

# Same protein that fires up cancer-promoting Erk also blocks its activation

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A protein which is intimately involved in cancer-promoting cell signaling also keeps a key component of the signaling pathway tied down and inactive, a team led by scientists from The University of Texas MD Anderson Cancer Center reports this week in *Nature Structural Molecular Biology*.

Shc, pronounced "schick," plays a key role in activating signals which lead to [cell proliferation](#) (and cancer) when cells are stimulated, however it unexpectedly turns out to be a tumor-suppressor, keeping Erk under wraps when a cell is less active, said senior author John Ladbury, Ph.D., professor in MD Anderson's Department of Biochemistry and Molecular Biology.

"Shc is a checkpoint to prevent out of control cell growth, binding to Erk when a cell is not being stimulated by [growth factors](#)," Ladbury said.

"Otherwise, the lower-level background signaling that's always present in a cell would be uncontrolled."

## Keeping Erk in check while the cell idles

Overexpression of Erk occurs in many [types of cancer](#), including ovarian and prostate cancer and [Hodgkin lymphoma](#), so [cellular control](#) of its activity is important.

In the absence of external stimulation by growth factors, cells remain

active but lower levels of cell signaling occur, which Ladbury compares to a car idling, ready to roll. Under these conditions [control mechanisms](#) are in place to prevent the cell kicking into gear. Shc turns out to be one of these controllers.

"We're essentially looking at the cell in a resting, but ready, state," Ladbury said. "I would argue that's probably more like a cell behaves in tissue, it's not normally getting a slug of growth factors as is often the way when we investigate signaling in experiments in the lab. There's still a lot going on in the cell, basically background activity."

These findings point to a number of therapeutic possibilities, including the measurement of Shc [concentration levels](#) as a diagnostic tool and of finding small [molecule drugs](#) that block growth-factor signaling to Shc, keeping it bound to Erk, Ladbury noted.

## **Growth factors provide double boost for Erk**

When the appropriate growth factor receptor is stimulated Erk is activated in the MAP Kinase pathway. It dives into the cell nucleus and turns on a variety of genes, actions that contribute to cancer proliferation, blood vessel production and metastasis when signaling is out of control.

When receptor tyrosine kinases on the cell surface connect with growth factors, they normally send a signal via Shc that sets off a chain of actions leading to Erk activation. Ladbury and colleagues looked at Shc's connections to epidermal growth factor receptor (EGFR) signaling.

The team found in mammalian cell lines that:

- Under non-stimulated conditions Shc binds to Erk in the cell

- cytoplasm at binding sites that are unique on both proteins.
- Stimulation via EGFR reduces this connection, but not by competing with Shc at the Shc-Erk binding site.
  - Instead, on stimulation from outside the cells, EGFR adds phosphate groups to itself at specific sites. One of these forms a binding for Shc, which distorts the protein's shape, making it impossible for Erk to bind.
  - Overexpression of Shc decreases the amount of activated Erk, because Shc mops up free Erk molecules.
  - Depleting Shc expression with short hairpin RNA resulted in higher levels of activated Erk.
  - When separated from Shc, Erk moves into the nucleus and activates genes even when the cell is not receiving a stimulus. Thus without the controlling influence of Shc, Erk can run riot in the cell giving rise to unrestrained cell reproduction.

### **Shc-Erk connection confirmed**

Ladbury and colleagues then tested their results in the *C.Elegans*, a worm model frequently employed in biological research. Both Shc and Erk are greatly similar between humans and the worms.

Experiments showed that Shc blocks Erk function by sequestering it away from the Ras-Raf-Mek MAPK pathway in the worms. Without the Shc-Erk connection, the MAPK pathway is activated, causing excessive Erk activation.

EGFR stimulation not only sets off the normal activation of Erk via Shc and the MAPK pathway, Ladbury said, but also frees Erk for greater availability for activation by breaking the tie to Shc.

Provided by University of Texas M. D. Anderson Cancer Center

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