Hitting Lefty

By Lev Osherovich, Senior Writer

A study published in the *Proceedings of the National Academy of Sciences* shows that human embryonic stem cell–derived transforming growth factor-β superfamily proteins can control tumor proliferation *in vitro* and *in vivo*. However, the development of therapeutics based on these morphogens remains a challenge given the potential for an array of immunological and developmental side effects.

The report, from a team led by Mary Hendrix, scientific director at **Northwestern University Children's Memorial Research Center**, identifies two transforming growth factor-β (TGF-β) relatives called Nodal and Lefty as key regulators of tumor growth.[1]

Nodal is expressed during embryogenesis and triggers a signaling cascade that promotes growth and tissue differentiation. Other embryo-specific proteins such as Lefty, a Nodal inhibitor, and Cripto, a co-receptor for Nodal, precisely control the timing and location of Nodal activity. The expression of Nodal, Lefty and Cripto tails off following the initial stages of embryogenesis.[2]

A previous study has already shown how expression of Nodal in melanoma cells contributes to tumor growth.[3] When secreted by tumor cells, Nodal indiscriminately stimulates proliferation through a positive-feedback loop. This leads to rapid growth and invasiveness of tumors, as well as embryo-like morphological changes in surrounding tissues.

In the new study, Hendrix's team asked whether the presence of embryonic factors in the microenvironment surrounding tumor cells could influence their growth and, more specifically, trump the proliferative effect of Nodal signaling.

The group grew melanoma and breast carcinoma cells on a synthetic matrix preconditioned by cultivating human embryonic stem (hES) cells on it. Both Nodal expression and tumor proliferation were lower than in cells grown on fresh matrix, suggesting the presence of an hES cell–derived tumor-inhibiting factor.

Using a combination of cell culture and mouse models, Hendrix's team homed in on Lefty as the major hES-derived Nodal antagonist. "Lefty released into the microenvironment can inhibit Nodal, decreasing proliferation and promoting apoptosis" of tumor cells, Hendrix told *SciBX*.

The findings present several therapeutic avenues for cancer companies, including agonizing Lefty or antagonizing Nodal or Cripto.

Jasbir Seerha, CSO at **Acceleron Pharma Inc.**, told *SciBX* that the finding that abnormal presence of Nodal in adult cells promotes tumor growth highlights the importance of precise regulation of morphogens. "When they are not tightly controlled, this leads to cancer," he said.

Acceleron is targeting morphogens in the TGF-β family to treat musculoskeletal and metabolic diseases and cancer. The company's ACE-011 targets activin, a negative regulator of bone growth that contributes to the overall balance of bone maintenance. In patients with multiple myeloma (MM) and other kinds of cancer, this process is deregulated, leading to bone loss.

ACE-011 is a fusion protein combining the activin-binding portion of activin receptor type 2a with soluble IgG. This approach results in a target-specific therapeutic of extended serum half-life. The fusion protein binds to activin before it can interact with its natural receptor, thereby decreasing bone resorption and increasing new bone growth.

ACE-011 is expected to start Phase IIa testing for bone loss in MM this year.[4]

One potential way to disrupt Nodal signaling in cancer is to block its interaction with surface receptors such as Cripto. Cripto is abundantly expressed in many tumor types and is already a molecular target for cancer therapies.

> **"There's been a growing awareness that the cells that surround the tumor are increasingly important in tumor therapeutics."**
> *—Dan Shawler, NovaRx Corp.*

Biogen Idec Inc.'s BIIB015 is an immunoconjugate developed in partnership with **ImmunoGen Inc.** to target Cripto-positive solid tumors. BIIB015 combines a Cripto mAb from Biogen Idec with ImmunoGen's tumor-activated prodrug DM4. Biogen Idec has filed an IND for a Phase I trial that is slated to begin this year.

Another therapeutic approach stemming from Hendrix's work would be to introduce synthetic Lefty protein into tumors.

"I really think [Lefty] is a good target," said Acceleron's Seerha. However, he predicted that it will prove a "technical challenge" to produce adequate amounts of biologically active protein.

Indeed, Hendrix's team has already found that recombinant Lefty is not as effective at blocking tumor proliferation as hES-derived protein, suggesting a need for additional hES-associated factors or for modifications such as glycosylation.

Hendrix told *SciBX* her group is now focusing on how to make active synthetic Lefty.

Overall, relatively few companies are pursuing direct modulation of TGF-β superfamily proteins as a therapeutic strategy for cancer. The main reason is the complex biology of TGF-β signaling between tumors and their neighboring noncancerous cells.[5]

"There's been a growing awareness that the cells that surround the tumor are increasingly important in tumor therapeutics," said Dan Shawler, VP of operations at **NovaRx Corp.** Thus, the wide-ranging effects of TGF-β-related proteins "frighten off companies interested in clinical work."

For example, in addition to promoting tumor growth, TGF-β proteins secreted by cancer cells can modulate the activity of immune

cells such as macrophages. Such complex interplays require a cautious approach in developing TGF-β-based cancer therapeutics, according to Shawler.

Oncoantigen escape is another concern about therapeutics aimed directly at tumor-associated extracellular proteins, Shawler told *SciBX*. This process, during which tumor cells mutate and no longer need proliferative factors such as Nodal, results in resistance to the corresponding therapeutics.

Shawler said the Hendrix study had "the right approach by looking at the microenvironment." However, he added that further animal experiments are needed to resolve whether Lefty itself or Lefty agonists would make promising therapeutics.

NovaRx is developing a cancer vaccine that eliminates the immunosuppressive cloak around tumor cells caused by TGF-β signaling. The company's Lucanix allogeneic vaccine consists of four attenuated non–small cell lung cancer (NSCLC) cell lines carrying antisense oligonucleotides against TGF-β2 and is slated to enter Phase III trials for NSCLC in 2008.

Hendrix, together with co-inventors at Children's Memorial Research Center, has filed international patent applications on the use of hES cell–derived proteins to treat cancer and is interested in negotiating with companies to license the technology.

REFERENCES

1. Postovit, L.-M. *et al. Proc. Natl. Acad. Sci. USA*; published online March 2, 2008; doi:10.1073/pnas.0800467105
   Contact: Mary J.C. Hendrix, Children's Memorial Research Center, Northwestern University, Ill.
   e-mail: mjchendrix@childrensmemorial.org
2. Tabibzadeh, S. & Hemmati-Brivanlou, A. *Stem Cells* **24**, 1998–2006 (2006)
3. Topczewska, J.M. *et al. Nat. Med.* **12**, 925–932 (2006)
4. Flannagan, M. *BioCentury* **16**(9), A10; Feb. 25, 2008
5. Mishra, L. *et al. Science* **310**, 68–71 (2005)

COMPANIES AND INSTITUTIONS MENTIONED

Acceleron Pharma Inc., Cambridge, Mass.
Biogen Idec Inc. (NASDAQ:BIIB), Cambridge, Mass.
ImmunoGen Inc. (NASDAQ:IMGN), Cambridge, Mass.
Northwestern University Children's Memorial Research Center, Chicago, Ill.
NovaRx Corp., San Diego, Calif.