Hepatology Snapshot

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PI(3)K/PTEN/AKT pathway

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Introduction

Cancer and metabolic disorders are associated with an aberrant activity of the PI(3)K/PTEN/AKT pathway. In liver tumours, this pathway is activated by loss of function of PTEN [1] or gains of function of receptor tyrosine kinases and PI(3)K [2].

Binding of growth factors (insulin, IGF, EGF, HGF, FGFb, PDGF, VEGF) to receptor tyrosine kinases (RTKs) leads to autophosphorylation of the receptors. This activates class I_A PI(3)K either by direct docking to the receptor or by binding to the scaffolding adaptors insulin receptor substrate-1 (IRS-1) and IRS-2. PI(3)K is composed of a p85 regulatory subunit and a p110 catalytic subunit. The p85 subunit binds, stabilises and inhibits the p110 catalytic subunit until receptor activation occurs. PI(3)K phosphorylates phosphatidylinositol-4,5-bisphosphate (PI(4,5)P2) to generate phosphatidylinositol-3-4-5-trisphosphate (PI(3,4,5)P3). PI(3,4,5)P3 recruits and localises PDK1 and AKT to the inner leaflet of the plasma membrane, where PDK1 phosphorylates the activation loop of AKT at Thr308. Additional phosphorylation on Ser473 by mTOR complex 2 (mTORC2) is necessary to fully activate AKT. Ser473 site can also be phosphorylated by DNA-PKc and ATM following DNA damage. In addition to AKT activation, PDK1 also phosphorylates and activates aPKCs, promoting lipogenesis, inflammation and systemic insulin resistance and decreasing gluconeogenesis. AKT is negatively regulated by dephosphorylation. Protein phosphatase 2A (PP2A) dephosphorylates AKT on both sites, but particularly at Thr308. The phosphatase PHLPP directly dephosphorylates the Ser473 site.

The PI(3)K/AKT pathway is negatively regulated by the phosphatase and tensin homolog PTEN. PTEN is a lipid phosphatase which dephosphorylates the 3-position of PI(3,4,5)P3 to PI(4,5)P2, terminating signaling downstream of PI(3)K by reducing the recruitment of PDK1 and AKT to the plasma membrane and decreasing AKT activity. PI(3,4,5)P3 is also rapidly degraded at the 5-position by 5-phosphatases (such as SHIP2) forming PI(3,4)P2.

PTEN expression and activity are regulated by numerous mechanisms [3]. Expression of PTEN is upregulated by several transcription factors (Egr1, IGF-2, p53, PPAR-γ, Spry2, Atf2, and c-Myc), whereas other transcription factors negatively regulate PTEN transcription (NF-κB, p300/CBP, Hes-1, Cbf-1 and c-Jun). PTEN is also repressed post-transcriptionally by specific miRNAs (miR-21, miR-19a, miR-17-92, miR-214, miR-216a and miR-217). PTEN protein is regulated by several posttranslational modifications: phosphorylation, acetylation, ubiquitination and the redox state, which affect PTEN stability, degradation and enzymatic activity. Unsaturated fatty acids decrease the expression of PTEN.

Phosphorylated and activated AKT disassociates from the plasma membrane and translocates to different subcellular compartments (nucleus, endoplasmic reticulum, Golgi, mitochondria) where it exerts its biological activities [4] (Fig. 1).

a. AKT increases **cell survival** by inhibition of apoptosis through phosphorylation of FOXOs, BAD, MDM2, GSK3 and YAP.
b. AKT promotes **cell growth** through activation of mTOR complex 1 (mTORC1). Activated mTORC1 phosphorylates downstream targets such as 4E-BP1 and S6K1. These effects result in the stimulation of translation initiation and ribosome biogenesis. Importantly, active S6K1 can phosphorylate serine residues on IRS-1, targeting IRS-1 for degradation and resulting as a negative feedback mechanism to attenuate PI(3)K/AKT signaling and leading to decrease in insulin sensitivity.
c. AKT increases **cell proliferation**, mainly by regulation of FOXOs and p53.
d. AKT plays an important role in **angiogenesis**, either through direct phosphorylation and activation of endothelial nitric oxide synthase (eNOS), or through increased production of hypoxia-inducible factor α (HIF1α and HIF2α) via mTORC1.
e. AKT is implicated in the regulation of **glucose and lipid metabolism**. AKT stimulates glucose uptake in response to insulin through stimulation of Glut4 translocation to the plasma membrane. Glucose uptake may also be stimulated by increased expression of Glut1 through mTORC1 activation. Glucose is converted into glucose-6-phosphate by hexokinases, which are activated and stabilised by AKT. AKT induces glycogen synthesis by removing the inhibitory effects of GSK3 on glycogen synthase. GSK3 inactivation by AKT also induces lipogenesis through SREBP-1c activation. Through FOXOs inhibition, AKT decreases gluconeogenesis and triglycerides metabolism. Importantly, increased lipid synthesis by SREBP-1c also occurs through mTORC1 activation, but it remains unclear whether the downstream effect of mTORC1 on SREBP-1c is distinct of S6K1 [5,6].

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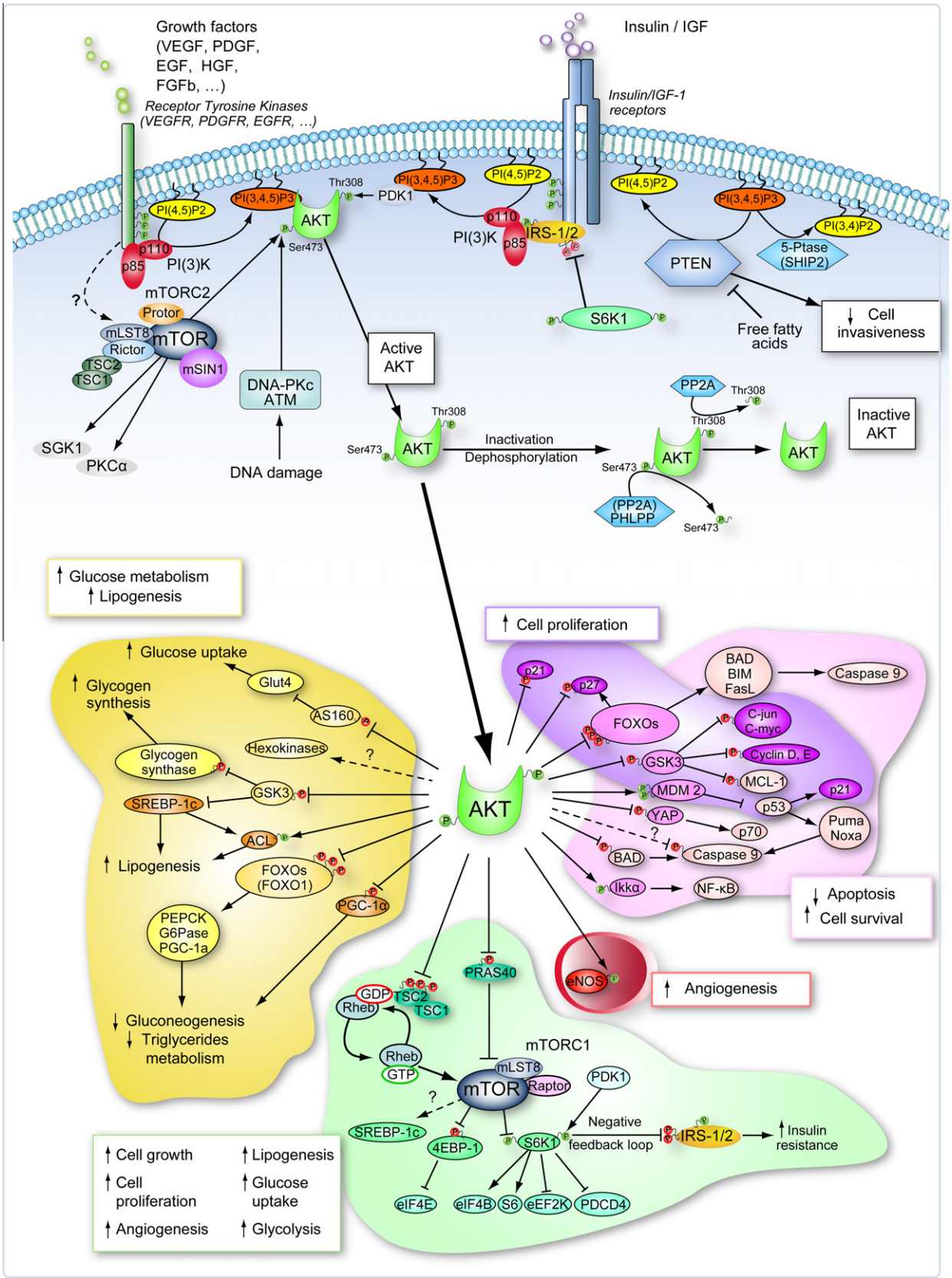

Fig. 1. The phosphatase PHLPP directly dephosphorylates the Ser473 site.

The pathway can be over-activated in HCC by an enhanced stimulation of receptor tyrosine kinases particularly the IGF receptor and EGFR [2]. PTEN is a tumour suppressor whose gene is mutated in 5% of HCCs and its expression reduced in nearly half of all HCCs. PTEN expression can also be downregulated directly by the HBX protein in HBV-infected patients [2]. Rare somatic mutations in the PI(3)K catalytic α gene *PIK3CA* may activate its kinase function. p85α expression is significantly reduced in many human cancers including HCC [7]. The levels of the phosphorylated form of mTOR have been shown to be elevated in 15% of HCC and the levels of total S6K1 in 45% of cases [2]. PTEN expression is decreased by unsaturated fatty acid, through a mechanism involving the activation of mTOR and NFκB, resulting in miR-21 upregulation and PTEN mRNA degradation [8,9]. PTEN downregulation and deletion in the liver induces steatosis development, but the mechanisms for this remain unclear [8,10].

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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