Key protein that may cause cancer cell death identified

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Researchers at A*STAR's Institute of Molecular and Cell Biology (IMCB) have become the first to discover and characterize a human protein called Bax-beta (Baxβ), which can potentially cause the death of cancer cells and lead to new approaches in cancer treatment. The finding is published in the 16 Jan. report of *Molecular Cell*.

Detection of Baxβ has eluded scientists until now. Said Dr Victor Yu, principal investigator of the IMCB research team, "Our research findings reveal that Baxβ protein levels are normally kept at essentially undetectable levels in healthy cells by the protein degradation machine in cells known as proteasomes.

Proteasomes are "protein-digesting machines" that regulate cellular levels of various proteins including that of the lethal Baxβ, by breaking them into smaller components within the cell.

"Thus, the proteasomes are there to keep the lethal Baxβ in check," he added. "This is exciting — if the proteasome-mediated degradation of Baxβ could be inhibited specifically in cancer cells, it could cause the harmful cancer cells to go through apoptosis". In apoptosis, unwanted, damaged and infected cells are eliminated.

Until the discovery of Baxβ by Dr. Yu's team, only one single protein called Bax-alpha (Baxα) had been extensively studied in cells. Earlier evidence had suggested that more than one protein was encoded by the Bax gene.

However, only a single protein called Baxα had ever been detected and extensively studied in cells. Bax is known to be a key gene needed for the execution step of apoptosis, or programmed cell death.

The researchers also found that Baxβ is able to associate with, and promote, Baxα activation, and that Baxβ, in its native form, is 100 times more potent than its sibling Baxα in triggering a key step in apoptosis.

The future development of novel compounds that can selectively elevate levels of Baxβ or stimulate its interaction with Baxα could also lead to new drug approaches to cancer treatment, as these compounds are likely to enhance the apoptotic signals triggered by many conventional cancer drugs, which frequently cause toxic side effects in patients when higher doses of drugs are needed.

Dr. David Andrews, Professor of Biochemistry and Biomedical Sciences at McMaster University, Canada added, "The beta-isoform4 of Bax has been enigmatic for several years. Although earlier research had hinted at its existence, the protein has proven extremely difficult to detect or examine functionally. Even attempts to produce the protein in the laboratory have been largely unsuccessful. In this study the Yu group resolves these issues by demonstrating that in cells Baxβ is normally rapidly degraded and kept at low levels, and when it is not degraded, it is profoundly apoptotic on its own and works in concert with Baxα. These studies provide information necessary for the elucidation of the importance of Baxβ in cell physiology."

The research findings are reported in the article, "Baxβ: A Constitutively Active Human Bax Isoform that is under Tight Regulatory Control by the Proteasomal Degradation Mechanism," in the Jan. 16, 2009 print issue of *Molecular Cell*.

Source: Agency for Science, Technology and Research (A*STAR),

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