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How the tilt of a cell-surface receptor prevents cancer

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Clear communication between cells is essential to every aspect of the body's internal function. But since cells can't talk, or send emails, how do they communicate?

The answer, in a nutshell, is by dispatching signaling molecules that selectively bind to protein receptors on the outer surface of other cells with which they must "talk." This activates the tail end of such receptors inside the cell, initiating a cascade of enzymatic reactions, or signaling pathways that reach into the nucleus, turning genes on and off. All such signaling is tightly regulated, and mutations that permanently activate certain receptors can drive the uncontrolled proliferation of cells, a defining characteristic of cancers.

In a paper published this week in the Proceedings of the National Academy of Sciences, a team led by Ludwig researcher Stefan Constantinescu, MD PhD, in Brussels based at the de Duve Institute, Université catholique de Louvain and Steven Smith, PhD, of Stony Brook University in New York shows how a mutation that alters a single amino acid in the thrombopoietin receptor turns it on permanently, explaining how it leads to the blood malignancies essential thrombocythemia (ET) and primary myelofibrosis.

"The thrombopoietin receptor is important in hematopoiesis, or the formation of blood," says Constantinescu. "It is activated by a factor known as thrombopoietin, and is required for the wellbeing of stem cells in the bone marrow and the generation of platelets, which are involved in

clotting." A mutation that continuously turns on the signaling pathway it controls has been shown to lead to certain kinds of blood cancer. But some forms of ET and primary myelofibrosis do not bear that mutation.

In 2006, Constantinescu's lab identified a unique chain of five amino acids at the bottom of a coiled portion of the thrombopoietin receptor (TpoR) that traverses the membrane. They subsequently showed that a mutation of one of those amino acids—known as tryptophan, and symbolized by the letter W—found at position 515, led to the receptor's permanent activation in mice. Constantinescu and his colleagues predicted then that mutations of W515 would turn up in human cancers—and were proved correct by other laboratories and their own studies. "But what remained unclear for the field," says Constantinescu, "was why this tryptophan in particular is so important, why, if you mutate it, TpoR is spontaneously activated."

Biochemical and functional analyses of mutant and normal TpoR conducted by Constantinescu's lab and structural studies of receptors conducted by Smith's lab, established that the tryptophan has a pronounced effect on the function of TpoR through control of the receptor's spatial orientation. "Basically, we found that the tryptophan forces TpoR to tilt," says Constantinescu. "This means that when two normal TpoRs that have not yet been switched on by thrombopoietin come together in the cellular membrane, the tilted coils that normally span the membrane cross each other to form something like an X, not two parallel lines. When parallel, these coils attract each other specifically. Tilting prevents the two coils from contacting each other within the membrane and, in effect, prevents their spontaneous activation."

"If you replace the tryptophan with a variety of amino acids other than tryptophan," explains Constantinescu, "the receptor straightens up. It can then pair up with another TpoR—even without thrombopoietin

binding—and begin signaling continuously." The result, it would appear, is the unrestrained transmission of proliferative signals and the development of ET and primary myelofibrosis.

This finding is significant for both the basic science of signal transduction and applied cancer research. Tryptophan is found at similar points in some other cell surface receptors, but molecular biologists had presumed that its main function was as a marker for the point at which the receptor emerges from membrane into the cell's cytoplasm. "We think these tryptophans may be more than just border markers, that they may generally prevent the spontaneous activation of some receptors by impairing the close apposition of membrane coils," says Constantinescu. He and his colleagues have begun bioinformatics studies to test this hypothesis—and determine if similar mutations on other single-pass receptors are also associated with cancer.

The current findings could have implications for cancer drug development as well. Constantinescu's lab has already established a partnership with a group at the Experimental Therapeutics Center in Singapore to develop experimental methods to rapidly evaluate the ability of small molecules to force membrane-embedded coils of mutated TpoR to return to their normal, tilted position. "Such molecules," says Constantinescu, "could have some potential as cancer therapeutics."

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