Cutaneous T-cell lymphoma (CTCL) is characterized by accumulation of malignant T cells in the skin. These cells undergo increased proliferation and decreased apoptosis compared with benign CD4 T cells, and show immunological aberrancies, such as decreased TH1 and increased TH2 cytokine profiles. There are no satisfactory treatments at present. Recently, we revealed that CTCL cells contained aberrantly up-regulated interleukin-2-inducible T-cell kinase (ITK), a key molecule regulating cell growth and immunoregulatory function of T cells. This study aims to evaluate the therapeutic potential of ITK inhibition for CTCL. We quantified ITK expression in skin biopsies and cultured CTCL cells (HU7T8 and SZ4) by RT-PCR and Western Blotting. ITK suppression was achieved using lentivirus-mediated shRNA approach. Chemical inhibition of ITK function was achieved using commercially available kinase inhibitor. The impact of ITK silencing and chemical inhibition was measured in both in vitro and in vivo models. CTCL skin biopsies and purified CTCL cells contained 5-fold more expression of ITK compared with benign controls (p<0.008). Increased ITK expression was correlated increased mortality of CTCL patients. Silencing of ITK expression led to dramatic reduction of proliferation and increased apoptosis of CTCL cells, both in cell culture and in CTCL mouse model. Further, treatment of CTCL cells with a small molecule inhibitor of ITK resulted in efficient killing of CTCL cells. This study provides strong rational for using ITK inhibition as a therapeutic approach to for CTCL.

Uncontrolled Hedgehog (Hh) signaling underlies the development of basal cell carcinoma (BCC), with superficial BCCs arising from interfollicular epidermis and nodular tumors from hair follicle epithelia. However, the precise cell populations that give rise to different BCC subtypes have not been fully defined. Moreover, although genetic or pharmacological shutdown of oncocgenic Hh signaling in BCC leaves behind a small population of dormant tumor cells, the long-term fate of these cells has not been investigated. We generated Gli2- CreERT2;R26-Luci-NTA;OR2GL2A transgenic to drive doxycycline (dox)-dependent expression of the Hh pathway oncogene GLI2A in progenitor cells in the interfollicular epidermis, sebaceous gland, and hair follicle isthmus. Two weeks after GLI2A induction, microscopic BCC-like tumors were detected arising from each of these three epithelial lineages. Despite widespread initiation of BCC development, 5-6 weeks after transgene induction the major proportion of full-blown tumors were associated with hair follicle epithelium, with relatively few superficial BCCs in interfollicular epidermis. Stopping dox treatment led to rapid regression of nodular BCCs, leaving behind a small population of residual K17+ tumor cells with undetectable levels of GLI2A and the Hh pathway target gene Gli1. Reactivation of GLI2A expression led to rapid tumor re-growth even after multiple cycles of regression and a prolonged regression/dormancy phase of 24 months, suggesting that BCC cure may not be achievable solely by blocking oncogenic Hh signaling. Our findings also underscore the preferential development of full-blown BCCs from LG6+ cells in hair follicle epithelium, even though BCC initiation is also abundant in interfollicular epidermis in this model.

The prevalence of alopexia areata (AA) in the United States (US) is not well known. A commonly cited self-reported period prevalence of 0.16% is sourced from the National Health and Nutrition Examination Survey (NHANES) over 40 years ago (1971-70). Other studies focused on alopecia totalis (AT) and alopecia universalis (AU); complete body hair loss. We administered an online cross-sectional survey to a representative sample of the US population with respect to age (18-65 years represented by parent proxy), gender, race, income, and region. Participants screening positive for AA using the Alopecia Assessment Tool completed the Severity of Alopecia Tool (SALT) to determine severity (mild=50%; moderate/severe=50% hair loss). Self-reported cases were then asked to upload photographs for adjudication by 3 clinicians. Self-reported AA point prevalence overall was 1.14% (95% CI: 1.04–1.24%; mild=1.03%; moderate/severe=0.11%, AT/AU=0.04%). Among adults it was 1.24% (95% CI: 1.13–1.35%) and among adolescents it was 0.24% (95% CI: 0.10–0.36%). Overall average SALT score was 1.25 ± 4. Based on 104 adults with photographs, clinician- adjudicated prevalence overall was 0.21% (95% CI: 0.17−0.25%, mild=0.12%, moderate/severe=0.09%, AT/UA=0.04%). Among adults with photographs, clinician- adjudicated to 1.14% self-reported vs. 0.16% self-reported from NHANES with mild AA being over 9 times more prevalent than moderate/severe. This study provides a new and updated context for the burden of AA in the United States.

The prevalence of alopecia areata (AA) in the United States is higher than estimated in the 1970s (range: 0.21%, AT/AU=50%, moderate/severe ¼ 50%, mild AA being over 9 times more prevalent than moderate/severe). This study provides a new perspective that thin neonates contain nuclei of two similar phenotypes, in different proportions. In lesions likely to progress to metastatic disease, one of these phenotypes predominates. We propose that intermediate-thickness melanomas carry a unique nuclear profile that highlights their metastatic potential. Histopathologic sections from 14 cases (n=2201, mean 2.37 mm) that progressed to metastasis, and 17 cases (n=2553, mean 2.27 mm) that did not progress to metastatic disease were analyzed. Five karyometric features were selected by statistical hypothesis testing as markers of progression to metastatic disease. However, it was less definite about the nuclear features that predict non-metastatic lesions. The proportion of nuclei of an aggressive phenotype may lend itself as an effective prognostic clue for intermediate melanoma lesions. The algorithm appears to identify malignant at high-risk, for metastasis, as well as a basis for further study to assess the utility of prognostic clues for intermediate melanomas.