MOLECULAR BIOLOGY

A New Blocker for the TGF-β Pathway

Two proteins, Ski and Sno, are plucked from obscurity and revealed as regulators of a key growth-controlling pathway

For more than a decade, researchers have suspected that two proteins known as Ski and Sno play a role in the unrestrained cell growth that leads to cancer. Both can transform normal cells into cancerous ones in culture dishes, and both turn up in a variety of human tumor cell lines. But because no one was able to determine their role in the cell, they received little attention amid the throng of potential cancer-causing molecules. Now that's changing. Five separate papers—including one on page 771 of this issue—show that Ski and Sno can block one of the cell's major growth-controlling pathways, the transforming growth factor–β (TGF-β) signal. The finding puts the proteins at the center of one of the hottest areas of cell biology and sheds new light on this ubiquitous pathway.

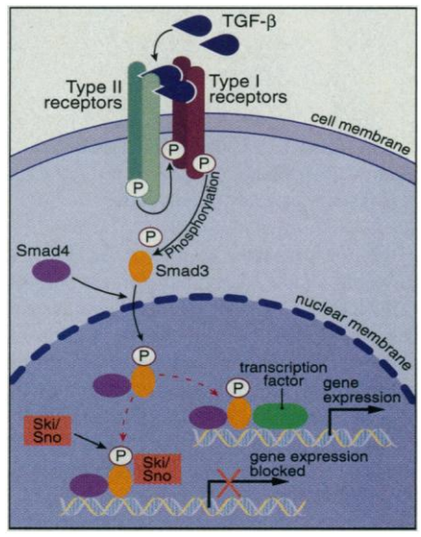
The TGF-β signal acts like a powerful molecular traffic light, ordering certain cells to slow down and stop dividing. But sometimes cells manage to speed through this checkpoint, triggering runaway growth and cancer. The new findings suggest that when Ski and Sno work properly, they may help cells resume normal growth after stopping for TGF-β's red light. But when the system gets out of whack, the molecules can shut down TGF-β entirely, and tumors may therefore form. It's "a plausible explanation" for the action of the two proteins, says cell biologist Carl-Henrik Heldin of the Ludwig Institute for Cancer Research in Uppsala, Sweden. "If you inhibit a growth inhibitor, you have more growth."

The finding also connects Ski and Sno to one of the most intensively studied molecules in cell biology. TGF-β is hot in part because it affects everything from inflammation to tissue repair to bone formation; a meeting on it this summer attracted more than 600 scientists. Surprisingly, this influential signaling pathway is relatively simple. The TGF-β molecule docks at a pair of receptors on the cell membrane, which then attach a phosphate molecule to one of two intracellular proteins, Smad2 or Smad3 (see diagram). The activated protein joins with another member of the Smad family, Smad4, and moves inside the nucleus, where the complex triggers the expression of a variety of genes, depending on the state of the cell.

Given TGF-β's importance, researchers have been searching for molecules that interact with the pathway, but they had come up with only a handful of actors so far. Now on page 771 and in last month's *Genes and Development*, Kunxin Luo of Lawrence Berkeley National Laboratory in California and her colleagues describe how they stepped up the search by engineering cells to produce a molecular "hook" attached to Smad4. They used an antibody to the hook to reel in any protein complexes that included Smads—and landed both Sno and Ski.

The catch has brought the two proteins in from the cold. Ski is named for the Sloan-Kettering Institute, where it was identified in the early 1980s as the culprit gene in a virus that causes tumors in chickens. The sequence of Sno (Ski-related NOvel gene), found a few years later, is very similar to the human version of Ski. But because scientists couldn't figure out how Ski and Sno caused abnormal cell growth, "Ski had been a backwater," says Ed Stavnezer of Case Western Reserve University in Cleveland, who first identified the gene. "It had never been tied to a major pathway that people could latch onto," he says. No longer.

Both Ski and a form of Sno called SnoN can block the action of Smad3 and Smad4, according to Luo's work as well as reports by Robert Weinberg and Harvey Lodish's team at the Massachusetts Institute of Technology's Whitehead Institute, which will be published in today's issue of *Molecular Cell* and in next week's *Proceedings of the National Academy of Sciences* (*PNAS*). Kohei Miyazono of the Japanese Foundation for Cancer Research in Tokyo and his colleagues have similar results in press at the *Journal of Biological Chemistry*. Meanwhile, Estela Medrano of Baylor College of Medicine in Houston, in collaboration with Stavnezer's group, attacked the problem from the other side, seeking proteins that bind to Ski, and found the Smads, in work presented at a recent meeting and now under review.



Cell cycle slalom. Sno and Ski proteins can block the TGF-β signaling pathway, speeding up cell growth.

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Although their results differ slightly, all four groups found that when they forced a cell to produce extra Ski, it ignored the growth-slowing signal. The MIT group and Luo's team also found that high levels of SnoN have a similar effect. The link seems to explain Sno and Ski's tumor-causing propensities, says Luo: "If the balance gets tipped the wrong way, you get cancer."

Scientists are still puzzling out the mechanics, but it seems that Ski and Sno interact in a feedback loop with the TGF-β pathway. The initial TGF-β signal boosts levels of Smad3 in the nucleus—which in turn degrades Sno, according to Luo and her colleagues. (Lodish and Weinberg also report in next week's *PNAS* that the TGF-β signal degrades both Sno and Ski.) Lowered levels of Sno evidently allow the Smad complex to turn on its target genes, so that the TGF-β signal gets through. But Luo found that two hours after the cell receives the signal, the level of Sno increases once more, to above its original levels. She thinks the extra Sno helps shut off the Smads so TGF-β's red light isn't stuck on indefinitely.

Such modulating factors "make a lot of sense," says Joan Massagué of the Memorial Sloan-Kettering Cancer Center in New York City. One would expect several layers of control over a pathway that "is involved in every aspect of life and death in virtually every group of organisms," he says.

Indeed, the importance of the find may go beyond cancer. In addition to playing a growth-slowing role, TGF-β can act as a green light to certain cells, encouraging growth and differentiation. Ski and Sno may also affect these TGF-β signals, says Luo. Ski is known to affect muscle development: Mice with extra copies of Ski turn into "Arnold Schwarzenegger mice," says Stavnezer, whereas those missing the molecule have underdeveloped muscles.

Stavnezer is thrilled that his long-ago discovery has found a place in the sun. "There have been six labs in the world that worked on Ski," he says. "I guarantee there will be more now."

—GRETCHEN VOGEL