EPD/22/13 - Establishing The Therapeutic Potential Of Inhibiting IKKβ In Colorectal Cancers.

Bowel cancer is a major worldwide health problem and the 2nd most common cause of cancer-related death. Approximately 60% of patients will survive 5 years beyond their diagnosis, however this drops to around 10% in patients who are diagnosed with advanced disease. Current treatment involves surgery to remove the tumour coupled with either chemotherapy, where drugs are used to kill the cancer cells, in the case of colon cancer; or in the case of rectal cancer, chemoradiotherapy, where either drugs and/or radiation is used to kill the cancer cells.

We now know that the make-up of each individual patient's tumour can be very different and new therapies which target specific proteins driving tumour growth need to be developed to improve patient survival. One such protein, IKKα, could be a good therapeutic target for a subgroup of colorectal cancer (CRC) patients. IKKα is involved in cell signalling and switches on a protein known as NF-κB. When the NF-κB pathway is turned on, tumours are thought to grow more aggressively, and the tumour is also thought to be able to change its immediate environment – known as the tumour microenvironment – and prevent the body's immune cells from attacking the tumour.

There are two arms to the NF-κB pathway known as canonical and non-canonical signalling. Most research so far has focused on canonical signalling but turning this pathway off was not successful in the clinic due to unwanted side effects. The IKKα protein is mainly known for its role in non-canonical NF-κB signalling, however new evidence suggests a role in the canonical pathway. Data from our lab observed that patients with high levels of the IKKα protein in their tumour tissue had poor prognosis and this effect was worse in tumours located in the right side of their colon.

This project will further explore which patients would benefit from new drugs which target the IKKα protein. To do this, we will stain CRC tumour tissue, that have been removed from patients by surgery, for IKKα using a technique called multiplex immunohistochemistry (mIF). We will examine levels of IKKα protein expression in these tumours and relate this to how the patient's immune cells interact with tumours which show either low or high IKKα protein expression. We will then correlate this to the clinical characteristics of these patients. This will help identify which patients would most likely benefit from treatment that blocks the IKKα protein.

This project will also, for the first time, study how effective new drugs that inhibit IKKα are by using sophisticated human cell models, which replicate the characteristics of the tumour. We will test these new IKKα drugs in combination with either chemotherapy or radiation, using our human cell models, to determine how effective these drugs will be in treating either colon or rectal cancer. We therefore hope to assess drug/therapy combinations in a highly representative model of CRC which also captures patient to patient variability. The overall aim of this project is to gather the necessary evidence which would support early phase clinical trials examining the use of drugs that block IKKα in treating colorectal cancer.