Gene network illuminates stress, mutation and adaptation responses

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For much of her professional life, Dr. Susan Rosenberg has studied the puzzling response of bacteria to stress and the mutations that result. In the current issue of the journal *Science*, she puts together the pieces of that puzzle, describing most of the members of an elaborate gene network that functions in causing mutations during repair of double-stranded breaks in the DNA of stressed cells.

"We now know the 93 genes more than half of which are funneling into three nodes that go down the mutagenesis pathway," said Rosenberg, professor of molecular and human genetics at Baylor College of Medicine and 2009 winner of the National Institutes of Health Director's Pioneer Award.

Rosenberg's groundbreaking work has shown that the rate of mutation can be increased in response to stress such as starvation or environmental challenges such as antibiotics. This changes old ideas about constant and gradual accumulation of mutations over time. Some mutations are detrimental; others can promote survival. In this work, she and her colleagues sought to define the cellular pathways that result in this stress response.

"We screened for every gene in Escherichia coli that is needed to make this happen," said Rosenberg. *E. coli* is a "model" organism often used in the laboratory to study cells, because its DNA and other components work similarly to those in humans.

They have found that the mutagenic part of the process is not required to repair the broken DNA strands. When they "knock out" or remove the special "error-prone" DNA copying enzyme or polymerase, "the DNA is repaired beautifully and there are no mutations." So, cells do not make mutations because they have to, to repair DNA. Rather, this mechanism appears to regulate production of mutations, making more during stress, when cells are poorly adapted to their environments, and most likely to benefit from mutations.

"Fewer than 16 proteins that are needed to accomplish stress-inducible mutagenesis were known previously. This is about the number known for any molecular mechanism of DNA biology," said Rosenberg. "Our screen sought the whole list of all proteins the cell uses to make it happen."

The painstaking process, begun by then postdoctoral fellow Dr. Mary-Jane Lombardo, now of Seres Health, Inc., in Cambridge, Mass., was completed by Dr. Amar Al Mamun, an assistant professor in Rosenberg's laboratory at BCM.

Large fractions of the network work "upstream" of the activation of the stress response, showing that these proteins apparently "sense" the stress. In delineating how the network functions, Rosenberg and her colleagues identified specific pathways through which the proteins sense the environment and connected them to the molecular mechanism that promotes the mutations.

The findings reveal key factors about the cells, such as that stress-response regulators act as key network hubs, she said. Most of the proteins in the network deal with whether or not the cells feel stress, said Rosenberg.

"The cell devotes a large number of proteins to controlling the process

that generates diversity," she said. "And most of them are sensing the environment and coupling mutagenesis to stress."

They have determined the function of about half the network and are working on the rest.

"It's a resounding confirmation of the regulation of mutagenesis by stress responses, which causes mutations specifically when cells are maladapted to their environment—when mutations might allow the cell to adapt," said Rosenberg.

It is also a demonstration that one can hope to detangle large protein networks into specific biological functions. Large protein networks are being discovered in many areas of biology, but what roles the proteins play in particular biological processes is often difficult to determine. Rosenberg's study shows that by working backwards from a defined molecular mechanism, they could assign roles to more than half the network proteins. Rosenberg thinks this strategy will be useful for many other protein networks.

More information: "Identity and Function of a Large Gene Network Underlying Mutagenic Repair of DNA Breaks," by A.A.M. Al Mamun, *Science*, 2012.

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