Rapidly proliferating cells promote glycolysis in aerobic conditions, to increase growth rate. Expression of specific glycolytic enzymes, namely pyruvate kinase M2 and hexokinase 2, concurs to this metabolic adaptation, as their kinetics and intracellular localization favour biosynthetic processes required for cell proliferation. Intracellular factors regulating their selective expression remain largely unknown. Here we show that the peroxisome proliferator-activated receptor gamma transcription factor and nuclear hormone receptor contributes to selective pyruvate kinase M2 and hexokinase 2 gene expression in PTEN-null fatty liver. Peroxisome proliferator-activated receptor gamma expression, liver steatosis, shift to aerobic glycolysis and tumorigenesis are under the control of the Akt2 kinase in PTEN-null mouse livers. Peroxisome proliferator-activated receptor gamma binds to hexokinase 2 and pyruvate kinase M promoters to activate transcription. In vivo rescue of peroxisome proliferator-activated receptor gamma activity causes liver steatosis, hypertrophy and hyperplasia. Our data suggest that therapies with the insulin-sensitizing agents and peroxisome proliferator-activated receptor gamma agonists, thiazolidinediones, may have opposite outcomes depending on the nutritional or genetic origins of liver steatosis.
Glycolysis generates energy and intermediates for macromolecule biosynthesis. Hence the growth factors, anabolic hormones and oncogenic events perfected molecular mechanisms to upregulate glycolytic enzyme activities and gene expression. The phosphatidylinositol-3-kinase (PI3K) pathway, a master regulator of cell growth, proliferation and metabolism in response to insulin, growth factors and oncogenic insults, is a potent stimulator of glycolysis by acting on different levels, from the upregulation of glucose uptake at the membrane, to the post-translational modifications of glycolytic enzymes, to the induction of glycolytic gene expression. In the nucleus, the transcription factor c-Myc, encoded by the MYC oncogene, directly binds and activates the majority of glycolytic gene promoters. In addition, the hypoxia-inducible factor 1 (HIF–1), which can accumulate in cells as a consequence of inactivating mutations in the Von Hippel–Lindau (VHL) tumour suppressor gene, cooperates with c-Myc on the transcriptional activity of the glycolytic gene promoters. Further complexity comes from the existence of multiple isoforms catalysing specific reactions in glycolysis. For instance, four hexokinases (HK1–4) catalyse the first step of glycolysis, that is, the phosphorylation of glucose, while four pyruvate kinases (PKM1, PKM2, PKL, PKR) catalyse the last step of glycolysis, that is, the final conversion of phosphoenolpyruvate to pyruvate. These isoforms display differential tissue distribution and confer specific kinetic and regulatory properties to the glycolytic flux. However, the molecular mechanisms favouring selective expression of specific isoforms remain mysterious.

Pyruvate, the end product of glycolysis, can be reduced in the cytosol during anaerobic conditions or enter the mitochondria to be further oxidised during aerobic respiration. In rapidly dividing cells, lactate production is also observed under normal oxygen conditions, a phenomenon called aerobic glycolysis or Warburg effect, which may provide a growth advantage by producing carbon intermediates as building blocks for cellular components. Among the glycolytic isoforms, the expression of hexokinase 2 (HK2) and the M2 isoform of pyruvate kinase (PKM2) may particularly favour aerobic glycolysis and cell proliferation owing to their intracellular localization and kinetic properties. The features of HK2 that may favour aerobic glycolysis are mitochondrial localization that allows the consumption of mitochondrial-produced ATP to start glycolysis, a relatively high affinity for glucose and presence of two catalytically active domains that double the rate of glucose-6-phosphate formation. Although the other pyruvate kinase isoforms are exclusively tetrameric enzymes, PKM2 can also switch to a less active dimeric form by allosteric regulation in presence of mitogenic signals, leading to the accumulation of glycolytic intermediates that can be used to increase the biomass. Consistently, HK2 and PKM2 isoforms are reported to be predominantly expressed in highly malignant tumours, and their functional role in promoting tumour progression has been demonstrated. Particularly, a relative switch from HK4 (also named glucokinase) to HK2, and from PKL to PKM2 has been demonstrated during progressive stages of liver transformation.

In liver, insulin signalling through the PI3K pathway has a fundamental role in the regulation of lipid and glucose metabolism, and pathophysiologically. Gene deletions abrogating PI3K activity in mouse liver lead to severe insulin resistance, glucose intolerance, increased glucose output and defective lipid neogenesis. Conversely, mutations activating the PI3K pathway, including the liver-specific deletion of the phosphatidylinositol (3,4,5)-triphosphate-lipid phosphatase and tumor suppressor Pten (phosphatase and tensin homologue) gene, caused insulin hypersensitivity, improved glucose tolerance, hepatomegaly, steatosis in young adult mice, followed by adenocarcinoma formation since 7 months of age. Among the PI3K-dependent effectors, the serine/threonine kinase Akt2 is required for the regulation of hepatic glucose output, lipid accumulation, and tumorigenesis in Pten-null livers. In this report, we therefore performed genetic epistasis experiments to address the impact of PI3K/Akt2 activity on liver glycolysis. Strikingly, we find that, whereas Pten deletion causes a general upregulation of glycolytic gene expression, Akt2 selectively controls HK2 and PKM2 isoforms. We identify pexosomate proliferator-activated receptor gamma (PPARγ) nuclear hormone receptor as a novel transcription factor turning on these specific glycolytic isoforms that are frequently upregulated in pathophysiologically.

### Results

**Activation of glycolysis in Pten-null liver.** Consistent with the positive role of the PI3K pathway on the cell switch to glycolytic metabolism, Pten-null mouse livers showed a global upregulation of glycolytic enzymes (Fig. 1). The expression of multiple glycolytic enzymes that are commonly expressed in liver, including glucokinase (GCK), glucose phosphate isomerase 1 (GPI1), glyceraldehyde 3-phosphate dehydrogenase (GAPDH), enolase 1 (ENO1), phosphoglycerate kinase 1 (PGK1) and L-type pyruvate kinase (PKL) was augmented at the messenger RNA and protein levels (Fig. 1a,b). The increase in expression paralleled increased enzymatic activity, while mitochondrial enzymes such as citrate synthase and cytochrome c oxidase were not affected (Supplementary Fig. S1). These metabolic changes were concomitant with liver triglyceride accumulation (steatosis) and hyperplasia, hypoglycaemia and insulin hypersensitivity, and preceded the adenocarcinoma formation that was observed since 7 months of age (Supplementary Fig. S2). As Akt2 has a crucial role mediating the action of insulin and P13K on hepatic glucose homeostasis, steatosis, hyperplasia and tumorigenesis, particularly, a relative switch from HK4 to HK2 and PKM2 further increased liver mass to 134% as compared with control livers (Supplementary Fig. S3). PKM2 overexpression in Pten-null cultures (Supplementary Fig. S1), ruling out an involvement of Akt2 in this general activation of glycolysis.

**Akt2 controls expression of HK2 and PKM2 in Pten-null liver.** Specific glycolytic isoforms, namely HK2 and PKM2, have been demonstrated to favour aerobic glycolysis and growth. PKM2 and HK2 are expressed at low levels in wild-type adult mouse livers. As shown in Figure 1b and in Figure 1c, Pten deletion upregulated HK2 and PKM2 mRNA and protein expression. Importantly, Akt2 deletion was sufficient to reduce by 40–60% the expression of both isoforms at 3 months of age, well before tumour onset. In addition, Akt2 deletion also blunted mitochondrial levels of HK2 (Fig. 1d), which should affect ATP usage towards glycolysis. Finally, the upregulation of all the above mentioned glycolytic enzymes was also observed in AlbCre;Ptenf/f;Akt2−/− livers (Fig. 1a,b, Supplementary Fig. S1), taking together, these data indicate that Akt2 promotes aerobic glycolysis in Pten-null fatty liver.

**Expression of HK2 and PKM2 isoforms promotes liver growth.** To evaluate the functional outcome of glycolytic isoforms expression on liver pathophysiology, adenoviral-mediated Hk2 overexpression was achieved in vivo (Fig. 2a). Hk2 overexpression led to a 100% increase in liver mass in wild type, and a 135% increase in AlbCre;Ptenf/f;Akt2−/− mice (Fig. 2b). In addition, Hk2 promoted lactate production, steatosis and hepatocyte proliferation (Fig. 2c,d,e). Hk2 also upregulated triglyceride content and lactate release after 60 h of overexpression in wild-type primary hepatocyte cultures (Supplementary Fig. S3). Pkm2 overexpression in vivo in wild-type mice caused a 74% increase in liver mass, an effect that was comparable to Hk2 (Fig. 2b). The combination of both Hk2 and Pkm2 further increased liver mass to 134% as compared with green fluorescent protein (GFP)-treated control mice. Thus Hk2 and Pkm2 overexpression at supraphysiological levels is sufficient to cause liver steatosis and growth. In conclusion, a specific pattern
of glycolytic isozyme expression correlates with the Akt2-dependent steatosis, hyperplasia and oncogenic potential of PTEN-null liver cells.

Akt2 controls PPARγ activity in PTEN-null liver. Given the distinctive features of PKM2 and HK2 isozymes in regulating cell metabolism, we set out to determine the transcription factor(s) responsible for their selective Akt2-dependent regulation in PTEN-null hepatocytes. We initially considered the involvement of c-Myc and HIF1α transcription factors, two potent stimulators of glycolytic gene transcription4. Consistently, adenoviral transduction of c-Myc and HIF1α in primary hepatocytes increased PKM2 and HK2 expression in addition to other glycolytic enzymes such as GAPDH, PGK1, ENO1 as well as LDHA, a known non-glycolytic target of both factors (Supplementary Fig. S4a). However, we failed to reveal a significant regulation of c-Myc and HIF1α expression at the level of mRNA, total protein and nuclear protein in the wild type, AlbCre;PTENf/f and AlbCre;PTENf/f;Akt2−/−livers (Supplementary Fig. S4b,c,d). Furthermore, the HIF1α- and c-Myc-target genes GAPDH, PGK1, ENO1, were not regulated in an Akt2-dependent manner in livers (Fig. 1). These observations would be consistent with extra mechanisms downstream of Akt2 controlling PKM2 and HK2 expression. We noticed that fat storing tissues also contained abundant amount of PKM2 and HK2. This was the case for the epididymal adipose tissues in wild-type mice (Fig. 3a), and for steatotic livers in AlbCre;PTENf/f mice (Fig. 1). PPARγ is a master regulator of adipogenesis and fat storage21. In liver, PPARγ levels are increased during steatosis induced by high fat diet22, 23, leptin deficiency23, or the genetic deletion of PTEN14. Importantly, we found that the increase of PPARγ mRNA and nuclear protein
PKM2 and HK2 are novel transcriptional targets of PPARγ.

By *in silico* analysis, it appeared that the promoter regions of PKM2 and HK2 genes also contained several PPAR response elements (PPRE). Namely, for HK2, they were localized at positions ≈ −2,694 bps, −1,216 bps, −1,162 bps, −756 bps, −495 bps and for PKM2 at −2580 bps, −2108 bps, −2086 bps, −1,927 bps, −1,028 bps and −235 bps from the transcription start site. Independent chromatin immunoprecipitation assays demonstrated that, in *PTEN*-deficient livers, PPARγ binding to one PPRE in the promoter of PKM2 (at −2,580 bp) and to one PPRE in the promoter of HK2 (at −495 bp position) was enriched more than tenfold over the IgG control immunoprecipitations (Fig. 3e). Importantly, this
binding required Akt2 activity as it was reduced in *AlbCre;PTEN*^f/f^; *Akt2*^−/−^ livers. Taken together, these findings indicate that PKM2 and HK2 are novel and direct targets of PPARγ, consistent with their expression in adipose tissue and fatty liver.

**Figure 3 | PPARγ controls HK2 and PKM2 expression in PTEN-null liver.** (a) Immunoblot analysis of protein expression in liver and WAT tissue of WT mice. (b) RT–QPCR analysis of relative transcript levels of PPARγ in the mouse livers of indicated genotypes. Data are mean ± s.e.m., n = 5 (P < 0.05 (a) versus WT; (b) versus *AlbCre;PTEN*^f/f^, 2-tailed, unpaired Student’s t test). (c) Immunoblot analysis showing levels of PPARγ in liver nuclear extracts. The ratio to TATA-binding nuclear protein of the densitometric assay ± s.e.m. is presented, n = 4-5 (P < 0.05 (a) versus WT; (b) versus *AlbCre;PTEN*^f/f^, 2-tailed, unpaired Student’s t test). (d) Relative transcript levels of CD36 and CIDE-C in the mouse livers of indicated genotypes. Data are mean ± s.e.m., n = 7 (P < 0.05 (a) versus WT; (b) versus *AlbCre;PTEN*^f/f^, 2-tailed, unpaired Student’s t test). (e) Endogenous PPARγ chromatin immunoprecipitation assessed for CD36, PKM2 and HK2 murine promoters relative to immunoprecipitation with nonspecific IgG. Data are presented as an average of fold induction over WT control mice of two independent experiments, n = 4.

**Pioglitazone treatment induces growth of PTEN-null liver.** Our data suggest that PPARγ may promote metabolic adaptations downstream of PI3K and Akt2 pathway favouring hepatocyte steatosis and proliferation. However, PPARγ in other systems may also promote cell differentiation and cell-cycle withdrawal. Intriguingly, PTEN expression has been shown as one of the possible mechanisms by which PPARγ may exert anti-tumoral actions. Therefore, the functional outcome of PPARγ activity on PTEN-negative liver growth is difficult to predict and is important to assess, given the potential for pharmacological intervention with PPARγ synthetic ligands to treat metabolic diseases. To this end, PPARγ activity was modulated in PTEN-null livers. *AlbCre;PTEN*^f/f^ and wild-type mice were daily treated for 12 days with the PPARγ agonist pioglitazone. This reduced fed glycaemia in both genotypes (Fig. 4a), consistent with the insulin-sensitizing systemic effect of pioglitazone. However, pioglitazone promoted a 62% increase in liver/body ratio (Fig. 4b), and a threefold increase in BrdU-positive cells (Fig. 4c), exclusively in PTEN-null livers, whereas growth was not induced in wild-type liver controls in agreement with the lower PPARγ expression in this genotype. Strikingly, pioglitazone selectively raised the levels of PKM2 and HK2 proteins in *AlbCre;PTEN*^f/f^ livers with no effect on PKL and GAPDH levels (Fig. 4d).

**PPARγ overexpression in vivo induces liver growth.** To analyse the effects of cell-autonomous activation of PPARγ on liver growth, wild-type, *AlbCre;PTEN*^f/f^ and *AlbCre;PTEN*^f/f^; *Akt2*^−/−^ mice were in vivo transduced with PPARγ-expressing adenoviral vector that has a pronounced tropism for liver. In line with the results of PPARγ activation by pharmacological agents, PPARγ overexpression led to a significant increase in liver/whole body ratio in wild type, *AlbCre;PTEN*^f/f^ and *AlbCre;PTEN*^f/f^; *Akt2*^−/−^ livers as compared with control transduced livers (Supplementary Fig. 5a). The effect on liver hypertrophy and steatosis was particularly striking in wild type and *AlbCre;PTEN*^f/f^; *Akt2*^−/−^ tissues, that express low levels of endogenous PPARγ (Fig. 5a). Induction of PKM2 and HK2 by PPARγ expression was comparable to well-established PPARγ isoforms transcribed from the same PKM locus and arise from tissue-specific promoters (Fig. 5b). The massive and selective upregulation of PKM2 and HK2 proteins in *AlbCre;PTEN*^f/f^ livers with no effect on PKL and GAPDH levels (Fig. 4d).

**Figure 5b, Fig. 4**
Viral transduction, where increasing doses of PPAR γ modulating PPAR γ on PKM2 expression. It was also independently confirmed by going out the contribution of other cell types to the observed effects in liver, PPAR γ acts in vivo on PKM and HK2 gene transcription, and that hepatocytes are competent for PKM2 production. To address that PPAR γ upregulated, leading to increased levels of both PKM1 and PKM2 gene was deleted and Akt2 upregulated in hepatocytes. In these cases, we show that PPAR γ activation is detrimental, leading to massive steatosis and hepatocyte proliferation.

Regulation of HK2 and PKM2 by hepatic PPAR γ is observed well before tumour onset, which in PKM-deficient liver appears since 7 months of age. It is tempting to speculate that these effects may be causally involved in the well-established correlation between liver steatosis and increased cancer risk. Whereas PPAR γ may act as a tumour suppressor in colon, breast and prostate cancers, PPAR γ agonists could be beneficial against steatosis-associated human liver diseases, though the outcome is not conclusive yet. The rationale behind these clinical trials is that PPAR γ agonists should alleviate liver steatosis, promoting lipid accumulation in adipose tissue and suppressing hepatic inflammation. This strategy may be appropriate when the origin of liver steatosis is environmental, owing to nutritional habits. However, liver steatosis and hepatic PPAR γ expression may arise from genetic insults, as observed when PTEN is deleted and Akt2 upregulated in hepatocytes. In these cases, we show that PPAR γ activation is detrimental, leading to massive steatosis and hepatocyte proliferation.

Methods
Animal experiments. Generation of AlbCre;PTENγf/f;Akt2−/− mice has been previously described. Mice were maintained at 22 °C with a 12-h-dark/12-h-light cycle and had free access to food. All animal studies were approved by the Direction Départementale des Services Vétérinaires, Préfecture de Police, Paris, France (authorization number 75-1313). Pioglitazone was diluted in 0.5% carboxymethyl cellulose and was administered at 30 mg kg−1 dose by daily gavage for 12 days. Group of wild type mice transduced with PPAR γ adenovirus were treated with 4 mg kg−1 3-BrPA (Sigma) freshly prepared in PBS and adjusted to pH 7.4. The drug was injected intraperitoneally every day for 7 days. The first injection was 12 h after transduction with adenovirus.

Adenoviruses. Recombinant adenovirus expressing untagged full-length human PKM2 was a generous gift from Renaud Dentin (Institut Cochin, INSERM U1016, UMR8104). Recombinant adenovirus expressing c-Myc was a generous gift from Heiko Herrmeking (Institute of Pathology Ludwig-Maximilians-University Munich). Recombinant adenovirus expressing HIF-1α was a generous gift from Gregg L. Semenza (The Johns Hopkins University School of Medicine). Recombinant adenovirus expressing V5-tagged PPAR γ was described previously. Recombinant adenovirus expressing V5-tagged PPAR γ was described previously. Recombinant adenovirus expressing V5-tagged PPAR γ was described previously.
full-length human HK2 was custom-generated at GeneCust. Recombinant adenosine expressing untagged human PKM2 was acquired from Excellgen. Viruses were generated through homologous recombination between a linearized transfer vector pAD-Track and the adenoviral backbone vector pAD-Easy. Viruses were purified by the CsCl method and dialysed against PBS buffer containing 7% glycerol. For in vivo transduction, 10^7 of adenoviral infectious particles were diluted in 0.9%NaCl and administered retro-orbitally, using 26G needle in total volume of 100 µl per mouse, and mice were killed 7 or 14 days postinfection. Adenovirus coding for GFP was used as a control in all experiments.

**Metabolic studies in mice.** At 3 months of age, a glucose tolerance test was performed in mice after an overnight fasting (14h). Mice were intraperitoneally injected with 2 g/kg body weight (g) glucose, and blood was collected from the tail vein for determination of glucose levels at 0, 15, 30, 45 and 100 min by Glucotrend glucometer (Roche Diagnostics). Insulin tolerance test was performed at 3 months of age. Overnight-fasted mice were intraperitoneally injected with 1 U kg^-1 insulin (Actrapid), and the glucose concentration in whole blood from the tail vein was measured at 0, 15, 30 and 60 min. Fasting insulin levels were measured by ELISA assay (Crystal chem).

**Immunohistochemistry and morphometric analysis.** Liver tissue was fixed overnight in phosphate-buffered 10% formalin and embedded in paraffin, sectioned in 1 cm thickness, deparaffinized, rehydrated, and stained with hematoxylin. Immunohistochemistry was performed using anti-BrdU antibody (Roche), anti-ß-catenin (Calbiochem) and anti-PKM2 antibody (Cell Signalling Technology) antibodies. For 5-bromo-2′-deoxyuridine (Brdu) incorporation, mice were fed with BrdU (3 mg ml^-1, Sigma-Aldrich) dissolved in drinking water for either for 5 days (PIO treatment) or last 24 h (adenoviral transduction) before killed. The results were expressed as the ratio of BrdU-positive nuclei and total number of nuclei in at least 10 areas of 33,500 µm² for anti-BrdU staining analysed.
Subcellular fractionation and western blot. Mitochondria were isolated as previously described43. Briefly, 50–100 mg of snap-frozen liver tissue was homogenized in ice cold buffer containing complete protease inhibitors (Roche). After centrifugation at 600 × g for 10 min, the supernatant containing the mitochondria was centrifugated at 7,000g for 10 min. The pellet of mitochondria was washed three times with ice cold buffer, and, after the final centrifugation, the mitochondria were lysed in extraction buffer (20 mM Tris–HCl (pH 8.0), 5% glycerol, 138 mM NaCl, 2.7 mM KCl, 1% NP-40, 20 mM NaF, 5 mM EDTA, 1 mM DTT) complemented with complete protease inhibitors (Roche). Nuclear extracts were prepared using NE-PER Kit (Pierce), according to manufacturer's recommendations, using 50–100 mg of snap-frozen liver tissue or pelleted primary hepatocytes were used for acetone extraction. Lactate concentrations were assayed in liver extracts of random-fed mice as described previously44. Briefly, metabolates were extracted in 9% perchloric acid from clamp-frozen liver tissues, neutralized using potassium hydroxide, and assayed using a spectrophotometric enzymatic procedure. Lactate levels after adenosin-mediated HK2 overexpression were determined using lactate reagent (Trinity Biotech) and protein complexes were eluted and cross-linking was reversed by heating the recovered with Protein A sepharose beads (Amersham). After washing, DNA–protein complexes were analyzed using NE-PER Kit (Pierce), according to manufacturer's recommendations, using 50–100 mg of liver tissue or cell culture medium supernatants. Liver tissue extracts before measurement were filtered using 10 K Amicon Ultra columns (Millipore).

Hepatic metabolites analysis. TG levels were determined using Triglycerides FS Kit (Duasyis) according to the manufacturer's instructions. 50–100 mg of powdered liver tissue or pelleted primary hepatocytes were used for acetone extraction. The critical role of AKT2 in hepatic steatosis induced by PTEN loss. J. Clin. Invest. 77, 2553–2561 (1996).
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Acknowledgements
We are grateful to the members of INSERM-U845 for support, and to David Sabatini, Stefano Fumagalli, Benoit Viollet, Fabienne Foufelle, Renaud Dentin, Pascal Pineau, Isabelle André-Schmutz, Olivier Danos and Anne Dejean for helpful discussions and sharing reagents. We thank Sophie Berissi, Dominique Chretien and Sylvie Fabrega for technical support. This work was supported by grants from the European Research Council, from Fondation de la Recherche Medicale (DEQ20061107956) and from Fondation Schlumberger pour l’Education et la Recherche to M.P. and from the Association pour la Recherche sur le Cancer to M.P. and J.-E.R. L.A.P received a fellowship from the Région Provence-Alpes-Cote-d Azur and INSERM, C.E. from Ministere de Recherche et Technologies and from Fondation de la Recherche Medicale.

Author contributions
G.P. designed, performed most of the experimental work and analysed data with contribution of C.E. and C.C. M.I.B., Y.H. and A.S. provided expertise and the mouse lines. M.P. provided adenosiviral vectors. J.-S.A., L.F., F.V., M.Po. shared reagents and expertise, helped with in vivo CIMP experiments. L.A.P., J.-E.R., P.F. performed the lactate metabolite measurements and enzymatic assays. J.-Y.S. conceived, directed the study and wrote the manuscript. All authors discussed the results and commented on the manuscript.

Additional information
Supplementary Information accompanies this paper at http://www.nature.com/naturecommunications

Competing financial interests: The authors declare no competing financial interests.
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How to cite this article: Panasyuk, G. et al. PPARγ contributes to PKM2 and HK2 expression in fatty liver. Nat. Commun. 3:672 doi: 10.1038/ncomms1667 (2012).

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