A pilot study using immunohistochemical staining to characterize dihydropyrimidine dehydrogenase expression in keratinocyte neoplasms

To the Editor: Topical 5-fluorouracil (5-FU) is a chemotherapeutic agent used to treat actinic keratoses (AK), superficial basal cell carcinoma, and squamous cell carcinoma in situ (SCCis). 5-FU is metabolized and inactivated by the enzyme dihydropyrimidine dehydrogenase (DPD), which is highly active in the liver but can be expressed in tumors as well. In several visceral malignancies, tumor DPD expression predicts response to systemic 5-FU: tumors with lower DPD expression correlate with higher 5-FU reactivity and better clinical response.[1-3] Although this association has been studied in visceral tumors, the expression of DPD in keratinocyte neoplasms is not known. In this pilot study, we assessed DPD expression in benign, premalignant, and malignant keratinocyte neoplasms to assess the range and level of DPD activity.

We performed DPD immunohistochemistry (IHC) staining of 26 superficial and nodular basal cell carcinomas (BCCs), 10 SCCis, 16 AKs, and 8 seborrheic keratoses from formalin-fixed paraffin-embedded specimens collected within the past 3 years. Diagnoses were confirmed by dermatopathologists (B.H., B.D.). DPD IHC was performed with anti-DPD antibody (Abcam #134922, 1:500 dilution). DPD expression was scored by intensity ranging from 0 to 3 by 2 authors (O.I. and B.D.), with hepatic staining as a positive control (Table I). Fisher's exact test was used to compare DPD scores between classes of keratinocyte neoplasms (R software, version 4.0.3, https://www.r-project.org).

The results showed a significantly enriched proportion of BCCs (81%, 21/26) displaying no DPD expression (DPD IHC intensity score of 0), compared to 0% (0/10) of SCCis and 6% (1/16) of AKs ($P = 3.95 \times 10^{-9}$, Table I). By contrast, 15% of BCC, 40% of SCCis, and 56% of AK had an intensity score of 1; 3% of BCC, 40% of SCCis, and 37.5% of AK had an intensity score of 2; and 0% of BCC, 20% of SCCis, and 0% of AK had an intensity score of 3 (Table I). The DPD intensity scores of seborrheic keratoses, a noncancerous keratinocyte neoplasm control, were distributed between 1 and 3.

Table I. Dihydropyrimidine dehydrogenase immunohistochemistry intensity score in patient samples ($n = 60$)

	DPD IHC intensity score			
	0	1	2	3
Seborrheic keratosis	0	4	2	2
Actinic keratosis	1	9	6	0
SCC in situ	0	4	4	2
Basal cell carcinoma	21	4	1	0

Basal cell carcinoma includes both superficial and nodular subtypes. DPD IHC intensity was scored from 0 to 3 (0: no expression, 1: weak expression, 2: moderate expression, 3: strong expression). Fisher's exact test P value $= 3.95 \times 10^{-9}$.
DPD, Dihydropyrimidine dehydrogenase; *IHC*, immunohistochemistry; *SCC*, squamous cell carcinoma.

Our results suggest that DPD expression varies both within and across different keratinocyte neoplasms, and that a substantial fraction of BCC may have lower DPD expression compared to AK, squamous cell carcinoma (SCC), and seborrheic keratoses. Clinical studies have reported a wide range of efficacy in the use of topical 5-FU treatment for early-stage BCC and SCC, with success rates in SCC ranging from 27% to 93%.[4,5] While differences in treatment regimens and study design are likely to contribute to this variability, our results raise the possibility that differences in keratinocyte tumor DPD expression could also play a role in topical 5-FU treatment efficacy.

The results of this pilot study support the value of a larger prospective study to investigate if DPD expression predicts clinical response of low-grade BCC and SCC to topical 5-FU. If true, then DPD IHC staining could be performed by pathology services to identify keratinocyte neoplasms that are more likely to respond favorably to topical 5-FU, reducing the uncertainty of treatment efficacy to this useful therapeutic option.

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Conflicts of interest

None disclosed.

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