The Preventive Effect of Calcitriol on Skin Squamous Cell Carcinoma May be Due to Its Effect on Prostaglandin E2 Metabolism and Biologic Activity

1, 25(OH) 2D3 (calcitriol) and its analogs, which are important regulators of calcium and bone metabolism, have some non-calciotropic activities that include inhibition of cell proliferation and promotion of cell differentiation (1). Calcitriol is a potent antiproliferative agent against various tumor cells such as colorectal, breast and lung cancer, and also lymphoma and leukemia (2). It retards proliferation of several neoplastic cell types and acts as a chemopreventive agent in animal carcinogenesis (2,3). The antineoplastic effects of vitamin D3 derivatives are exerted at several steps in tumor progression (3). Nowadays, it has been shown that calcipotriol may exhibit antitumor activity against squamous cell carcinoma (SCC) (1,4,5).

Further studies are needed to evaluate the preventive effect of calcipotriol in the development of SCC; nevertheless, below the authors would like to propose a novel hitherto unexplained mechanism for the probable calcitriol preventive effect against human skin SCC.

Both UVB (280-320 nm) and UVA (320-400 nm) radiation lead to an enhanced expression of cyclooxygenase-2 (COX-2) in epidermal cells in various *in vitro* and *in vivo* models (5). COX-2 is highly inducible and plays a major role in inflammation (6). In addition to its association with inflammation, COX-2 plays a role in regulating cellular proliferation, differentiation and tumorigenesis (7). On the other hand, it has been shown that prostaglandins play a critical role in skin cancer development (8-10). Elevated COX-2 expression and PGE2 production have been demonstrated in several types of epithelial neoplasms (9,10), while COX-2 expression in normal skin is usually very low and restricted to regions of differentiated epidermis (7).

Using a human skin SCC line, it was shown that retinoid (9-cis-RA) could significantly suppress cell growth rate by inhibition of COX-2 expression and PGE2 biosynthesis. These findings indicate that 9-cis-RA may have preventive effects on skin carcinogenesis, at least in part, by inhibiting COX-2 expression (12). These results suggest that pharmacological interventions using specific COX-2 inhibitors could have anticarcinogenic effects in UVB-induced human skin cancer (11).

Calcitriol regulates the expression of genes involved in the metabolism of prostaglandins (13,14). Calcitriol significantly repressed the mRNA and protein expression of prostaglandin endoperoxide synthase/cyclooxygenase-2 (COX-2), the key prostaglandin synthesis enzyme (13). Calcitriol also up-regulated the expression of 15-hydroxyprostaglandin dehydrogenase, the enzyme initiating prostaglandin catabolism (13,14). This dual action was associated with decreased prostaglandin E2 levels (13,14). Calcitriol also repressed the mRNA expression of the prostaglandin receptors EP2 and FP, providing a potential additional mechanism of suppression of the biologic activity of prostaglandins (13). So, in conclusion, putting all these facts together, the inhibitory effect of calcitriol on PGE2 level and its biologic activity may be a novel mechanism for its probable SCC preventive effect.

References

1. Kensler TW, Dolan PM, Gange SJ, Lee JK, Wang Q, Posner GH. Conceptually new deltanoids (vitamin D analogs) inhibit multistage skin tumorigenesis. Carcinogenesis 2000; 21:1341-5.

2. Trump DL, Muindi J, Fakih M, Yu WD, Johnson CS. Vitamin D compounds: clinical development as cancer therapy and prevention agents. Anticancer Res 2006; 26(4A):2551-6.
3. Koh HK, Kligler BE, Lew RA. Sunlight and cutaneous malignant melanoma: evidence for and against causation. Photochemistry 1990; 51:765-79.
4. Ma Y, Yu WD, Hershberger PA, Flynn G, Kong RX, Trump DL, Johnson CS. 1alpha, 25-Dihydroxyvitamin D3 potentiates cisplatin antitumor activity by p73 induction in a squamous cell carcinoma model. Mol Cancer Ther 2008; 7: 3047-55.
5. Gombart AF, Luong QT, Koeffler HP. Vitamin D compounds: activity against microbes and cancer. Anticancer Res 2006; 26:2531-42.
6. Mahns A, Wolber R, Stäb F, Klotz LO, Sies H. Contribution of UVB and UVA to UV-dependent stimulation of cyclooxygenase-2 expression in artificial epidermis. Photochem Photobiol Sci 2004 Mar; 3:257-62.
7. Smith WL, Garavito RM, DeWitt DL. Prostaglandin endoperoxide H synthases (cyclooxygenases)-1 and -2. J Biol Chem 1996, 271:33157-60.
8. Dubois RN, Shao J, Tsujii M, Sheng H, Beauchamp RD. G1 delay in cells overexpressing prostaglandin endoperoxide synthase-2. Cancer Res 1996, 56:733-7.
9. Fischer SM. Is cyclooxygenase-2 important in skin carcinogenesis? J Environ Pathol Toxicol Oncol 2002; 21:183-91. 12086405
10. Buckman SY, Gresham A, Hale P, Hruza G, Anast J, Masferrer J, *et al.* COX-2 expression is induced by UVB exposure in human skin: implications for the development of skin cancer. Carcinogenesis 1998, 19:723-9.
11. Athar M, An KP, Morel KD, Kim AL, Aszterbaum M,*et al.* Ultraviolet B (UVB)-induced cox-2 expression in murine skin: an immunohistochemical study. Biochem Biophys Res Commun 2001; 280:1042-7.
12. Kanekura T, Higashi Y, Kanzaki T. Inhibitory effects of 9-cis-retinoic acid and pyrrolidinedithiocarbamate on cyclooxygenase (COX)-2 expression and cell growth in human skin squamous carcinoma cells. Cancer Lett. 2000 Dec 20; 161:177-83.
13. Moreno J, Krishnan AV, Swami S, Nonn L, Peehl DM, Feldman D. Regulation of prostaglandin metabolism by calcitriol attenuates growth stimulation in prostate cancer cells. Cancer Res 2005; 65:7917-25.
14. Swami S, Krishnan AV, Moreno J, Bhattacharyya RB, Peehl DM, Feldman D. Calcitriol and genistein actions to inhibit the prostaglandin pathway: potential combination therapy to treat prostate cancer. J Nutr 2007; 137:205S-210S.

Amir Feily[1], Mohammad R. Namazi[2]

[1]Department of Dermatology, Jondishapur University of Medical Sciences, Ahvaz; [2]Faghihi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

Corresponding author:
Amir Feily, MD
Department of Dermatology
Jondishapur University of Medical Sciences
Ahvaz
Iran
Dr.feily@yahoo.com

Received: July 20, 2009
Accepted: November 5, 2009