TC-PTP overexpression attenuates skin cancer formation during environmental skin carcinogenesis.

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Background: T-cell protein tyrosine phosphatase (TC-PTP), encoded by *Ptpn2*, has been shown to function as a tumor suppressor during skin carcinogenesis.

Methods: we generated a novel epidermal specific TC-PTP-overexpressing (*K5HA.Ptpn2*) mouse model to show that TC-PTP contributes to the attenuation of chemically induced skin carcinogenesis through the synergistic regulation of STAT1, STAT3, STAT5, and PI3K/AKT signaling.

Results: We found overexpression of TC-PTP increased epidermal sensitivity to DMBA-induced apoptosis and it decreased TPA-mediated hyperproliferation, coinciding with reduced epidermal thickness. Inhibition of STAT1, STAT3, STAT5 or AKT reversed the effects of TC-PTP overexpression on epidermal survival and proliferation. Mice overexpressing TC-PTP in the epidermis developed significantly reduced numbers of tumors during skin carcinogenesis and presented a prolonged latency of tumor initiation. Examination of human papilloma and squamous cell carcinomas (SCCs) revealed that TC-PTP expression was significantly reduced and TC-PTP expression was inversely correlated with the increased grade of SCCs.

Conclusion: Our findings demonstrate that TC-PTP is a potential therapeutic target for the prevention of human skin cancer given that it is a major negative regulator of oncogenic signaling.

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