ERGIC3 promotes tumour progression and modulates immune microenvironment in head and neck squamous cell carcinoma

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In the present study, we examined the role of *ERGIC3* in head and neck squamous cell carcinoma (HNSCC) by combining the Cancer Genome Atlas (TCGA)-based bioinformatic analyses with validation in HNSCC cell lines, aiming to clarify its regulatory relevance and potential therapeutic value. Public TCGA datasets were used to profile *ERGIC3* across cancers and to determine its relationships with prognosis and clinicopathological features in HNSCC. Genes co-expressed with *ERGIC3* were identified, and differential expression between *ERGIC3*-high and *ERGIC3*-low tumours was computed in R, followed by GO/KEGG and GSEA enrichment analyses. Tumour immune infiltration was estimated with CIBERSORT, while candidate drug response was inferred with oncoPredict. Finally, *ERGIC3* was silenced in HNSCC cell lines to evaluate changes in proliferation/viability, migration, and invasion *in vitro*. *ERGIC3* was upregulated in many malignancies and was markedly increased in HNSCC. Patients with high *ERGIC3* expression showed poorer overall and progression-free survival. *ERGIC3* expression was strongly co-expressed with NFS1 in HNSCC. Enrichment analyses suggested that *ERGIC3*-associated transcriptional changes were linked to immune-related processes, and *ERGIC3* levels were associated with CD8+ T-cell infiltration. Immunotherapy scores were reduced in the *ERGIC3*-high group, implying a comparatively better response in patients with low *ERGIC3* expression. Drug prediction indicated differential sensitivity to LGK974 between *ERGIC3* strata. In cell experiments, *ERGIC3* knockdown attenuated HNSCC cell viability, migration, and invasion. *ERGIC3* expression is associated with clinical characteristics and immune infiltration patterns in HNSCC. In addition, LGK974 may represent a potential therapeutic option for tumours with high *ERGIC3* expression.

Keywords: Drug sensitivity prediction, *ERGIC3*, expression profiling, head and neck squamous cell carcinoma, immune infiltration, TCGA

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HEAD and neck squamous cell carcinoma (HNSCC) refers to squamous malignancies originating from mucosal sites of the upper aerodigestive tract, such as the oral cavity, pharynx, and larynx[1]. It represents >90% of head and neck cancers and is notable for frequent recurrence and a propensity for regional or distant spread[2]. Its incidence varies widely by region; rates are relatively high in many developing areas, particularly South and Southeast Asia, where tobacco and alcohol exposure are common contributors[3]. In several high-income regions (e.g., North America and Europe), a gradual year-by-year decline has been reported in parallel with reduced tobacco use[4]. For patients diagnosed at an early stage, surgery and/or radiotherapy can achieve a 5-year survival of roughly 70%–90% (ref. 5). By contrast, recurrent or metastatic disease remains challenging, with median overall survival close to one year[6]. When local therapies are not appropriate, platinum-based systemic regimens are often used; however, treatment is frequently accompanied by long-term functional impairment (chewing, swallowing, and speech) and complications such as xerostomia or aspiration pneumonia[7,8]. Accordingly, clarifying the molecular drivers of HNSCC is essential to support the development of more effective and less morbid therapeutic strategies.

ERGIC3 (also termed Erv46/Erp43) is located on chromosome 20q11.22 and contains 14 exons, encoding a 383-amino-acid protein (~43.2 kDa) belonging to the ER–Golgi intermediate compartment (ERGIC) membrane protein family. As a COPII vesicle component, *ERGIC3* participates in trafficking secretory cargoes from the rough endoplasmic reticulum toward the Golgi and contributes to the proper folding and glycosylation of newly synthesised proteins[9,10]. Increasing evidence indicates that *ERGIC3* is dysregulated in multiple cancers and may act as a tumour-associated factor; for instance, *ERGIC3* can promote the growth of HEK-293 cells[11] and has been implicated as an immune function-related gene in hepatocellular carcinoma[12]. Despite these observations, the biological role and mechanistic involvement of *ERGIC3* in HNSCC have not been systematically investigated. Here, we characterised *ERGIC3* expression, prognostic relevance, and immune-associated features in