Nature Reviews Cancer | Published online 25 Jan 2018; doi:10.1038/nrc.2018.2

> F3–T3-positive tumours generally formed clusters enriched for mitochondrial categories

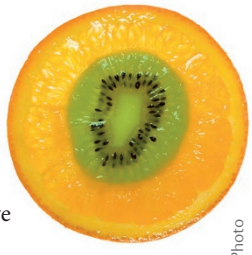
METABOLISM

Fusion power

About 3% of human glioblastomas (GBMs) harbour fusions of the genes that encode fibroblast growth factor receptor 3 (FGFR3; in the following referred to as F3) and transforming acidic coiled-coil-containing protein 3 (TACC3; in the following referred to as T3). These F3–T3 fusions are oncogenic, confer sensitivity to FGFR tyrosine kinase (TK) inhibitors and have been found to occur in many other cancers at similar frequencies. Frattini et al. have now discovered that F3–T3 fusions indirectly drive mitochondrial biogenesis, thereby promoting tumour growth.

The study, published in *Nature*, shows that human immortalized astrocytes, upon lentivirus-mediated expression of F3–T3, were enriched for expression of genes involved in mitochondrial biogenesis; they also exhibited increased levels of mitochondrial DNA and ATP as well as increased mass and oxygen consumption rates (OCRs) compared with astrocytes expressing a kinase-mutant form of F3–T3 or an empty vector as a control. Mouse tumours generated from mouse glioma stem cells (mGSCs) that express human F3–T3 and short hairpin RNA (shRNA) targeted against *Trp53* (shTrp53) (F3–T3;shTrp53) expressed higher levels of mitochondrial proteins and, when treated with the mitochondrial inhibitor tigecycline, showed reduced tumour growth compared with control tumours expressing oncogenic HRAS-V12 and shTrp53 (HRAS(12V);shTrp53). Cluster analysis of GBM and normal brain transcriptome data derived from The Cancer Genome Atlas (TCGA) identified a cluster of F3–T3-positive GBM and fusion-like GBM that was enriched for mitochondrial categories. When expanding this analysis to other cancer types, F3–T3-positive tumours generally formed clusters enriched for mitochondrial categories.

To identify potential targets of F3–T3, the researchers performed anti-phosphotyrosine immunoprecipitation and phosphopeptide identification by mass spectrometry of total cellular proteins from F3–T3-positive astrocytes and control cells. They identified increased phosphorylation of the peptidyl-prolyl *cis–trans* isomerase PIN4 at Y122 (phospho-PIN4(Y122)) as a key event; expression of a phospho-mutant PIN4 (PIN4(Y122F)) in F3– T3-positive astrocytes reversed increased ATP levels and OCR.



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Transcriptional network analysis of GBM and pan-glioma TCGA data sets revealed two highly active transcriptional regulators in F3–T3-positive tumours, peroxisome proliferator-activated receptor-γ co-activator 1-α (PGC1α) and oestrogen-related receptor-γ (ERRγ). PGC1α is a co-activator of ERRγ and a main driver for mitochondrial biogenesis. Indeed, overexpression of PGC1α in PIN4(Y122F)-expressing, F3–T3-positive astrocytes increased ATP levels and OCR. Similarly, loss of PGC1α reduced growth of F3–T3;shTrp53 tumours compared with HRAS(12V);shTrp53 tumours. PIN4 has a promoting role in peroxisome biogenesis, which can induce PGC1α via the production of reactive oxygen species (ROS). Acute lentivirus-mediated expression of F3–T3 in astrocytes increased peroxisome biogenesis, which generated ROS and thereby increased PGC1α expression in a manner that was sensitive to ROS inhibition by *N*-acetyl-L-cysteine.

Thus, F3–T3 exerts its oncogenic activity in GBM through promoting peroxisome and mitochondrial biogenesis via PIN4 and PGC1α. Although follow-up studies in larger cohorts are required, these findings suggest that the presence of the F3–T3 fusion gene in tumours can potentially be used to stratify patients for therapy with peroxisome-targeting drugs and/or mitochondrial inhibitors.

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ORIGINAL ARTICLE Frattini, V et al. A metabolic function of FGFR3–TACC3 gene fusions in cancer. *Nature* **555**, 222–227 (2018)