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


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