HEIDELBERG, 13 May 2014 – More than 60 years ago **Otto Warburg** recognized that **cancer cells** differ from normal cells in the **metabolic pathway** they use for the **oxidation of sugar**. Rather than the typical series of oxidative steps that take place in the citric acid cycle, cancer cells metabolize sugar via the glycolytic pathway irrespective of whether oxygen is present or not. In The EMBO Journal, researchers in the United States report that the reason for this difference in colon cancer is changes in the Wnt signaling pathway, an essential communication pathway operating in these tumours.

“Cancer cells have different metabolic demands than normal cells,” remarked Marian Waterman, Professor at the University of California, Irvine and the lead author of the study. “However, until now the molecular evidence for how this metabolic reprogramming takes place in cancers of the colon has not been very well defined. Our results show that Wnt signaling plays an important role in establishing aerobic glycolysis as the predominant sugar-metabolizing pathway to support colon cancer. We have also been able to identify one of the key molecular targets for the Wnt signal in cancer cells.”

Wnt signaling has been implicated for some time in the development of many cancers, including colon cancer. However, these effects have been attributed to its action on the cell cycle. The researchers decided to investigate if Wnt had another role in cancer, specifically on metabolism, due to their observations of changes to the genes of metabolic enzymes in microarray experiments for colon cancer cells.

Biochemical assays and advanced imaging techniques in live cells revealed that blocking the activity of Wnt reduced glycolysis, promoted a shift to sugar metabolism by the citric acid cycle, and reduced tumour growth. The researchers also identified the enzyme pyruvate dehydrogenase kinase 1 as one of the targets for Wnt activity related to its effects on metabolism.

“In addition to reducing the size of tumours, blocking Wnt in the colon cancer cells reduced the number of blood vessels feeding the tumour. These effects could be reversed by restoring the activity of glycolysis-promoting pyruvate dehydrogenase kinase 1 in the cancer cells,” said Waterman. “Our findings illustrate that glycolysis in the cancer cells promotes blood vessel development in the nearby environment for glucose delivery to the growing tumour.”

The findings of the study have implications for the development of cancer therapies targeting the Wnt pathway. The choice of system or assay used to study the effects of Wnt inhibitors can make a big difference to drug testing. “Just because a Wnt inhibitor or potential drug candidate

shows no effect on cell division in one molecular test does not mean that it might not have beneficial effects for cancer treatment due to its impact on metabolism in another test," said Waterman.

"Although more work is needed to define the complete effects of Wnt signaling on metabolism, it appears that this mechanism can be added to the growing list of signal transduction pathways that directly contribute to the regulation of cellular metabolism," said Craig Thompson, professor at the Memorial Sloan Kettering Cancer Center in the United States who is not an author of the paper.

Wnt signaling directs a metabolic program of glycolysis and angiogenesis in colon cancer

Kira T. Pate, Chiara Stringari, Stephanie Sprowl Tanio, Kehui Wang, Tara TeSlaa, Nate P. Hoverter, Miriam M. McQuade, Chad Garner, Michelle A. Digman, Michael A. Teitell, Robert A. Edwards, Enrico Gratton, Marian L. Waterman