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Cell biology

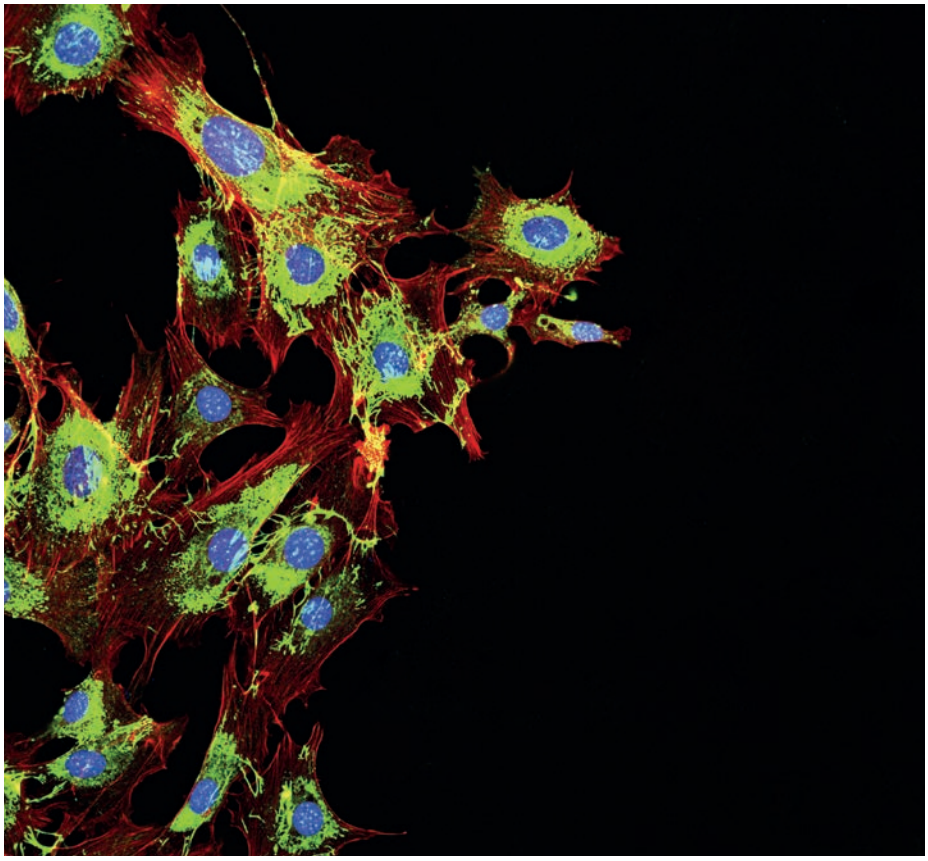
Regulator of tumour suppression found

Novel protein promotes degradation of cell cycle inhibitor p27 by facilitating its translocation from the nucleus to the cytoplasm

Cancer is a group of diseases characterized by out-of-control cell division. The cyclin-dependent-kinase (Cdk) inhibitory protein p27 helps prevent the development of cancer by slowing or stopping cell division, particularly that of tumour cells. Although mutations in p27 are rarely found in human tumours, reduced expression of the protein has been associated with poor survival of patients with breast and colorectal cancers.

Previous studies have identified several mechanisms for the regulation of p27: for example, phosphorylation by the cyclinE/Cdk2 complex; degradation by the ubiquitin-proteasome pathway; and sequestration by the transcription factor c-Myc. In 1999, Junya Kato and co-workers at Japan's Nara Institute of Science and Technology (NAIST) identified another important mechanism for p27 regulation – they found a protein called p38 that specifically binds p27 and promotes its degradation in mammalian cells[1].

Kato and co-workers at NAIST's Graduate School of Biological Sciences screened a mouse T-cell lymphoma library to identify genes encoding proteins that are able to interact with p27. Among them was a mouse gene that shared 91.5 per cent of its sequence identity with the human gene *Jab1*. This gene – the mouse homologue of *Jab1* – encodes a protein with a relative molecular weight of 38 kilodalton.



The nucleus (blue) and cytoplasm (green) of fibroblasts.

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The researchers dubbed the protein p38, and found that it binds to p27 but no other proteins (eg., cyclinB1, cyclinE and Cdk2). Moreover, they showed that overexpression of p38 in mouse fibroblasts resulted in the translocation of p27 from the nucleus to the cytoplasm — the place where p27 is broken down by degradation machinery.

Taken together, the findings showed that p38 is a negative regulator of the cell cycle inhibitor p27. The reduction or absence of p27 in the nucleus can lead to a host of detrimental effects, including, but not limited to, the promotion of cell cycle progression and the disruption of controlled cell division. Although not well understood, these processes are likely contributing factors to the poor survival of cancer patients observed in clinical studies.

"Our findings affected many fields and led to a host of new discoveries, for example, the combination of the upstream of proteolytic machinery with cell cycle regulation and intracellular translocation with proteolytic regulation," says Kato. "We have recently uncovered a novel mechanism by which *Jab1* contributes to cancer. The discovery will form the basis of our future development in drugs for treating cancer."

Kato and co-workers are still figuring out the precise role of p38 in the regulation of p27. Nevertheless, the protein may serve as a potential therapeutic target for the treatment of breast and colorectal cancers.

Reference

1. Tomoda, K., Kubota, Y. & Kato, J. Degradation of the cyclin-dependent-kinase inhibitor $p27^{Kip1}$ is instigated by Jab1. *Nature* **398,** 160–165 (1999).

More information about the group's research can be found at the Tumor Cell Biology Laboratory webpage:
http://bsw3.naist.jp/kato/?cate=205