Figs 3h, 10a, b). Using mass spectrometry analysis of PIN4 immunoaffinity complexes, we found that the peroxisomal biogenesis complex[25] formed by PEX1 and PEX6 is the top ranking PIN4 interactor. Other PIN4-associated proteins are implicated in vesicle formation and trafficking, nuclear and mitochondrial RNA metabolism and translation, ribosomal activity and nuclear pore/envelope functions (Extended Data Fig. 10c, d and Supplementary Table 8). Quantitative immunofluorescence revealed that PEX1 increased 2.7-fold in F3–T3 human astrocytes without changes in *PEX1* mRNA (Fig. 4a, b and Extended Data Fig. 10e, f). To investigate whether F3–T3 signals through phospho-PIN4(Y122) to promote peroxisome biogenesis, we acutely transduced human astrocytes with a F3–T3-expressing lentivirus, and found that both phospho-PIN4(Y122) and the total number of PMP70-positive peroxisomes were increased after four days (4.3 fold increase in peroxisomes per cell; Fig. 4c, d and Extended Data Fig. 10g). Phospho-PIN4(Y122)-positive cytoplasmic structures in F3–T3 human astrocytes, but not unphosphorylated PIN4 in vector-transduced human astrocytes, colocalized with PMP70, indicating that phospho-PIN4(Y122) trafficks to new peroxisomal membranes (Fig. 4e). Increased peroxisome biogenesis induced by acute expression of F3–T3 was prevented when F3–T3 was introduced in cells in which PIN4 had been replaced by the unphosphorylatable PIN4(Y122F) mutant (Fig. 4f). F3–T3 also induced a phospho-PIN4(Y122)-dependent early increase in new protein synthesis (Fig. 4g and Extended Data Fig. 10h). Conversely, PGC1α and mitochondrial gene expression were unchanged four days after acute expression of F3–T3 but increased after eight days (Fig. 4h and Extended Data Fig. 10i). Peroxisome biogenesis and new protein synthesis can both generate ROS, and ROS are crucial inducers of PGC1α[20,26,27]. F3–T3 but not F3–T3(K508M) increased ROS at the four-day time point and this effect required PIN4(Y122) phosphorylation (Fig. 4i, j and Extended Data Fig. 10j). Treatment of F3–T3 human astrocytes with the ROS inhibitor *N*-acetyl-L-cysteine eliminated approximately 70% of the increase in PGC1α induced by F3–T3 (Fig. 4k), thus indicating that ROS are responsible for most of the increase in PGC1α induced by F3–T3.

In conclusion, we describe, using an integrated computational and experimental framework, the chain of events propagated by F3–T3 in cancer. Signalling through phospho-PIN4(Y122) triggers vesicle trafficking to deliver building blocks for biogenesis of peroxisomes and new protein synthesis. The coordinated activation of these anabolic pathways results in the accumulation of ROS, which in turn increases PGC1α–ERRγ and mitochondrial metabolism. Thus, rather than impinging exclusively on mitochondrial circuits, the oncogenic signals driving mitochondrial respiration operate within larger contexts of anabolic effectors. Dependency on mitochondrial metabolism of GBM with F3–T3 suggests that inhibitors of oxidative phosphorylation may be beneficial for patients with F3–T3-positive tumours.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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1. Ali, M. A. Chronic myeloid leukemia in the era of tyrosine kinase inhibitors: an evolving paradigm of molecularly targeted therapy. *Mol. Diagn. Ther.* **20,** 315–333 (2016).
2. Di Stefano, A. L. *et al.* Detection, characterization, and inhibition of FGFR–TACC fusions in IDH wild-type glioma. *Clin. Cancer Res.* **21,** 3307–3317 (2015).
3. Gerber, D. E. & Minna, J. D. ALK inhibition for non-small cell lung cancer: from discovery to therapy in record time. *Cancer Cell* **18,** 548–551 (2010).
4. Singh, D. *et al.* Transforming fusions of FGFR and TACC genes in human glioblastoma. *Science* **337,** 1231–1235 (2012).
5. Costa, R. *et al.* FGFR3–TACC3 fusion in solid tumors: mini review. *Oncotarget* **7,** 55924–55938 (2016).
6. Lasorella, A., Sanson, M. & Iavarone, A. FGFR–TACC gene fusions in human glioma. *Neuro-oncol.* **19,** 475–483 (2017).
7. Niola, F. *et al.* Mesenchymal high-grade glioma is maintained by the ID–RAP1 axis. *J. Clin. Invest.* **123,** 405–417 (2013).
8. Škrtić, M. *et al.* Inhibition of mitochondrial translation as a therapeutic strategy for human acute myeloid leukemia. *Cancer Cell* **20,** 674–688 (2011).
9. Uchida, T., Fujimori, F., Tradler, T., Fischer, G. & Rahfeld, J. U. Identification and characterization of a 14 kDa human protein as a novel parvulin-like peptidyl prolyl *cis/trans* isomerase. *FEBS Lett.* **446,** 278–282 (1999).
10. Uchida, T. *et al.* Pin1 and Par14 peptidyl prolyl isomerase inhibitors block cell proliferation. *Chem. Biol.* **10,** 15–24 (2003).
11. Yeh, E. S. & Means, A. R. PIN1, the cell cycle and cancer. *Nat. Rev. Cancer* **7,** 381–388 (2007).
12. Frattini, V. *et al.* The integrated landscape of driver genomic alterations in glioblastoma. *Nat. Genet.* **45,** 1141–1149 (2013).
13. He, H. & Garcia, E. A. Learning from imbalanced data. *IEEE Trans. Knowl. Data Eng.* **21,** 1263–1284 (2009).
14. Carlsson, G. Topology and data. *Bull. Am. Math. Soc.* **46,** 255–308 (2009).
15. Nicolau, M., Levine, A. J. & Carlsson, G. Topology based data analysis identifies a subgroup of breast cancers with a unique mutational profile and excellent survival. *Proc. Natl Acad. Sci. USA* **108,** 7265–7270 (2011).
16. Carro, M. S. *et al.* The transcriptional network for mesenchymal transformation of brain tumours. *Nature* **463,** 318–325 (2010).
17. Mall, R. *et al.* RGBM: regularized gradient boosting machines for the identification of transcriptional regulators of discrete glioma subtypes. Preprint at https://doi.org/10.1101/132670 (2017).
18. Devarakonda, S. *et al.* Disorder-to-order transition underlies the structural basis for the assembly of a transcriptionally active PGC-1α/ERRγ complex. *Proc. Natl Acad. Sci. USA* **108,** 18678–18683 (2011).
19. Lin, J., Handschin, C. & Spiegelman, B. M. Metabolic control through the PGC-1 family of transcription coactivators. *Cell Metab.* **1,** 361–370 (2005).
20. St-Pierre, J. *et al.* Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. *Cell* **127,** 397–408 (2006).
21. Xiong, W. C., Okano, H., Patel, N. H., Blendy, J. A. & Montell, C. repo encodes a glial-specific homeo domain protein required in the *Drosophila* nervous system. *Genes Dev.* **8,** 981–994 (1994).
22. Tiefenböck, S. K., Baltzer, C., Egli, N. A. & Frei, C. The *Drosophila* PGC-1 homologue Spargel coordinates mitochondrial activity to insulin signalling. *EMBO J.* **29,** 171–183 (2010).
23. Read, R. D. *et al.* A kinome-wide RNAi screen in *Drosophila* glia reveals that the RIO kinases mediate cell proliferation and survival through TORC2–Akt signaling in glioblastoma. *PLoS Genet.* **9,** e1003253 (2013).
24. Read, R. D., Cavenee, W. K., Furnari, F. B. & Thomas, J. B. A. A *Drosophila* model for EGFR–Ras and PI3K-dependent human glioma. *PLoS Genet.* **5,** e1000374 (2009).
25. Smith, J. J. & Aitchison, J. D. Peroxisomes take shape. *Nat. Rev. Mol. Cell Biol.* **14,** 803–817 (2013).
26. Boveris, A., Oshino, N. & Chance, B. The cellular production of hydrogen peroxide. *Biochem. J.* **128,** 617–630 (1972).
27. Han, J. *et al.* ER-stress-induced transcriptional regulation increases protein synthesis leading to cell death. *Nat. Cell Biol.* **15,** 481–490 (2013).

Supplementary Information is available in the online version of the paper.

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