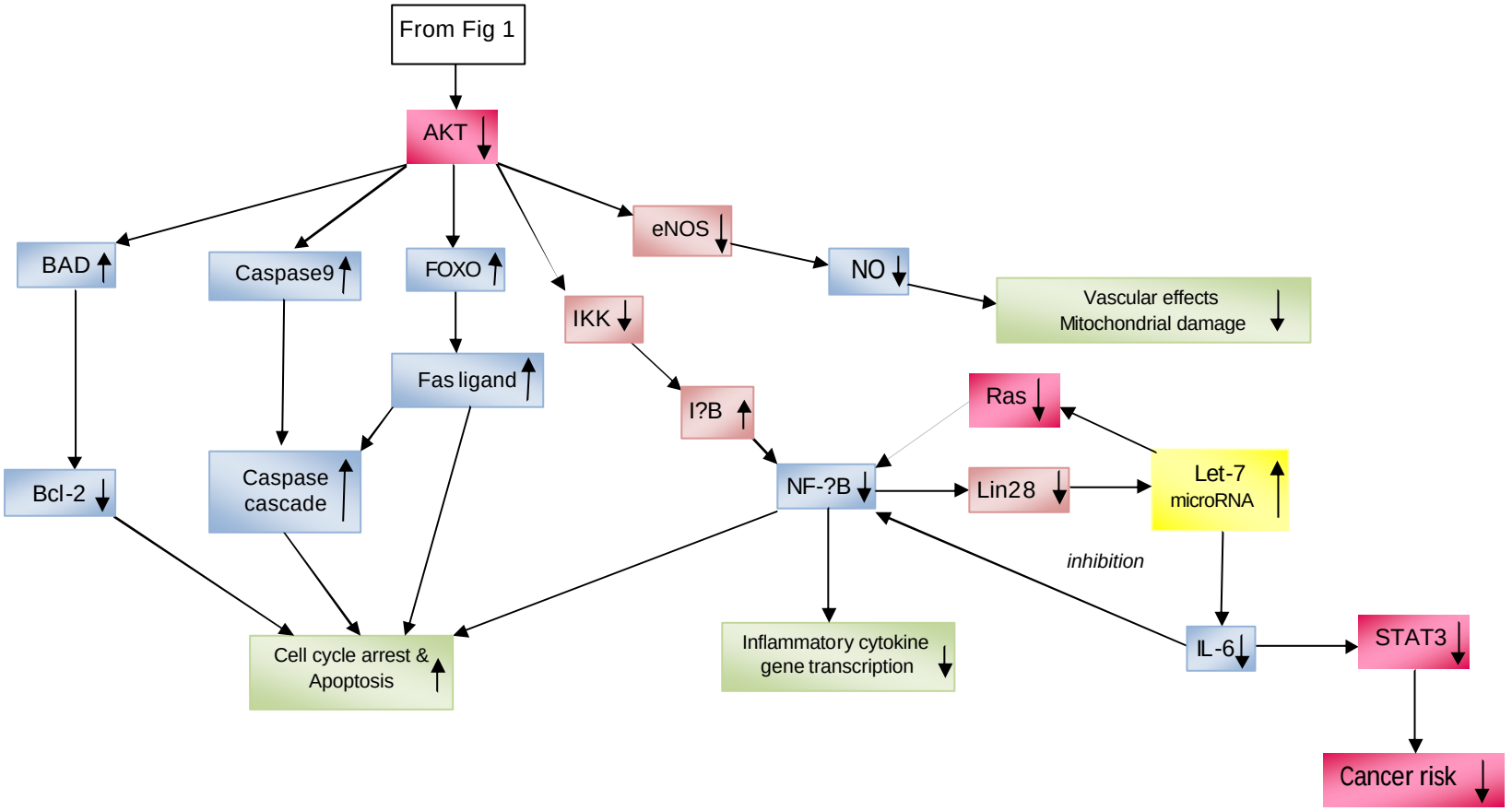
Fig 3 Proposed effects of metformin on AKT pathways



Legend

Abbreviations
AKT - serine/threonine protein kinase
BAD - Bcl-2-associated death promoter
Bcl-2 – b-cell lymphoma 2
eNOS – endothelial Nitric Oxide Synthase
FOXO - Forkhead family of transcription factors
IL-6 – Interleukin 6 - A cytokine derived from activated T lymphocytes that has many functions, including induction of B-cell growth; induction of B-cell differentiation and antibody production; induction of differentiation and proliferation of T cells; synergistic induction with IL-3 of hematopoietic cell growth; and induction of hepatocyte secretion of acute-phase inflammatory proteins
I?B - Inhibitor of ?B
I?K – I?B kinase
Let-7 microRNA - inhibits IL6 expression
Lin28 - microRNA inhibitor processing factor
NF-?B – nuclear factor kappa B
NO – Nitric Oxide
STAT3 – transcription 3 transcription factor

In red – activating oncogenic mutations

In yellow – inactivating tumour suppressor mutations

References (In text)

Cai 2005
Illiopoulis 2009
Maiese 2009
Ozes 1999
Roy 2010
Yap 2008

Maiese 2009 –"Akt is a primary mediator of phosphorylation of FoxO1, FoxO3a, and FoxO4 that can block activity of these proteins". "Activation of Akt is usually cytoprotective, such as during hyperglycemia,[23] hypoxia,[24] ß-amyloid (Aß) toxicity,[25] cardiomyopathy,[26] cellular aging,[27] and oxidative stress.[28 - 30] Akt can prevent cellular apoptosis through the phosphorylation of FoxO proteins."

Illiopoulis 2009 "NF-kappaB directly activates Lin28 transcription and rapidly reduces let-7 microRNA levels. Let-7 directly inhibits IL6 expression, resulting in higher levels of IL6 than achieved by NF-kappaB activation. IL6-mediated activation of the STAT3 transcription factor is necessary for

transformation, and IL6 activates NF-kappaB, thereby completing a positive feedback loop. This regulatory circuit operates in other cancer cells lines, and its transcriptional signature is found in human cancer tissues. Thus, inflammation activates a positive feedback loop that maintains the epigenetic transformed state for many generations in the absence of the inducing signal" (all reversed by metformin) "malignant transformation, cell motility, cancer cell growth, self-renewal of tumour initiating cells" (stem cells)

Cai 2005 – "NF-kappaB and transcriptional targets are activated in liver by obesity and high-fat diet" "lipid accumulation in the liver leads to subacute hepatic 'inflammation' through NF-kappaB activation and downstream cytokine production. This causes insulin resistance both locally in liver and systemically" (all reversed by metformin)

Roy 2010 – "inhibition of PI3K/AKT and ERK pathways acts together to activate FOXO transcription factor and enhances SFN-induced FOXO transcriptional activity, leading to cell cycle arrest and apoptosis"

Wikipedia – "Activation of the NF-?B is initiated by the signal-induced degradation of I?B proteins. This occurs primarily via activation of a kinase called the I?B kinase (IKK)."

Anfossi 2009 – see diagram – "insulin increases expression of eNOS and NO synthesis via the IRS/PI3-K/Akt pathway". ((See different pathways and effects of NO)).

Wang 2009 – "Inhibition of PI3K-Akt pathway using wortmannin certainly inhibited insulin-stimulated NO production (Fig. 3E).

Martinez-Outshoorn 2010 "cancer cells use "oxidative stress" in adjacent fibroblasts (i) as an "engine" to fuel their own survival via the stromal production of nutrients and (ii) to drive their own mutagenic evolution towards a more aggressive phenotype, by promoting genomic instability. We also present evidence that the "field effect" in cancer biology could also be related to the stromal production of ROS and NO species. eNOS-expressing fibroblasts have the ability to downregulate Cav-1 and induce mitochondrial dysfunction in adjacent fibroblasts that do not express eNOS"

Ozes 1999 "Akt mediates IKKa phosphorylation at threonine 23. Mutation of this amino acid blocks phosphorylation by Akt or TNF and activation of NF-?B. These findings indicate that Akt is part of a signalling pathway that is necessary for inducing key immune and inflammatory responses"