1C3. Given that the function of AKR1C3 to increase the potency of weak androgens (and estrogens) for example from Δ4-androstene-3,17-dione to testosterone, it is very likely that AKR1C3 could be involved in a positive feed-back loop which promotes AGA. Since PGD_2 production itself is commonly promoted by androgens, then the increased levels found in AGA would be thought to promote AKR1C3 which would likely generate additional testosterone which would enhance PGD_2 production further—and exacerbate AGA. Also, since it has been known that AKR1C1 and AKR1C2 are induced in skin by UV light exposure (11), it will be interesting to determine functions of these and AKR1C3 in prostaglandin physiology as it relates to skin cancer and alopecia. As in all science, more questions multiply whenever we try to answer any.

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