Review Article

Molecular landscape of eyelid sebaceous gland carcinoma: A comprehensive review

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Eyelid sebaceous gland carcinoma (SGC) is an aggressive skin cancer characterized by a heightened risk of recurrence and metastasis. While surgical excision is the primary treatment, unraveling the molecular intricacies of SGC is imperative for advancing targeted therapeutic interventions and enhancing patient outcomes. This comprehensive review delves into the molecular landscape of eyelid SGC, emphasizing key genetic alterations, signaling pathways, epigenetic modifications, and potential therapeutic targets. Significant findings include aberrations in critical signaling pathways (β-catenin, lymphoid enhancer binding factor, hedgehog, epidermal growth factor receptor, P53, and P21WAF1) associated with SGC progression and poor prognosis. Notably, eyelid SGC manifests a distinctive mutational profile, lacking ultraviolet signature mutations in tumor protein 53 (TP53), indicating alternative mutagenic mechanisms. Next-generation sequencing identifies actionable mutations in genes such as phosphatase and tensin homolog (*PTEN*) and Erb-B2 receptor tyrosine kinase 2 (*ERBB2*), facilitating the emergence of personalized medicine approaches. Molecular chaperones, specifically X-linked inhibitor of apoptosis protein (XIAP) and BAG3, emerge as pivotal players in promoting tumor survival and proliferation. The review underscores the role of epithelial–mesenchymal transition, where regulators like E-cadherin, vimentin, and ZEB2 contribute to SGC aggressiveness. Epigenetic modifications, encompassing DNA methylation and microRNA dysregulation, further elucidate the molecular landscape. This review consolidates a comprehensive understanding of the molecular drivers of eyelid SGC, shedding light on potential therapeutic targets and providing a foundation for future investigations in diagnostic, prognostic, and personalized treatment strategies for this formidable malignancy.

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Sebaceous gland carcinoma (SGC) is a rare yet potentially aggressive skin cancer. About 40% of these carcinomas develop in the periocular region, constituting around 5% of all eyelid malignancies.[1,2] This aggressive malignancy is characterized by a heightened risk of recurrence and metastasis, necessitating immediate attention for effective management.[3] Presently, surgical excision remains the sole available treatment option, with some cases requiring surgical exenteration to address the aggressive nature of SGC.[4,5] The emerging role of neoadjuvant systemic chemotherapy (NACT) is gaining attention, particularly for advanced tumors infiltrating the orbital structures beyond the eyelid.[6]

Intriguingly, SGC has been found to co-occur with Muir–Torre syndrome (MTS), a subtype of hereditary nonpolyposis colorectal cancer.[7] MTS patients often harbor germline pathogenic variants in DNA mismatch repair (MMR) genes, emphasizing the significance of exploring genetic markers associated with SGC.[8] However, it is important to note that periocular and extraocular tumors exhibit distinct behaviors and genetic characteristics.[9]

Recent advancements in molecular research have shed light on crucial cell signaling mechanisms linked to differentiation and metastasis, which have implications not only in various skin tumors but also in noncutaneous malignancies. Notably, aberrations in β-catenin, lymphoid enhancer binding factor-1, Indian hedgehog (IHH) signaling, sonic hedgehog (SHH), cyclooxygenase-2 (COX-2), epidermal growth factor receptor (EGFR), P53, and P21 pathways have been closely associated with poor prognoses in SGC patients.[10–15] Of particular interest is the lack of ultraviolet (UV) signature mutations in the *TP53* gene, a common occurrence in basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), pointing toward alternative mechanisms of mutations in eyelid SGC.[16]

Advancements in high-throughput analysis, such as next-generation sequencing (NGS), have further unraveled potentially actionable mutations in genes like phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PI3K3CA*), neurofibromatosis type 1 (*NF1*), MutS homolog 2 (*MSH2*), MutL homolog 1 (*MLH1*), pRB,

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