

M003 Functions of p53 in metabolism and invasion
**Karim Bensaad, Patricia Muller, Eric Cheung,
Pat Caswell, Wendy Lambie, Owen Sansom,
Eyal Gottlieb, Jim Norman and Karen H Vousden**

*The Beatson Institute for Cancer Research, Garscube Estate,
Switchback Road, Bearsden, Glasgow G61 1BD*

The p53 protein can function as a tumour suppressor through the activation of a number of different cell responses, including cell cycle arrest, senescence and apoptosis. While each of these responses can result in the elimination of nascent tumour cells, recent evidence has suggested that under conditions of low or transient stress, p53 can also contribute to the prevention or repair of damage. p53 can transcriptionally activate the expression of a number of genes that encode proteins with antioxidant activities, which function to lower intracellular ROS levels and help protect the cell from ROS-associated apoptosis and autophagy. One of these proteins, named TIGAR, shows similarity to the bisphosphatase domain of the bifunctional enzyme PFK-2/FBPase, which is one of the principal regulators of glycolysis. Expression of TIGAR can drive the pentose phosphate pathway, resulting in enhanced NADPH production and so restoring reduced glutathione levels. However, the ability of TIGAR to modulate metabolic pathways would be predicted to have additional effects that could be important for the anti-apoptotic and repair functions of p53, but that might also contribute to tumor cell growth and survival if not tightly regulated. Interestingly, preliminary studies in colon cancers have revealed an over-expression of TIGAR (regardless of p53 status) in a significant proportion of cancer and metastases compared to normal tissue.

Almost all human cancers show loss of normal p53 function. In about half of these cases this is due to point mutations within the DNA binding domain of p53, giving rise to the expression of proteins that have lost the capacity to regulate transcription. Interestingly, expression of these mutant forms of p53 have been associated with increased metastasis in tumour models, compared to cancer that arise following loss of p53 expression. By Investigating the mechanism by which mutant p53 affects the motility and invasion of cancer cells, we have revealed a novel cellular pathway involved in mutant p53-mediated invasion.