Decreased FOXO3 within advanced human colon cancer: implications of tumour suppressor function

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The FOXO family of transcription factors controls diverse cellular functions, including suppression of tumour growth in numerous tissues (Myatt and Lam, 2007). In the last decade, researchers extensively studied the role of FOXO3 in colonic cancer cell lines, yet its role in suppressing colonic cancer in human tissue remained unclear. In a current study, Bullock *et al* (2013) demonstrated a decreased expression of FOXO3 in a considerable number of human colon cancer tissues, associated with advanced pathology, recurrence, and poor survival. This novel finding demonstrates the possible role of FOXO3 as a tumour suppressor in human colon cancer and establishes FOXO3 as a new biomarker in evaluating pathobiology within colonic cancer.

Uncontrolled proliferation of transformed cells, a hallmark of colon cancer progression, is associated with the activation of growth factor receptors, activation of cellular proliferative pathways, and loss of cell cycle arrest in cancer cells. Both (a) increased expression and activation of epidermal growth factor receptors and (b) activation of proliferative signalling phosphatidylinositol 3-kinase pathway have been found in human colon cancer tissue. As previously shown, both events lead to a loss of FOXO3 in colonic cancer cell lines (Kops *et al*, 1999; Qi *et al*, 2011a), providing a reason to believe their activation decreases FOXO3 found in human colonic cancer tissue. Moreover, as downstream active FOXO3 regulates factors responsible for cell cycle arrest (Medema *et al*, 2000), decreased FOXO3 within affected human tissues would lead to stimulated proliferation in colonic cancer cells. Consequently, in proliferative colonic cancer cells, decreased FOXO3 might be a phenotype critical in promoting cancer. In addition, recurrence and poor survival in colon cancer patients have been associated with mutations and impaired function of the p53 transcription factor, which interacts with FOXO3. FOXO3 interaction with wild-type p53 is critical in eliminating cells with mutations (Chung *et al*, 2012), while interaction with mutated p53 promotes cell cycle arrest, attenuating proliferation

in colon cancer cells (Qi *et al*, 2011b). Therefore, impaired p53 function, dependent on a decrease in FOXO3, could promote survival and proliferation of cells harbouring mutations. Based on this combined knowledge, decreased FOXO3 in human colon cancer tissue could, in part, be responsible for uncontrolled proliferation and recurrence.

Colon cancer progression, including recurrence and metastasis, is also supported by a microenvironment enriched with inflammatory mediators and oxidative stress. As FOXO3 negatively controls inflammation, its deficiency leads to increased chemokine in immune cells as well as in colonic cells (Lin *et al*, 2004; Snoeks *et al*, 2009). Therefore, lowered FOXO3 in human colonic cancer tissue would lead to an immune environment that further fosters cancer cell growth and metastasis. Moreover, oxidative stress leading to chronic inflammation also supports colon cancer progression. In a reciprocal fashion, during cancer progression, recruited inflammatory cells further promote oxidative stress, thus enhancing proliferation, survival, and migration of cancer cells. As active FOXO3 has been found to negatively regulate oxidative stress (Kops *et al*, 2002; Nemoto and Finkel, 2002), ultimately, a decrease in FOXO3 within human colonic cancer tissue would lead to a microenvironment that supports proliferation, survival, and migration of colon cancer cells.

In colon cancer progression, the sustained growth of cancer cells requires high metabolic energy. As shown recently, human colon cancer tissue has an abundance of lipid droplets, a viable source of intracellular metabolic energy (Straub *et al*, 2010). As FOXO3 negatively regulates lipid droplet density in colonic cancer cells (Qi *et al*, 2013), decreased FOXO3 in human colon cancer tissue would increase lipid droplet density and the availability of metabolic energy necessary to sustain colon cancer growth. Additionally, FOXO3 controls Sirtuin6, a negative regulator of lipid metabolism (Kim *et al*, 2011) recently found to act as a tumour suppressor (Sebastian *et al*, 2012). Hence, further understanding of this newly

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identified function of FOXO3 as a regulator of intracellular metabolic energy in colon cancer progression is necessary.

Bullock *et al*'s (2013) findings indicate the existence of FOXO3's tumour suppressor function in human colon cancer, providing the opportunity to establish FOXO3 as a new biomarker and stimulate FOXO3 activity as a novel pharmacological approach in treating colon cancer.

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