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miR-21 joins the oncogene ranks

By Tim Fulmer, Senior Writer

Yale University researchers have reported that *microRNA-21* is an oncogene that drives the development—and maintenance—of hematological malignancies in mice.[1] The team now plans to antagonize the molecule to treat blood cancers and, potentially, solid tumors.

Previous tissue profiling studies have found that multiple tumor types abnormally overexpress *miR-21*, including hematological malignancies,[2,3] glioblastomas[4] and colorectal, lung, breast and pancreatic cancers.[5] The open question was if *miR-21* overexpression merely correlated with disease or if it was a true oncogene capable of triggering cancer and driving disease progression.

To answer that question, a group led by Frank Slack, professor of molecular, cellular and developmental biology at Yale, generated transgenic mice whose overexpression of *miR-21* could be modulated with doxycycline.

Signs of hematological malignancies developed in the mice about two months after doxycycline was withdrawn, which activated *miR-21* overexpression. By three months, the mice showed clear signs of lymphoma, with lymphadenopathy and rear limb paresis. By comparison, transgenic mice fed doxycycline, which blocked *miR-21* expression, showed no signs of lymphoma at three months ($p<0.0001$).

The spleens, thymuses and lymph nodes of the sick mice also had subpopulations of neoplastic cells, a development that is consistent with the precursor stages of B cell lymphoblastic lymphoma and leukemia.

After establishing that *miR-21* is necessary to trigger lymphoma, Slack's group went on to address the question of whether *miR-21* also is required to maintain established tumors.

Indeed, all mice with lymphoma recovered from lymphadenopathy within two to four days and from paresis within four to seven days after doxycycline was added to their meals. The recovered animals' spleens, lymph, bone marrow, livers, kidneys and blood were indistinguishable from those of both wild-type and healthy controls. The doxycycline-fed animals also survived significantly longer than mice with continued *miR-21* overexpression ($p<0.0001$).

"Our results reveal that miR-21 is a genuine oncogene and demonstrate the importance of miR-21 in haematological malignancies," wrote the researchers in a paper in *Nature*. Taking into account previous *in vitro* studies that found a potential role for *miR-21* in multiple cancer types, the authors concluded that their findings "support efforts to treat human cancers by inactivating miR-21."

"Based on cell culture studies, *miR-21* has been on the radar as a potential oncogenic miRNA for some time," said Andreas Bader, associate director research at **Mirna Therapeutics Inc.** Slack's paper provides the key *in vivo* data that "show the molecule has an oncogenic mechanism and is predominant enough to drive tumor development in the animal. Inhibiting *miR-21* might be a promising approach to treat many cancer types."

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> ***—Frank Slack, Yale University***

Mirna's lead compound is miR-34, a tumor suppressing miRNA that is in preclinical development to treat cancer. The company hopes to submit an IND in late 2011.

Slack, who is a scientific advisor to Mirna, agreed that targeting *miR-21* "might have broad relevance to many or all tumor types." His group initially will focus on hematological malignances because the team's mouse model rapidly develops that form of cancer.

"We plan to continue to use the paper's mouse model to test various therapeutic strategies such as antagomirs to see if we can show some therapeutic benefit," he told *SciBX*.

According to Slack, none of the *miR-21* findings published in *Nature* is patented. The mouse model is available for licensing "to parties seeking to test anti-*miR-21* therapies," he said.

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COMPANIES AND INSTITUTIONS MENTIONED

Mirna Therapeutics Inc., Austin, Texas
Yale University, New Haven, Conn.