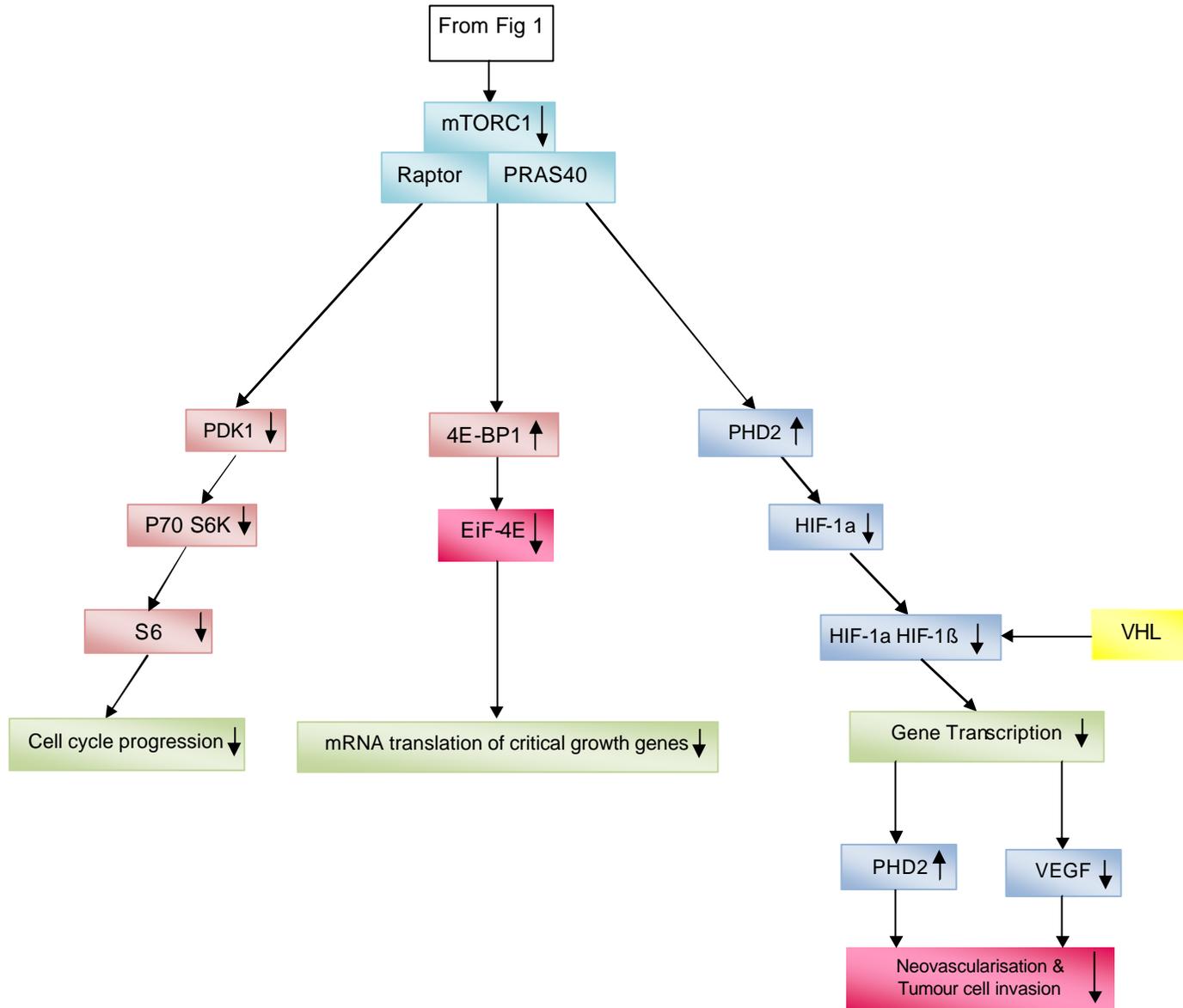


Fig 4 Proposed effects of metformin on mTORC1 effectors



## Legend

### Abbreviations

4E-BP1 – Eukaryotic initiation factor 4E binding protein-1  
EiF-4E - Eukaryotic initiation factor 4E (the binding (dimerization) partner of 4EBP1)  
HIF-1a & 1 $\beta$  – Hypoxia inducible factor - 1a & 1 $\beta$   
mTORC1 – mammalian target of Rapamycin complex 1  
P70 S6K - Ribosomal protein S6 kinase  
PHD - HIF-prolyl hydroxylase domain  
VHL - von Hippen-Lindau protein tumour suppressor

**In red – activating oncogenic mutations**

**In yellow – inactivating tumour suppressor mutations**

### References

Darb-Esfahani (2009)  
Inoki (2003)  
Shaw (2006)  
Spinella (2010)  
Treins (2006)  
Yap (2008)

Shaw 2006 “mTORC1-dependent translation is known to control a number of specific cell-growth regulators, including the HIF -1a hypoxiainducible factor-1a) transcription factor, which in turn drive diverse processes including cell growth, glycolysis and angiogenesis, all contributing to enhanced tumorigenesis. Interestingly, HIF -1a protein degradation is independently negatively regulated by the von HippeI–Lindau (VHL) tumour suppressor, providing another link between this pathway and cancer, and another genetic setting in tumours in which mTOR inhibitors may prove efficacious”

Shaw 2006 “Two well-characterized substrates of the mTORC1 complex that control translation and cell growth are the 4EBP1 family of proteins and the S6 protein kinases (S6K1 and S6K2).” mTORC1 mediates phosphorylation of S6K at a threonine residue in a hydrophobic motif at the C terminus of the kinase domain, and this phosphorylation allows the recruitment and subsequent phosphorylation and activation of S6K by PDK1 (the same kinase that activates AKT; see Box 2).

Treins 2006 "AMPK activation inhibits the expression of HIF-1[alpha] induced by insulin and IGF-1" "AICAR and metformin inhibited the ability of insulin and IGF-1 to induce HIF-1[alpha] expression. These results show that AICAR and insulin/IGF-1 regulate VEGF expression through different mechanisms"

Sabatini 2006 "By phosphorylating the 4EBP (eukaryotic translation initiation factor 4E binding protein) family of proteins mTORC1 represses their capacity to inhibit the mRNA cap-binding protein eIF4E (eukaryotic initiation factor 4E).

Darb-Esfahani 2009