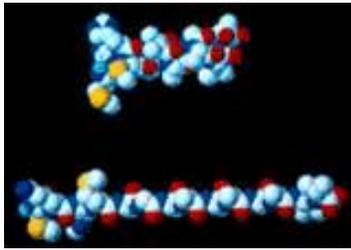


Sugars Help Fold Proteins Correctly - A Significant Discovery

by J. C. Spencer



Misfolded proteins are responsible for neurodegenerative disorders, cancers, and viruses. Here are three articles from München, Germany, M. D. Anderson Cancer Center in Houston, Texas, and Oxford University plus a reference to an article I wrote about the common cause for neurodegenerative diseases. Correct the protein folding problem and you correct a wide range of problems. Specific sugars help explain how a string of amino acids consistently folds into a protein's three-

dimensional shape — one of the more enduring mysteries in biology. Studies have revealed that sugars can regulate when a newly minted protein interacts with so-called chaperone molecules, which help it fold. The sugars "*actually help a protein to fold,*" says Raymond Dwek, director of the Oxford University Glycobiology Institute. "*That is one of the most significant discoveries in glycobiology.*" Doctors and scientists, let us connect the dots in these related articles and we will better understand why MIT said, Glycomics is one of the emerging technologies that will change the world.

Association of Bcl-2 with misfolded prion protein is linked to the toxic potential of cytosolic PrP.

Rambold AS, Miesbauer M, Rapaport D, Bartke T, Baier M, Winklhofer KF, Tatzelt J.

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Protein misfolding is linked to different neurodegenerative disorders like Alzheimer's disease, polyglutamine, and prion diseases. We investigated the cytotoxic effects of aberrant conformers of the prion protein (PrP) and show that toxicity is specifically linked to misfolding of PrP in the cytosolic compartment and involves binding of PrP to the anti-apoptotic protein Bcl-2. PrP targeted to different cellular compartments, including the cytosol, nucleus, and mitochondria, adopted a misfolded and partially proteinase K-resistant conformation. However, only in the cytosol did the accumulation of misfolded PrP induce apoptosis. Apoptotic cell death was also induced by two pathogenic mutants of PrP, which are partially localized in the cytosol. A mechanistic analysis revealed that the toxic potential is linked to an internal domain of PrP (amino acids 115-156) and involves coaggregation of cytosolic PrP with Bcl-2. Increased expression of the chaperones Hsp70 and Hsp40 prevented the formation of PrP/Bcl-2 coaggregates and interfered with PrP-induced apoptosis. Our study reveals a compartment-specific toxicity of PrP misfolding that involves coaggregation of Bcl-2 and indicates a protective role of molecular chaperones.

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KEAP1 Keeps Major Cancer-Promoting Protein At Bay

Main Category: Cancer / Oncology
Also Included In: Biology / Biochemistry
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A tumor-suppressing protein snatches up an important cancer-promoting enzyme and tags it with molecules that condemn it to destruction, a research team led by scientists at The University of Texas M. D. Anderson Cancer Center reports this week in the journal *Molecular Cell*.

"KEAP1 is a recently discovered tumor suppressor, but how it works has not been known. IKK β is a known oncoprotein that promotes cancer in at least two different ways, but we did not know how it was regulated. We think we've answered both questions with this research," said senior author Mien-Chie Hung, Ph.D., chair and professor of M. D. Anderson's Department of Molecular and Cellular Oncology.

The researchers showed that KEAP1, short for the tongue-twisting Kelch-like ECH-associated protein 1, binds to IKK β and attaches molecules known as ubiquitins to the oncoprotein, which targets it for dissolution by the cell's proteasome complex.

They also showed that underexpression of KEAP1 is associated with poor survival among breast cancer patients, and that it's mutated and inactivated in some breast, liver, lung and colon tumors.

"KEAP1 underexpression or inactivation is involved in multiple cancers, so we are working now to identify its activation mechanism, which could lead to development of new anti-cancer drugs," Hung said. He and his colleagues also want to know whether KEAP1 works on other known oncoproteins.

Blocking overexpression of IKK β , short for I κ B kinase β , is crucial for at least two reasons. Hung and colleagues have shown that the protein inhibits at least two other important tumor suppressors. More importantly, IKK β activates the NF κ B (nuclear factor κ B) signaling pathway, which regulates expression of genes involved in the immune response, cellular proliferation, growth of new blood vessels, cell survival, tumor invasion, and the lethal spreading of cancer known as metastasis.

Hung and colleagues first demonstrated that the presence of KEAP1 inhibits the NF κ B signaling pathway and then conducted a series of experiments to find out how that happens. They found that depletion of KEAP1 leads to the accumulation of IKK β , and then discovered that the tumor suppressor binds to a specific site on IKK β , capturing it to feed it to the proteasome.

Hung likens this snatching of IKK β to plucking stuffed animals with a mechanical claw out of an arcade game, imagery that wound up on the cover of *Molecular Cell*.

KEAP1 is a ubiquitin ligase that attaches to the target protein and works in a complex with another protein, CUL3, that connects the ubiquitins to the bound protein.

The team analyzed both KEAP1 and CUL3 expression in the tumors of 119 breast cancer patients and correlated the findings to overall survival. They found that underexpression of KEAP1 alone was associated with poor survival. Patients with

strong expression of both KEAP1 and CUL3 had an 80 percent survival rate at five years while those with little expression of either had a 43 percent 5-year survival rate.

Next, they sequenced KEAP1's genes in 26 cancer lines (18 breast, four liver, four lung) and in 119 primary tumors (17 breast, 78 liver, 13 lung, 11 colon) and found two functional genetic mutations that shut down the protein's ability regulate IKK β . The mutations affected the portion of the protein that binds to IKK β .

The research in this paper was funded by grants from the National Cancer Institute, including M. D. Anderson's Specialized Program in Research Excellence (SPORE) grants in breast, pancreatic and ovarian cancers, the Breast Cancer Research Foundation, Kadoorie Charitable Foundations, Patel Memorial Breast Cancer Endowment Fund, the National Breast Cancer Foundation, and by the Taiwan National Science Council.

Hung noted that first author Dung-Fang Lee, Ph.D., led his lab's research on IKK β as a doctoral candidate in The University of Texas Graduate School of Biomedical Sciences at Houston, a joint program of M. D. Anderson and The University of Texas Health Science Center at Houston. Lee received the GSBS Alfred Knudson Jr. Outstanding Dissertation Award when he graduated last year. Lee is now a postdoctoral fellow at Mount Sinai School of Medicine in New York.

Co-authors with Lee and Hung are Hsu-Ping Kuo, Ph.D., Mo Liu, Chao-Kai Chou, Ph.D., Weiya Xia, M.D., Yi Du, Jia Shen, Chun Te Chen, Longfei Huo, Ph.D., Ming-Chuan Hsu, Ph.D., Chia-Wei Li, Ph.D., and Qing-Qing Ding, all of M. D. Anderson's Department of Molecular and Cellular Oncology; Kuo, Liu, Chou, Du, Shen, and Chen are also students in the GSBS. Also, Tsai-Lien Liao, Ann-Chi Lin, Ya-Hui Chang, Shih Feng Tsai, M.D., Ph.D., all of the Division of Molecular and Genomic Science, National Health Research Institutes, Taiwan; Chien-Chen Lai, Ph.D., Division of Molecular and Genomic Medicine, National Health Research Institutes, and the Graduate Institute of Chinese Medical Science, China Medical University, both in Taiwan; and Long-Yuan Li., Ph.D., Center for Molecular Medicine and Graduate Institute of Cancer Biology, China Medical University and Hospital, and Asia University, both in Taiwan.

About M. D. Anderson

The University of Texas M. D. Anderson Cancer Center in Houston ranks as one of the world's most respected centers focused on cancer patient care, research, education and prevention. M. D. Anderson is one of only 40 comprehensive cancer centers designated by the National Cancer Institute. For six of the past eight years, including 2009, M. D. Anderson has ranked No. 1 in cancer care in "America's Best Hospitals," a survey published annually in U.S. News & World Report.

Source: University of Texas M. D. Anderson Cancer Center

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