RESEARCH LETTERS

Retinoic Acid Receptor Isoform mRNA Expression Differs Between BCC and SCC of the Skin

Treatment with the retinoic acid receptor (RAR) ligands retinol, isotretinoin, and acitretin has a chemopreventive effect on squamous cell carcinoma (SCC) but not on basal cell carcinoma (BCC). This disparity is well documented but incompletely understood. In lung cancer, RARβ1 was recently found to mediate antiproliferative effects of retinoids.1 We compared RAR isoform messenger RNA (mRNA) expression in BCC with that in SCC.

Figure 1. Fold expression of complementary DNA retinoic acid receptor (RAR) isoforms in basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). All data are reported as means (SEMs) normalized to glyceraldehyde-3-phosphate dehydrogenase as the internal standard. In all panels, error bars indicate SEMs.

A, RARα in BCC (n=28) (1.97×10^4 [2.55×10^4] [1.24×10^4]) and SCC (n=22) (6.70×10^3 [4.79×10^3] [1.42×10^3] and SCC (n=22) (6.26×10^3 [1.13×10^3]); P<.001. B, RARβ in BCC (n=28) (1.25×10^2 [1.24×10^2]) and SCC (n=22) (7.91×10^1 [4.39×10^1]) and SCC (n=22) (7.65×10^1 [1.97×10^1]). C, RARγ in BCC (n=28) (7.27×10^1 [1.24×10^1]) and SCC (n=22) (7.27×10^1 [1.97×10^1]) (P=.001). D, RARβ1 in BCC (n=27) (9.25×10^3 [1.78×10^3]) and SCC (n=22) (8.28×10^4 [1.67×10^4]) (P<.05). E, RARβ1 in BCC (n=24) (6.72×10^4 [2.96×10^4]) and SCC (n=22) (6.46×10^4 [1.13×10^4]) (P=.05). F, RARβ2 in BCC (n=28) (7.83×10^2 [2.07×10^2]) and SCC (n=22) (7.83×10^2 [2.07×10^2]).

Methods. With institutional review board approval, BCC and SCC tissue samples were acquired. The mean (SD) age of patients with BCC was 69.9 (11.2) years (n=28); the patients with SCC were aged 73.3 (12.4) years (n=22).

The real-time polymerase chain reaction primers used were glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (Search-LC GmbH, Heidelberg, Germany), RARα (5’-TGTGGAGTTGCACAGAAGCA-3’, 5’-CGTGTACCGCTGAGAGCA-3’), RARβ (5’-CTTCTGTGAGCTCCAGAA-3’, 5’-CGCTGACCCCATATGGTA-3’), RARβ1 (5’-ATGAGGAATGAAGCTGAGTAGA-3’, 5’-ATTGTCTGAGACGAGAAGCA-3’), RARβ2,4 (5’-GTCTGGCCACCGTGCGGGTGA-3’, 5’-CTTCTTTTCCACGAGAGCAAT-3’), RARγ (5’-CTGCTCCTCATCAGCGAGAC-3’, 5’-GCCCTTTCACGCTCCCTGGTA-3’), and RARβ1 (5’-TGGACTGACAGGTACTGTA-3’, 5’-GTGTTGACTCAGCATCAGA-3’). Samples were
processed in triplicate and verified by sequencing with GAPDH as the internal standard. Expression of mRNA was calculated by the delta threshold cycle. $P<.05$ (2-tailed, Mann-Whitney test), was considered significant.

Results. Retinoic acid receptor α, RARβ, RARγ, and RARβ2.4 amplified in 28 of 28 BCC samples and 22 of 22 SCC samples; RARβ1, in 27 of 28 BCCs and 22 of 22 SCC; and RARβ1', in 24 of 28 BCC and 2 of 22 SCC. Quantitatively, RARα was 3.46-fold increased ($P<.001$); RARγ, 1.63-fold increased ($P=.001$); and RARβ1', 23.73-fold increased in BCCs compared with SCCs ($P=.03$) (Figure 1 and Figure 2), but only 2 SCCs showed amplification for RARβ1'. The findings for RARβ, RARβ1, and RARβ2.4 were indistinct.

Comment. Based on the different retinoid sensitivity of BCC and SCC, we expected RAR isoform differences. Interestingly, only 2 of 22 SCCs expressed RARβ1' at a much lower level than BCCs (9%). In contrast to lung cancer, RARβ1' does not seem to be pivotal for retinoid chemoprevention in SCC. Levels of RARα and RARγ were higher in BCC than in SCC, which fits with reported RAR and retinoid X receptor (RXR) isoform expression.2

Other factors may mediate chemoprevention. Acitretin binds with low affinity to RARs but with high affinity to cellular retinoic acid binding proteins (CRABPs). Acitretin shifts the distribution of endogenous retinoic acid from CRABPs to RAR-RXR heterocomplexes, potentiating its effect. Tazarotene specifically activates RARβ and RARγ and only weakly activates RARα with chemopreventive effect on BCC in Pch1± mice.3 In human lung cancer, RARβ4 seems carcinogenic.4 Differential activation of RAR isoforms may therefore have carcinogenic or antiangiogenic effects as shown by the relative superiority of tazarotene in BCC over other retinoid-related compounds with simultaneous RARα and RARβ isoform activation.3

In summary, RAR isoform mRNA expression differs between BCC and SCC. Unlike in lung cancer, the mRNA levels of the recently reported isoform RARβ1' do not explain SCC retinoid sensitivity. Rather, we assume, the relative sensitivity to retinoid treatment of SCC vs BCC is mediated by differential RAR activation or indirect effects such as shifting endogenous retinoids from CRABPs to RAR-RXR heterocomplexes.

Teledermatology From a Combat Zone

Historically, dermatologic conditions account for between 15% and 75% of all outpatient visits in the combat environment during wartime.1 Teledermatology has proven to be an effective adjunct to extend dermatologic services to remote locations.2,3 Since July 2004, the US Army has operated a store-and-forward teledermatology consult service for deployed medical providers. This service is responsible for a substantial number of consults and enhances the care of deployed service members worldwide. Herein, we outline the uniqueness of this program and evaluate the cost savings.

Methods. We reviewed store-and-forward teledermatology consults and enhancement of care for deployed medical providers.

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