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ORIGINAL PAPER

Next-generation sequencing identifies high frequency of mutations in potentially clinically actionable genes in sebaceous carcinoma

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Abstract

Sebaceous carcinoma (SC) is a rare but aggressive malignancy with frequent recurrence and metastases. Surgery is the mainstay of therapy, but effective systemic therapies are lacking because the molecular alterations driving SC remain poorly understood. To identify these, we performed whole-exome next-generation sequencing of 409 cancer-associated genes on 27 SCs (18 primary/locally recurrent ocular, 5 paired metastatic ocular, and 4 primary extraocular) from 20 patients. In ocular SC, we identified 139 non-synonymous somatic mutations (median/lesion 3; range 0–23). Twenty-five of 139 mutations (18%) occurred in potentially clinically actionable genes in 6 of 16 patients. The most common mutations were mutations in *TP53* ($n = 9$), *RB1* ($n = 6$), *PIK3CA* ($n = 2$), *PTEN* ($n = 2$), *ERBB2* ($n = 2$), and *NF1* ($n = 2$). *TP53* and *RB1* mutations were restricted to ocular SC and correlated with aberrant TP53 and RB protein expression. Systematic pathway analyses demonstrated convergence of these mutations to activation of the PI3K signalling cascade, and PI3K pathway activation was confirmed in tumours with *PTEN* and/or *PIK3CA* mutations. Considerable inter-tumoural heterogeneity was observed between paired primary and metastatic ocular SCs. In primary extraocular SC, we identified 77 non-synonymous somatic mutations (median/lesion 22.5; range 3–29). This overall higher mutational load was attributed to a microsatellite instability phenotype in three of four patients and somatically acquired mutations in mismatch repair genes in two of four patients. Eighteen of 77 mutations (23%) were in potentially clinically actionable genes in three of four patients, including *BTK*, *FGFR2*, *PDGFRB*, *HRAS*, and *NF1* mutations. Identification of potentially clinically actionable mutations in 9 of 20 SC patients (45%) underscores the importance of next-generation sequencing to expand the spectrum of genotype-matched targeted therapies. Frequent activation of PI3K signalling pathways provides a strong rationale for application of mTOR inhibitors in the management of this disease.

Keywords: sebaceous carcinoma; PI3-kinase; next-generation sequencing; Muir–Torre syndrome; mismatch repair

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Introduction

Sebaceous carcinoma (SC) most commonly arises on the eyelid but also develops in extraocular locations. Ocular SC accounts for 5% of malignant epithelial eyelid tumours [1–5] and typically exhibits aggressive local behaviour [1,6,7], requiring surgical excision with high morbidity, including orbital exenteration in 13–23% of patients [5,7,8]. Regional (nodal) or distant metastasis occurs in 8–22% of patients at some point in the disease course, and different groups estimate the frequency of mortality due to SC at 6%, 10%, and