Researchers at the Buck Institute (CA, USA) have discovered a potential method to increase the speed of the drug-discovery process for Huntington’s disease (HD). Using RNAi technology they have identified hundreds of molecular targets that could be modified through the use of drug treatments, and which are associated with toxicity caused by the devastating genetic condition.

HD is an incurable, progressive, neurodegenerative disease that affects approximately 30,000 people in North America, with another 150,000 at risk. The disease is devastating and affects motor coordination, leading to severe physical and cognitive decline. The condition is caused by the build up of a toxic protein which results in neuronal cell death and systemic dysfunction. This disease pathology is the direct result of a mutation in the \textit{HTT} gene.

Using technology that silences specific genes, the research team screened over 7800 genes that were believed to be potential drug targets, with the aim of establishing which were modifiers of HD toxicity in humans. Although a wide range of modifiers were found, the study showed that a gene involved in neuronal development and cell motility, RRAS, had a marked effect on HD toxicity in cell models.

“Our data indicate that the pathogenic effects of the \textit{HTT} mutation on this pathway can be corrected at multiple intervention points and that pharmacological manipulation of RRAS signaling may confer therapeutic benefit in HD,” said Robert E Hughes, Baylor College of Medicine (TX, USA).

Work on the RRAS pathway is being followed-up both in the Hughes laboratory and the laboratory of Buck faculty member Lisa Ellerby.

Hughes said that the data, which will be available to the public, show that many of the molecular hits identified were validated in human cell, mouse cell and fruit fly models of HD.

“Our hope is that HD researchers will look at these targets and find modifiers relevant to the areas they already work on”, Hughes stated. “Ideally, pharmaceutical companies already working on some of these pathways could build on their current knowledge and expertise by focusing their attention on the challenge to develop therapies for HD.”

Mutation screening for **KRAS** and **BRAF** in metastatic colorectal cancer proves costly in relation to benefits

A new study published in *The Journal of the National Cancer Institute* shows that the cost of treatment for metastatic colorectal cancer can be reduced by screening for **KRAS** and **BRAF** mutations with a very small reduction in overall survival seen.

It is known that the presence of **KRAS** (and to a lesser extent **BRAF**) mutations in the tumors of metastatic colorectal cancer patients makes them less likely to respond to costly anti-EGFR therapies. In order to provide treatment only to those who will benefit, and prevent unnecessary costs and harm to those who will not, it is recommended that patients who are candidates for anti-EGFR therapies are screened for mutations of **KRAS** and **BRAF**. It is still unclear what impact this screening has in the real world.

Ajay Behl of the HealthPartners Research Foundation (MN, USA) and colleagues carried out a cost–effectiveness analysis taking into account the treatments, resection of metastases and survival for different kinds of metastases in order to evaluate the effects of mutation screening in terms of health outcomes, costs and value.

**“The researchers demonstrated a very high incremental cost:effectiveness ratio for screening, compared with no anti-EGFR therapy, which indicates that the intervention is very costly with regards to its benefits.”**

Four strategies of **KRAS** and **BRAF** mutation testing used to select treatments for metastatic colorectal cancer patients were compared using patient-level decision analytic simulation. These were: no anti-EGFR therapy (best supportive care); anti-EGFR therapy without screening; screening for **KRAS** mutations only (before providing anti-EGFR therapy); and screening for **KRAS** and **BRAF** mutations (before providing anti-EGFR therapy).

The researchers demonstrated a very high incremental cost:effectiveness ratio for screening, compared with no anti-EGFR therapy, which indicates that the intervention is very costly with regards to its benefits. Screening for **KRAS** mutations alone saved approximately US$7500 per patient compared with anti-EGFR therapy without screening; also, screening for **BRAF** mutations saved another US$1023, with little reduction in expected survival.

The authors state, “In general, our results are less supportive of the use of anti-EGFR therapy than previous analyses, and they indicate lower cost savings from **KRAS** testing than previously reported. Although we cannot confirm that anti-EGFR therapy is a cost-effective use of healthcare resources, we can affirm that **KRAS** testing is cost-saving. **BRAF** testing may offer additional savings.”

An editorial by Josh Carlson of the Department of Pharmacy, University of Washington (WA, USA) and Scott Ransney of the Division of Public Health Sciences Fred Hutchinson Cancer Research Center (WA, USA) highlighted two important points raised by the study. First, the purpose of molecular testing is to prevent unnecessary costs by identifying nonresponders, as well as improving survival by identifying responders. Second, it must also be taken into account when modeling treatments that community practice ‘is messy’. They say, “most importantly, this study of an unusually accurate test raises important issues that should be considered for other molecular tests in other settings.”

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**Lung tumor growth gene identified**

A gene involved in the growth and spread of non-small-cell lung cancer (NSCLC) tumors has been described by researchers at St Joseph’s Hospital and Medical Center (AZ, USA), the Translational Genomics Research Institute (AZ, USA) and other institutions. It is hoped this could pave the way for novel treatments for the disease.

“...while Fn14 overexpression promotes lung tumor formation and metastasis, its suppression reduces the metastasis of NSCLC tumors.”

The large majority of cases of lung cancer, which is the leading cause of cancer mortality worldwide, are NSCLCs. Frequently, NSCLC tumors have mutations in the **EGFR** gene and activation of this mutated gene results in tumor development and growth. Samples from lung cancer patients who had undergone tumor resection were analyzed by the researchers, who elucidated that many patients who had **EGFR** mutations also demonstrated above normal levels of the **Fn14** gene. It is the opinion of the researchers that **EGFR** activation can cause increased expression and activity of the **Fn14** gene.

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Discovery of drug resistance biomarker could improve cancer treatment

Genetic mutations that cause drug resistance often result in the benefit from cancer therapies being short-lived. A study published in Cell has determined a key gene causing resistance to a range of cancer drugs. This particular biomarker provides a possible strategy to treat drug-resistant tumors based on their genetic makeup by predicting which tumors will respond to cancer drugs.

It was also found that while Fn14 overexpression promotes lung tumor formation and metastasis, its suppression reduces the metastasis of NSCLC tumors.

“Other types of tumor, including glioblastoma and some breast cancers, also show elevated levels of the Fn14 gene. This could mean that Fn14 could be a therapeutic target in many cancers.”

Landon Inge, lead scientist in the thoracic oncology laboratory at St Joseph’s Center for Thoracic Disease and Transplantation, and member of the study research team stated that, “Our data suggest that Fn14 levels can contribute to NSCLC cell migration and invasion. Thus, tumor suppression through targeting of Fn14 may prove to be a therapeutic intervention in NSCLC and other tumor types.”

Other types of tumor, including glioblastoma and some breast cancers, also show elevated levels of the Fn14 gene. This could mean that Fn14 could be a therapeutic target in many cancers.


Senior study author René Bernards of The Netherlands Cancer Institute said, “We need to understand the mechanism of drug resistance to effectively prevent it from occurring in the first place. We have identified a mechanism of drug resistance that is caused by the activation of a specific signaling pathway in cancer cells.”

Patients with non-small-cell lung cancer, the most common type of lung cancer, who possess a certain type of tumor mutation, can be treated with the targeted therapy crizotinib. However, unknown genetic mechanisms frequently cause patients to develop drug resistance as a result of secondary mutations of the tumors.

To further investigate this effect a screening method to establish genes whose suppression causes resistance to crizotinib in non-small-cell lung cancer cells was developed by Bernards and his team. MED12, a gene that is mutated in cancers, was found to confer resistance to crizotinib when inhibited. This was also found to be true for targeted drugs used in the treatment of other cancers.

It was also found that the pathway by which suppression of MED12 caused drug resistance involved increased signaling through the TGF-β receptor, which plays a role in cell growth and cell death. Inhibition of this signaling in MED12-deficient cells restored drug responsiveness, the team showed. TGF-β receptor inhibitors, which are currently in clinical trials, may therefore possibly play a future role in the treatment of cancer patients with MED12 mutations.

Bernards stated, “We have shown that blocking this escape route restores sensitivity to the original drug, suggesting a way to treat patients that have undergone this type of drug resistance”.


About the News & Views
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