EMBO PLENARY LECTURE

The role of p53 in metabolic adaptation and survival

Oliver Maddocks, Celia Berkers, Eric Cheung and Karen Vousden

The Beatson Institute for Cancer Research, Glasgow, UK

The p53 protein is an important tumor suppressor that functions in a number of ways to prevent cancer development, including an ability to promote cell survival and modulate metabolism. 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. 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. Recent studies have shown that TIGAR also functions under conditions of hypoxia to limit mitochondrial ROS through mechanisms that are independent of its fructose-2,6-bisphosphatase activity. We have generated a TIGAR null mouse and are now investigating the potential role of TIGAR in malignant development.