Putting cancer in a PINCH

By Lauren Martz, Staff Writer

Although a combination of chemotherapy, radiation and surgery is one of the most widely adopted approaches to treating solid tumors, high resistance rates to chemotherapy and radiation therapy have spurred the search for ways to improve outcomes. Now, German researchers have found a way to increase the effects of both modalities by blocking PINCH1, a protein that is upregulated in cancer cells and is involved in their interaction with the surrounding extracellular matrix.¹ Whether PINCH1 itself or one of its downstream effectors is the best target will need to be elucidated next.

Interactions between cancer cells and their extracellular matrix, including adhesion and communication, are mediated by focal adhesions, which are multiprotein structures that can include integrins, growth factor receptors, cytoplasmic signaling molecules and adaptor molecules.

Besides their biomechanical function and role in sensing the cell microenvironment, focal adhesions also contribute to the survival of tumor cells by reducing their sensitivity to radiation or chemotherapy.²

Because they are large and heterogeneous, focal adhesions themselves are poor drug targets. Thus, a team at the **Dresden University of Technology** set out to determine whether molecules involved in regulating focal adhesion function might be better targets.

The team, led by Nils Cordes, team leader of the biological and molecular targeting group at the university's Center for Radiation Research in Oncology (OncoRay), chose to focus on PINCH1 (LIM and senescent cell antigen-like domains 1; LIMS1). This adaptor protein is known to be essential to focal adhesion regulation and to promote cell survival, spreading, adhesion and migration, albeit by unknown mechanisms.³

In a paper published in *The Journal of Clinical Investigation*, the team reported that *PINCH1* mRNA expression was higher in lung, colon, breast and prostate cancers than in normal tissues. PINCH1 levels were also higher in colorectal carcinoma biopsies than in normal colon tissue.

Cultured *Pinch1*^{-/-} mouse embryonic fibroblasts had greater sensitivity to radiation than *Pinch1*-expressing cells. Fibroblasts lacking *Pinch1* were also more sensitive to cisplatin.

Those results carried over to both human cell lines and to mouse models of cancer. In animals with *Pinch1*^{-/-} tumors, as compared to animals with *Pinch1*-expressing tumors, radiotherapy produced better reductions

in tumor volume. Similarly, small interfering RNA-mediated *PINCH1* knockdown increased the sensitivity of human colon, lung, cervix, skin and pancreatic cancer cell lines to either radiation or the chemotherapeutics 5-fluorouracil (5-FU) and Gemzar gemcitabine.

Eli Lilly and Co. markets Gemzar to treat multiple cancers; 5-FU is a generic.

The Cordes group also teased out the mechanism by which PINCH1 increases tumor resistance: PINCH1 directly binds to and inhibits protein phosphatase 1 catalytic subunit α -isoform (PPP1CA; PP-1A), a protein responsible for regulating protein kinase B (PKB; Akt).

Akt can promote tumor resistance and progression.

In addition to researchers from Dresden University of Technology, the team included researchers from the **Max Planck Institute** and **Cancer Research UK**.

Point of intervention

As an adaptor protein, PINCH1 is capable of mediating protein-protein interactions between signaling molecules. But its drawback as a target is it lacks any enzymatic activity of its own.

"Therapeutic approaches blocking PINCH1 could be difficult to develop because the protein lacks catalytic activity. Without catalytic activity, it is unclear how to block PINCH1," said Ellen Van Obberghen-Schilling, group leader of the Institute of Developmental Biology and Cancer at the **Centre National de la Recherche Scientifique** (CNRS).

"There are two pharmacological possibilities: the inhibition of PINCH1 expression, for example by siRNA, or the inhibition of the

protein-protein interactions" between PINCH1 and PP-1A, said Joachim Fensterle, director of discovery and preclinical development at **Aeterna Zentaris Inc.**

However, Michael Teifel, senior director and head of preclinical development at Aeterna Zentaris, added that "targeting PINCH1 expression faces all current obstacles of siRNA therapies, including efficient delivery to achieve sustained expression. And targeting protein-protein interactions is still considered a demanding task."

Aeterna Zentaris' Perifosine, an alkylphosphocholine modulator of phosphoinositide 3-kinase (PI3K) and Akt, is in Phase III testing to treat colon cancer and multiple myeloma (MM).

Obberghen-Schilling said the next steps toward the development of tumor-specific protein-protein interaction inhibitors should be "to define the molecular structure of the protein-protein interface" between PINCH1 and PP-1A. She also noted that "PINCH1 interacts with other proteins as well, so it will be important to determine whether targeting this interaction has an effect on those interactions as well, for example its interactions involved in fibronectin matrix assembly."

Mary Lou Cutler, professor of pathology and director of the Molecular and Cell Biology Graduate Program at the **Uniformed Services University of the Health Sciences**, suggested a different route of attack—PP-1A

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—Ellen Van Obberghen-Schilling,
Centre National de la
Recherche Scientifique

itself. “The identification of PP-1A, a druggable target, provides another potential inhibitory point in the pathway,” she said.

Tumor targeting

Although the *JCI* paper described overexpression of PINCH1 in various tumors, researchers contacted by *SciBX* were concerned that inhibiting its activity could lead to side effects because of the protein’s involvement in survival of noncancerous cells.

“PINCH1 is ubiquitously expressed and involved in many developmental processes, including neuronal survival and neuronal signaling transmission,” Fensterle noted. “Constitutive *Pinch1* knockout in mice leads to early embryonic lethality,” although it’s unknown what happens to adult mice with the target conditionally knocked out.

According to Obberghen-Schilling, the key for any PINCH1 modulator “will be to target the overexpression and not just the protein itself. It will be important to know in which cell populations within the tumor microenvironment PINCH1 is overexpressed.”

The authors of the *JCI* article did not respond to interview requests.

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