RNA regulator of melanoma could be a new target for cancer therapy

May 10 2012

Melanoma is the most deadly form of skin cancer, estimated by the National Cancer Institute to afflict more than 70,000 people in the United States annually and the incidence rate continues to rise. In a study published online in *Genome Research*, researchers have identified a previously unknown non-coding RNA that plays an important role in the biology of melanoma, a finding that could lead to a new target for therapy.

Most skin cancers are nonmelanomas, arising from cells other than melanocytes (the melanin-producing cells that are responsible for a suntan). Melanomas, skin cancers that arise from melanocytes, are less common but more dangerous because they can migrate deep into the skin to find blood and lymphatic vessels that help the tumor cells to grow and spread to other parts of the body.

Oncogenes are genes that have the potential to cause cancer, and are often mutated in tumor cells, including melanomas. Mutations in the oncogene BRAF are present in more than 70% of melanomas, and the vast majority of *BRAF* mutants are a single mutant form, $BRAF^{V600E}$. Inhibitors of $BRAF^{V600E}$ used in the clinic can induce tumor regression, but patients eventually relapse.

In order to better understand the biology of oncogenic *BRAF* and identify new targets for therapy, researchers are investigating the RNA world of cancer. RNAs are the messenger molecules that the cell primarily uses to transmit the information stored in the DNA sequence,

and translate it into functional proteins. However, about 50% of transcribed RNAs actually code for no proteins at all, but many RNAs may still have critical regulatory roles to play.

In this report, a team of researchers led by Drs. Ross Flockhart and Paul Khavari of the Stanford University School of Medicine has delved into the RNA world of $BRAF^{V600E}$ melanomas by sequencing and analyzing the RNA "transcriptome" of patient samples. They looked for RNA transcripts, including those that may never have been characterized before, that are rewired by $BRAF^{V600E}$ and may be relevant to melanoma.

"By digging deeper than ever before, we found more than 100 genes encoding long non-coding RNAs that are dramatically altered by $BRAF^{V600E}$," said Flockhart. Long non-coding RNAs (lncRNAs) are garnering significant interest, as these molecules have been implicated in diverse cellular functions, but the role of lncRNAs in cancer is not well understood. Of the lncRNAs altered by $BRAF^{V600E}$, Flockhart and colleagues homed in on a previously uncharacterized lncRNA gene that is recurrently and highly induced in melanomas, called *BANCR*. "Increased activation of the novel gene we discovered does not seem to be an isolated event," Flockhart noted. "It will be interesting to investigate if this is also the case in other cancers."

To test what role *BANCR* might be playing in melanoma, the team found that by turning off *BANCR* in the cancer cell by a technique called knockdown, the ability of the melanoma cells to migrate in a cell culture experiment was impaired. This indicates that *BANCR* is required for full migratory capacity in melanoma, and could be a potential target for therapy.

The authors explained that their work illustrates the power of RNA sequencing to study a cancer such as melanoma and identify a previously

unknown regulator of disease progression. As studies such as this paint a more complete picture of cancer biology, we will have a better understanding of how tumors evade drugs, and how previously unknown players such as *BANCR* could be new targets for treatment.

More information: Flockhart RJ, Webster DE, Qu K, Mascarenhas N, Kovalski J, Kretz M, Khavari PA. BRAFV600E remodels the melanocyte transcriptome and induces BANCR to regulate melanoma cell migration. *Genome Res* doi: 10.1101/gr.140061.112