CANCER

Converging on β-Catenin in Wilms Tumor

A common thread in some cancers is mutations in a developmental signaling pathway that ultimately affect the action of a single component.

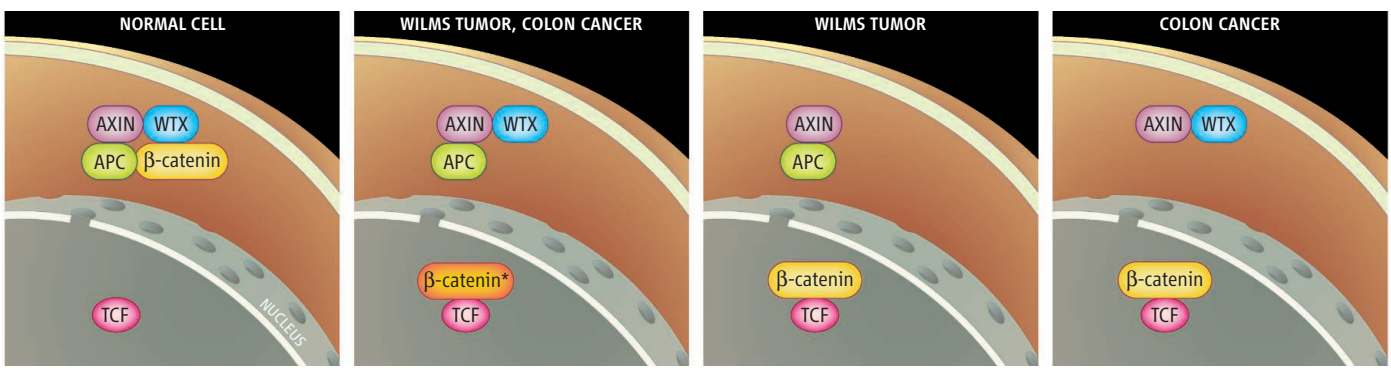
Roel Nusse

Wilms tumor is a cancer of the kidney, occurring mostly in children and sometimes running in families (*1*). Genetic alterations in these tumors include mutations in the protein β-catenin (*2*), a component of a signaling pathway controlled by the secreted morphogen WNT. WNT–β-catenin signaling is particularly important during animal development. A subset of these tumors not only has mutations in the gene encoding β-catenin, but also lacks a normal tumor-suppressor gene, *WT1*. There are, however, many cases of Wilms tumors without mutations in either gene. A recent paper in *Science* reported another tumor-suppressor gene in Wilms tumor, *WTX* (*3*). On page 1043 in this issue (*4*), Major *et al*. show that WTX operates through β-catenin, down-regulating its activity. Wilms tumor thereby joins a growing number of human cancers caused by β-catenin activation.

The story of WTX is a convergence of two independent lines of research. Rivera and colleagues (*3*) used a high-resolution screen to detect alterations in DNA copy number in Wilms tumor, identifying deletions in a gene on the X chromosome called *WTX*. This gene is inactivated in about one-third of Wilms tumors, at the somatic-cell level. Remarkably, *WTX* is inactivated by a monoallelic "single-hit" mutational event. This mode of oncogenesis differs from the inactivation of most tumor-suppressor genes, which are biallelic—that is, one allele is inactivated in the germ line, followed by mutation of the second allele at the somatic-cell level. A single hit can have phenotypic consequences if the gene is located on the X chromosome (X-linked), and indeed, *WTX* mutations are found on the single X chromosome in tumors from males and the active X chromosome in tumors from females. Tumors with mutations in *WTX* do not have *WT1* mutations. This pattern of exclusive mutations is interesting, because it may indicate separate pathways leading to a similar end point in causing cancers. So what would this end point be?

An early clue came from observations that many Wilms tumors with mutations in *WT1* also either have sustained activating mutations in the β-catenin–encoding gene or have β-catenin protein present in the nucleus of tumor cells (*5*). Both observations indicate that the WNT signaling pathway is activated (*6*) because the nuclear translocation and activity of β-catenin are key events in WNT signaling. In normal cells, β-catenin is destroyed in the cell's cytoplasm by a complex of proteins that include AXIN and adenomatous polyposis coli (APC) (see the figure). This keeps β-catenin expression levels low, because as a consequence of associating with the AXIN-APC complex, β-catenin becomes amended with ubiquitin molecules and thus, targeted for degradation by the proteasome (*7*, *8*). After WNT binds to its receptor at the cell surface, β-catenin is no longer degraded, accumulates in the cytoplasm, and eventually moves to the nucleus, where it partners with the T cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors to control gene expression. Several components of the WNT signaling pathway have already been implicated in human tumors or experimental cancer models, particularly APC, which was first isolated as a tumor-suppressor in human colon cancer. In addition, activating mutations in the human gene encoding β-catenin have been found in human colon cancer and melanomas, and Wilms tumor.

Working from the perspective of WNT signaling, Major *et al*. show that WTX is a new component of the protein complex that sequesters β-catenin in the cytoplasm and blocks its gene-regulatory activity. They used a proteomics approach: "fishing" for a binding partner of β-catenin in cell lysates by tandem–affinity protein purification and mass spectrometry (*4*). Such experiments are powerful but potentially problematic because of spurious protein interactions. However, because β-catenin is in a complex with AXIN and APC, these known binding partners can both serve as an internal control for the screen and as fishing "baits" in their own rights. Through these reiterative searches, WTX turned up as a partner for many known components in the β-catenin–AXIN–APC complex. WTX fulfills all the criteria of being yet another negative regulator of β-catenin: Overexpression of WTX reduces WNT–β-catenin signaling, whereas inhibiting WTX enhances β-catenin activity in



Variations en route to cancer. In normal cells, β-catenin is controlled by interactions with APC, AXIN, and WTX (**left**). Activating mutations in β-catenin (shown by an asterisk) can drive the protein to the nucleus, where it activates transcription together with the transcription factor TCF (**middle**, **left**). In Wilms tumor (**middle**, **right**), loss of WTX function results in translocation of β-catenin to the nucleus, whereas loss of APC function leads to colon cancer (**right**).

The author is in the Department of Developmental Biology, Howard Hughes Medical Institute, Stanford University, School of Medicine, Stanford, CA 94305–5323, USA. E-mail: rnusse@stanford.edu

the nucleus, both in cultured cells and in animals. The exciting conclusion is that *WTX* is a tumor-suppressor gene in Wilms tumors because its normal function is to control β-catenin activity.

These findings are revealing for a number of reasons. Apart from Wilms tumor, footprints of β-catenin activity have been detected in other human cancers, mostly by virtue of the nuclear presence of the β-catenin protein. In many of those cases, there has been no evidence that the known components of the WNT signaling pathway are mutated, suggesting that β-catenin becomes activated without any genetic alterations. But the new knowledge provided by Major *et al.* invites speculation that *WTX* is in fact mutated in these cancers.

In the absence of data on the possible involvement of *WTX* in other cancers, we may also speculate about the tissue specificity of tumor-suppressor genes. Clearly, Wilms tumors can be caused by activating mutations in the gene encoding β-catenin or by loss-of-function mutations in *WTX*. Other cancers, particularly colon cancer, may result from similar activating mutations in the β-catenin–encoding gene, but the major tumor-suppressor gene mutated in colon cancer is *APC*. Why this specificity? Are *WTX* and *APC* functionally redundant, meaning that loss of one will not lead to β-catenin activation, unless the other gene is not expressed? This possibility invites careful examination of the expression of *WTX* and *APC* in normal cells before they become cancerous. An X-linked tumor-suppressor gene is a time bomb waiting to go off, so there must be mechanisms to protect cells against loss of *WTX*. Such mechanisms could include *WTX* homologs on autosomes, perhaps expressed in cells other than kidney cells.

References and Notes

1. M. N. Rivera, D. A. Haber, *Nat. Rev. Cancer* **5**, 699 (2005).
2. R. Koesters *et al.*, *Cancer Res.* **59**, 3880 (1999).
3. M. N. Rivera *et al.*, *Science* **315**, 642 (2007).
4. M. B. Major, *Science* **316**, 1043 (2007).
5. R. Koesters, F. Niggli, M. von Knebel Doeberitz, T. Stallmach, *J. Pathol.* **199**, 68 (2003).
6. Despite the similarity, the acronym Wnt is not derived from Wilms tumor (like WT1 and WTX are), but from Wingless-related integration site.
7. H. Clevers, *Cell* **127**, 469 (2006).
8. C. Y. Logan, R. Nusse, *Annu. Rev. Cell Dev. Biol.* **20**, 781 (2004).

10.1126/science.1143337

PHYSICS

Condensates Made of Light

At low temperature, atom wave functions can lock together. Such a state has now been seen in trapped photons and electron-hole pairs.

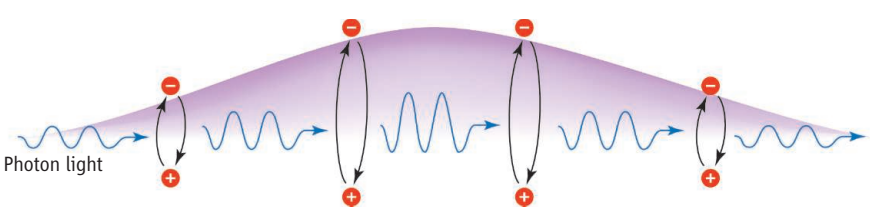
Peter Littlewood

A Bose-Einstein condensate (BEC) is the remarkable state of matter obtained when the collective quantum mechanical desire of atom waves to synchronize defeats their random motion in a normal liquid. Predicted by Einstein in 1924 and first observed with the discovery of superfluid helium in 1937, BEC has been subjected to intense study in the past decade, facilitated by the development of experimental methods of trapping and cooling of atomic gases at microkelvin temperatures. On page 1007 of this issue, Balili *et al.* (*1*) demonstrate trapping of a different kind of "atom" that can condense in the relative warmth of tens of kelvin, or perhaps even higher. By creating these warmer condensates, the researchers have now greatly expanded the variety of systems in which quantum coherence can be studied. Apart from the substantial fundamental interest in quantum coherence, such systems might become the building blocks of future quantum information processing systems.

BEC is a quantum phenomenon that depends on the overlap of atomic wave functions. An atom has a wave function whose size depends inversely on the atomic mass; hence, to reach BEC for massive atoms in a dilute gas, the temperature must be reduced below 1 μK, and even for dense liquid ^{4}He the transition temperature is only 2 K. But if it were possible to make a high-density gas of "atoms" whose mass is small, then quantum coherence might be expected to occur at much higher temperatures. Using a special kind of very light atom called a polariton—whose mass is as small as 0.0001 of the mass of an electron—several groups have been making progress toward this goal.

The trick to making a very light atom begins with the observation that the absorption of a photon by a semiconductor creates an electron in an excited state while leaving behind a positively charged "hole" (see the figure). This electron-hole pair can be bound into an atomic state, just like the proton and electron of the hydrogen atom, but the mass of the new particle—called an exciton—is much smaller. Of course such an "atom" is transient—it will vanish by reradiating a photon—but now one can play a second trick by placing mirrors on the sample. Then the photon bounces back and forth. If treated classically, it would be reabsorbed (by forming excitons) and re-emitted many times (by recombining excitons) before eventually escaping. In a quantum system, the superposition of the exciton and photon leads to the formation of yet another particle, which is known as a polariton. Because the photon is massless, polaritons are extremely light relative to the atoms typically found in BEC, and hence they offer the basis for exciting new quantum physics.

High-quality mirrors are difficult to make, but trapped "microcavity" polaritons were first made by semiconductor engineering in the early 1990s (*2*, *3*). Progress in making dense polariton gases inside these microcavities has been rapid in recent years but has usually occurred under nonequilibrium conditions. The challenges include cooling particles whose lifetime (from leaking through the mirrors) is measured in picoseconds, and making traps in which the particles can



Lightweight "atom." Photons from a laser (blue arrows) excite electron-hole pairs called excitons (black arrows). The excitons and photons form a quantum state called a polariton with a mass much less than that of an electron. Balili *et al.* have now trapped a quantum condensate of polaritons.

The author is at the Cavendish Laboratory, University of Cambridge, Cambridge CB3 0HE, UK. E-mail: pbl21@cam.ac.uk

Published by AAAS