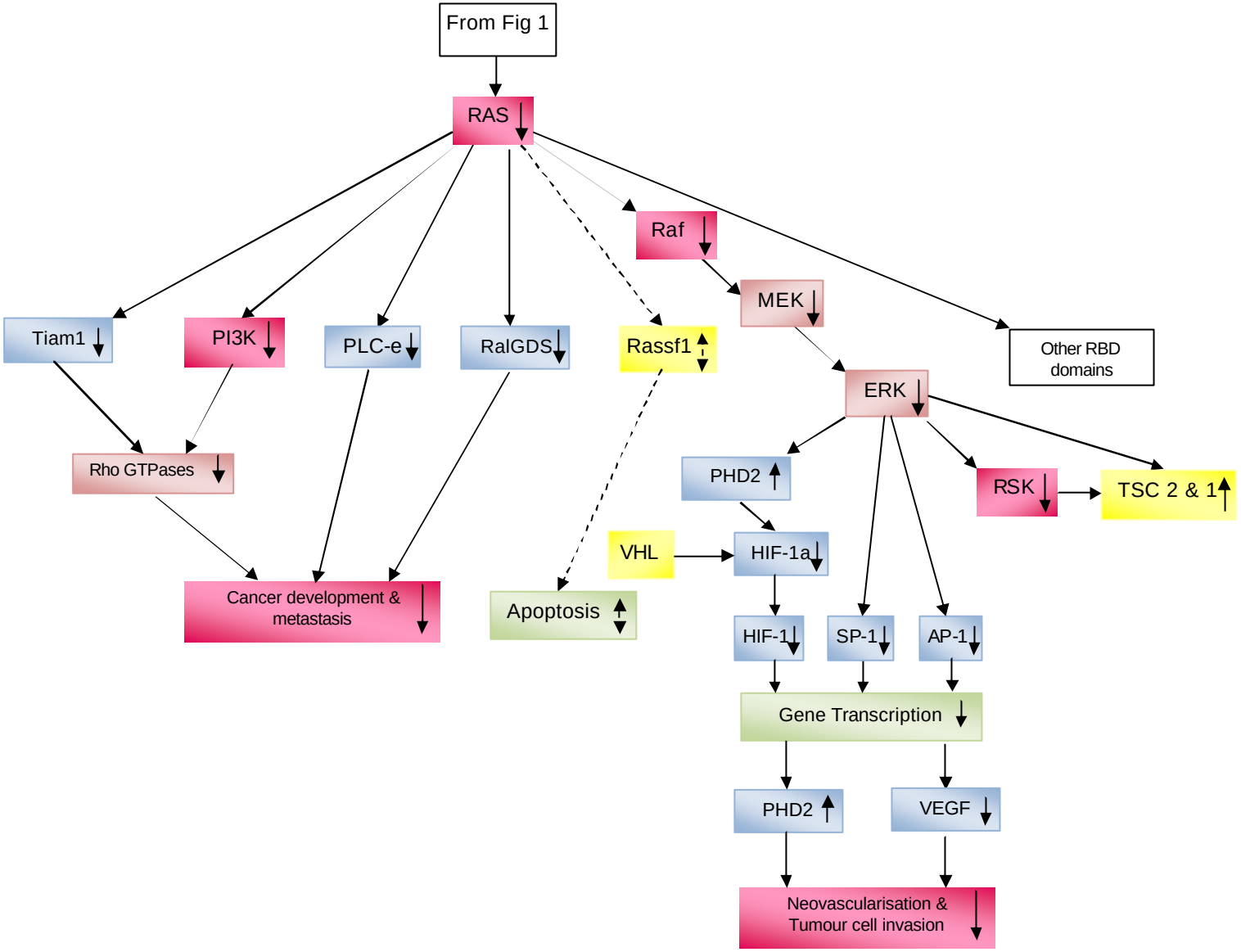
Fig 2 Proposed effects of metformin on RAS pathways



Legend

Abbreviations
ERK - extracellular-signal-regulated kinase
HIF-1a & 1ß – Hypoxia inducible factor - 1a & 1ß
MEK - mitogen-activated protein kinase kinase 1
PHD - HIF-prolyl hydroxylase domain
PI3K - phosphatidylinositol 3-kinase
PLC-e - phospholipase C family member
RAF - RAF proto-oncogene serine/threonine-protein kinase
RalGDS – Ral guanine nucleotide dissociation stimulator (Ral family of GTPases)
RAS- small GTPase
Rassf1 - Ras association domain-containing protein 1
Rho GTPases – activate Rho proteins
RSK - ribosomal protein S6 kinase
TIAM1 - T-cell lymphoma invasion and metastasis 1
TSC – Tuberous Sclerosis Complex
VHL - von Hippen-Lindau protein tumour suppressor

In red – activating oncogenic mutations

In yellow – inactivating tumour suppressor mutations

References (in text)

Ellenbroek et al. (2007)
Shaw 2006
Van der Wyden (2007)
Pouyssegur 2006
Spinella 2010

1. Ellenbroek et al. (2007) “outlined a number of different effects of rho activation in cancerous cells. First, in the initiation of the tumor modification of rho activity can suppress apoptosis and therefore contribute to artificial cell longevity. After natural apoptosis is suppressed, abnormal tumor growth can be observed through the loss of polarity in which rho proteins play an integral role. Next, the growing mass can invade across its normal boundaries through the alteration of adhesion proteins potentially caused by rho proteins[8].

Finally, after inhibition of apoptosis, cell polarity and adhesion molecules, the cancerous mass is free to metastasize and spread to other regions of the body." – Wikipedia

2. Ellenbroek 2007 – "Rho GTPases regulate important cellular processes ranging from cytoskeletal remodelling and gene expression to cell proliferation and membrane trafficking. Therefore it is not surprising that deregulated Rho signalling can contribute to disturbed cellular phenotypes in a wide range of diseases. The main focus of this review will be the diversity of functions of Rho GTPases and the effects of aberrant Rho GTPase signalling in various aspects of cancer"
3. Shaw 2006 "mice lacking RalGDS, PLC-e or Tiam1 showed reduced tumour incidence in Ras-dependent models of tumorigenesis72–74
4. Entrez-gene – "Loss or altered expression of this (RASSf1) gene has been associated with the pathogenesis of a variety of cancers, which suggests the tumor suppressor function of this gene"
5. Avruch 2009 "all Rassf proteins behave like tumor suppressors, exhibiting epigenetic silencing of expression in many human cancers and pro-apoptotic and/or anti-proliferative effects when re-expressed in tumor cell lines."
6. Van der Wyden 2007 - However, although Rassf proteins interact either directly or indirectly with activated Ras, their role in mediating its biological effects remains unclear. What is clear is that they seem to modulate some of the growth inhibitory responses mediated by Ras and may serve as tumour suppressor genes"
7. Pouysségur 2006 ERK - HIF