Discovery of mechanisms predicting response to new treatments in colon cancer

May 20 2012

The Stem Cells and Cancer Research Group headed by Dr Héctor G. Palmer at the Vall d'Hebrón Institute of Oncology (VHIO) has identified the molecular mechanisms that determine patients' response to certain drugs used in clinical trials for colon cancer treatment. The study led by VHIO also benefited from the collaboration with Professor Alberto Muñoz´s laboratory at the Instituto de Investigaciones Biomedicas Alberto Sols, Consejo Superior de Investigaciones Científicas (IIB-CSIC-Madrid). Published today in *Nature Medicine*, this work identifies biomarkers that predict response to treatment and proposes therapeutic solutions for patients who do not respond well. These advances will guide better selection of treatments and avoid the risk of administering ineffective drugs.

Colon cancer is a disease caused by a malignant tumour in the large intestine. When detected early the tumor is removed through surgery and patients are treated with adjuvant chemotherapy, eliminating the disease in the majority of cases. However, in advanced stages, colon tumours are resistant to a broad spectrum of anti-tumour drugs and cancerous cells escape treatment and disseminate around the body, giving rise to metastasis. Currently there are no effective treatments to halt the progression of colon cancer in these later stages and most patients die as a result of disease progression.

Over recent years new drugs have been designed to target and block the activity of certain molecules responsible for promoting tumor growth and metastasis. Some of these, which are currently in clinical trials, are

showing promising results in certain patients, while others show no improvement at all. This study headed by the VHIO examines the differential response to treatment and was supported by the Olga Torres Foundation (FOT), the Scientific Foundation of the Spanish Association Against Cancer (AECC), and the Carlos III Institute of Health (ISCIII).

New clinical horizons

Dr Héctor G. Palmer´s team has described for the first time the molecular mechanisms through which the interaction between the oncogenic pathways of Wnt/beta-catenin and RAS/PI3K/AKT determines the response to treatments with pharmacological PI3K or AKT inhibitors. Although both pathways are genetically altered in colon cancer, it is the over-accumulation of beta-catenin in the nucleus of cancer cells that makes them resistant to cell death induced by these anti-tumoral drugs.

Activation of the PI3K/AKT pathway retains the FOXO3a protein outside the cell nucleus, inhibiting its ability to act as a tumour suppressor that induces cell death. Therefore, "Targeting PI3K or AKT activity with these novel inhibitors allows relocation of FOXO3a in the nucleus promoting cell death. These drugs are being tested in clinical trials worldwide providing promising initial results in certain tumour types", explains Héctor G. Palmer, Head of VHIO´s Stem Cells and Cancer Group.

However, many colon cancer patients do not show any benefit. The reason for this is explained by Dr Palmer: "If the patients treated with these inhibitors show very high levels of nuclear beta-catenin, FOXO3a cannot induce cell death but promotes the opposite effect by escaping treatment and causing metastasis." According to Héctor Palmer, this finding has tremendous clinical value, since "the identification of nuclear beta-catenin as a biomarker to predict response guides the

selection of patients who will benefit from treatment with PI3K or AKT inhibitors and discard their use in candidates who would provoke an adverse response."

Furthermore, Dr Héctor Palmer and his collaborators have discovered a solution for those patients for whom treatment with PI3K or AKT inhibitors would be contraindicated. They used an experimental drug that reduces the levels of nuclear beta-catenin, allowing the cell death induced PI3K or AKT inhibitors. These findings propose the combination of both types of inhibitors in the future for a more effective target-directed therapy in colon cancer.

Delivering on the promise of personalized medicine

VHIO pioneers pre-clinical functional studies and clinical trials in the fight against cancer. Importantly, Dr. Palmer´s team has developed in vivo models that accurately recapitulate disease progression in colon cancer patients. They inoculate the animals with cells derived from the patient's tumour, creating a "xenopatient" model. These cells regenerate the the disease in the animals with the same distinctive characteristics as in the individual patient, retaining its original genetic, clinical and pathological alterations. The xenopatients represent a parallel reality of each patient in the laboratory. This approach allows the study of disease progression and response to experimental medicines before subjecting the patient to new treatments. This model could soon form the basis of future functional, predictive and personalized cancer treatments.

Provided by Vall d´Hebron Institute of Oncology