

## A role for p53 in metabolic adaptation and survival

### Abstract

The p53 protein is an important tumor suppressor that functions in a number of ways to prevent cancer development. p53 can promote growth inhibitory activities such as cell death and senescence that reflect the ability of p53 to control the expression of genes like *p21* and *PUMA*. Accordingly, in established cancer models, where cells are likely to be exposed multiple stress signals, the reactivation of p53 has been shown to result in tumor regression.

However, the activation of p53 in response to fluctuations in nutrient availability can help to promote cell survival and adaptation to these types of metabolic stress. In this context, we have recently found that p53 expression can help cells survive serine starvation.

Serine starvation induces *de novo* serine synthesis by up-regulating the expression of enzymes in the serine synthesis pathway, causing the diversion of glycolytic intermediates and disruption of glycolysis. Interestingly, p53 is not necessary for the activation of the serine synthesis pathway, but seems to be required to allow cells to undergo this metabolic adaptation.

Under these conditions, therefore, loss of p53 may impede, rather than promote, malignant progression. We have also been investigating the activities of TIGAR, a p53-inducible protein that functions to protect cells from cell death. TIGAR can act as a fructose-2,6-bisphosphatase, driving the pentose phosphate pathway (PPP), promoting NADPH production to restore reduced glutathione and protecting the cell from ROS-associated apoptosis and autophagy.

We have also found that TIGAR functions under conditions of hypoxia to limit mitochondrial ROS through mechanisms that are independent of its fructose-2,6-bisphosphatase activity. TIGAR therefore belongs to a group of p53-target genes that mediate survival responses, and may therefore also contribute to cancer development.

To investigate these potential roles of TIGAR *in vivo*, we have generated a TIGAR null mouse and are now investigating the potential role of TIGAR in supporting rapid cell proliferation under conditions of tissue repair or malignant development.