FGFR3-TACC3 fusion protein drives cell migration and aberrant calcium signaling response in glioblastoma

S. Mäntylä[1,4], L. Huhtala*[1,4], N.N.D. Epitagama Liyana Arachchige[1,4], N. Förster [1,4], G. Mutharasu[1,4], R. Nätkin[1,4], A.M. Tiihonen[1,4], I. Salonen[1,4], I. Koivisto[1,4], V. Simola[8], M. Valkonen[8], S. Häyryne[1,4], J. Fadjukov[1] , A. Hartewig[1,4], K. Nordfors[2,4], C. Krona[6], S. Nelander[6], B.C. Parker Kerrigan[7], F.F. Lang[7], J. Haapasalo[3,4,5], P. Ruusuvuori[8], S. Nymark[1], J. Kesseli[1,4], H. Haapasalo[4,5], S. Narkilahti[1], M. Nykter[1,4], and K.J. Rautajoki[1,4]*

[1]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
[2]Tampere Center for Child Health Research, Tampere University and Tampere University Hospital, Tampere, Finland
[3]Department of Neurosurgery, Tampere University Hospital and Tampere University, Tampere, Finland
[4]TAYS Cancer Center, Tampere University Hospital, Tampere, Finland
[5]Fimlab Laboratories Ltd. and Tampere University, Tampere, Finland
[6]Department of IGP, Uppsala University, Uppsala, Sweden
[7]MD Anderson Cancer Center, The University of Texas, USA
[8]Institute of Biomedicine, University of Turku, Turku, Finland

*These authors contributed equally to this work

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Abstract

Fibroblast growth factor receptor 3 gene fusions with transforming acidic coiled-coil 3 (FGFR3-TACC3) are present in a subset of aggressive glioblastoma (GB) brain tumors and other malignancies. FGFR3-TACC3 fusion genes act as oncogenic drivers for GB by increasing proliferation and anchorage-independent growth of tumor cells, but their oncogenic functions and downstream signaling are still partly unresolved. Our RNA-sequencing analysis revealed fusion-specific cell responses to FGF2 stimulation and FGFR inhibition compared to wild-type FGFR3-overexpressing or control cells. Fusion overexpressing cells proliferated and migrated faster than FGFR3 overexpressing cells and represented a lower cell differentiation state. Furthermore, faster invasion and migration of fusion overexpression cells were validated with a 3D-hydrogel culture experiment. Sequencing data analysis also suggested fusion-specificity in FGF-induced calcium (Ca^{2+}) signaling response, which was confirmed experimentally. Our results provide information about the downstream signaling and the cellular oncogenic effects of FGFR3 fusions. They clearly support the hypothesis that FGFR3 fusion proteins possess novel functions and do not solely drive malignancy via increased FGFR3-mimicking expression and activity.