MedicalXpress

# Research in mice identifies new treatment options for bowel cancer

July 8 2013

Researchers have discovered the genetic processes that cause specific types of bowel cancer. Using this knowledge, they identified cancer drugs that target these genes. Their findings offer the opportunity to develop personalised treatment based on a person's genetic profile.

More than one million people develop bowel cancer each year, which is one of the most common causes of death in cancer patients. One in ten colon cancers are caused by mutations in the BRAF gene, a gene commonly associated with skin cancers. Although successful treatments against BRAF mutations in skin cancers have been developed, these treatments have not been effective against BRAF mutations in colon cancer.

"Our approach encapsulates the aim of cancer genomics: to discover changes to DNA responsible for cancer development and pinpoint the "Achilles heels" of cancer in order to identify new treatments," says Professor Roland Rad, lead author from the Technical University of Munich and the German Cancer Research Center. "Our studies in mice revealed how genes co-operate to cause a specific subset of colon cancers. We identified main players, the order in which they occur during tumour progression, and the molecular processes how they turn relatively benign cell growth into threatening cancers. Such processes are targets for new treatments."

The team looked at the development of BRAF associated bowel cancer in mice, replacing the normal gene with a version containing a mutation

identical with that in human cancers. Mice with the mutated BRAF gene developed hyperplastic polyps – abnormal growth of cell bundles in their intestine wall. These polyps progressed from benign growths to malignant cancers.

In the mutant mice, the team uncovered a stepwise process of genetic alterations, which drive the development of this type of colon cancer. Some alterations activate genes such a BRAF, making them potentially cancerous. Others disrupt protective proteins such as p53, inactivating their ability to suppress cancer progression.

"Understanding the genetic makeup of different colorectal cancer subtypes will guide therapeutic decision making in the future" says Professor Allan Bradley, senior author from the Wellcome Trust Sanger Institute. "Our ability to engineer specific genetic alterations in mice allows us to study the function of cancer genes and to model specific cancer subtypes at an organismal level. Such mouse models are also invaluable for testing anticancer drugs before using them in clinical trials".

The team tested a wide range of existing and candidate drugs for their ability to slow down or prevent growth of mouse colon cancer and human colon cancer cells, finding several highly effective approaches. These were tested individually or in combination with one another to find the most powerful therapies.

Mice with the Braf-associated colon cancer had very similar therapeutic responses to those of BRAF-associated cancer cells from patients with colon cancer, highlighting the effectiveness of mice in preclinical cancer research.

The team found multiple drugs and drug combinations that were effective against human colon cancer cells. These are promising results

for alternative second- or third-line treatments after resistance to the first round of treatment against this occurs.

"Our results illustrate the power of combining genomic information with large-scale drug screening to provide new targeted treatment strategies for patients with specific cancer subtypes," says Dr Ultan McDermott, author from the Wellcome Trust Sanger Institute.

**More information:** Roland Rad, Juan Cadiñanos, Lena Rad, et al (2013). 'A genetic progression model of BrafV600E-induced intestinal tumourigenesis reveals targets for therapeutic intervention' Advanced online publication in *Cancer Cell*, 08 June 2013. DOI: 10.1016/j.ccr.2013.05.014

Provided by Wellcome Trust Sanger Institute