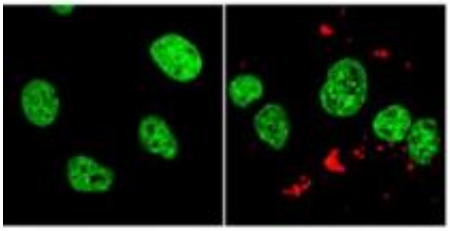
Medical Xpress

Surprising culprits behind cell death from fat and sugar overload

July 5 2011



Under normal conditions (left), the small nucleolar RNAs involved with cell death are not activated and are not visible around the nuclei of these mouse muscle cells (shown in green). In the presence of fats, however (right), the RNA molecules (shown in red) are activated and move out of the cell nuclei and into the cytoplasm, the liquid in the main body of the cell, where they help initiate cell death. This is the first time these small RNAs have been shown to function in the cytoplasm. Credit: Jean E. Schaffer, M.D.

Excess nutrients, such as fat and sugar, don't just pack on the pounds but can push some cells in the body over the brink. Unable to tolerate this "toxic" environment, these cells commit suicide.

Now, scientists at Washington University School of Medicine in St. Louis have discovered three unexpected players that help a cell overloaded with fat initiate its own demise. They have shown that these

molecules leading a cell to self-destruct are not proteins as might be expected, but small strands of RNA, a close chemical cousin to DNA. Since these small nucleolar RNAs play well-known roles in building proteins, the researchers were surprised to implicate them in killing cells.

The research, published July 6 in Cell Metabolism, is the first to link these small RNA molecules to the cellular damage characteristic of common metabolic diseases like diabetes.

"When these three RNAs are present, the cells die in response to metabolic stress, such as exposure to large amounts of fats," says cardiologist Jean E. Schaffer, MD, the Virginia Minnich Distinguished Professor of Medicine at Washington University. "But if these three RNAs are missing, the cells don't die."

Though cell suicide is a natural process that protects healthy tissues from damaged cells, it can sometimes fall out of balance. If the cell death pathway gets shut down, damaged cells may divide and lead to cancer. On the other hand, too much cell death due to abnormal metabolites, such as high levels of fats and sugar, can impair the function of tissues in the body. Such excess cell death is involved with diabetes complications such as heart failure. Understanding how abnormal metabolites cause cells to die will be helpful in the search for new therapies.

And the fact that small RNA molecules are involved in this cell death pathway is totally unexpected, according to Schaffer, also director of the Diabetic Cardiovascular Disease Center and Diabetes Research Training Center at the School of Medicine.

"When we set out to find genes causing cellular damage due to excess fat, we were expecting to find genes that code for proteins," she says. "Instead, we identified an entirely new function for three small nucleolar RNAs. Unrelated to their well-defined role in the cell's protein-making

machinery, we discovered they participate in how cells go on to die from overload of nutrients."

In a classic genetics experiment, Schaffer and her colleagues initially identified a genetic region that, when disabled, allows cells to continue living in high fat and high sugar conditions. While the region codes for a protein, they showed that the protein itself is not involved in initiating cell death.

"At first this result really puzzled us," Schaffer says. "The mutation occurs in a region that encodes a protein, as we might expect. But returning the protein to the mutated cells did not return the cell death response."

When reintroducing the protein did not restore the cell's ability to commit suicide, Schaffer's team turned its attention to the non-protein-coding areas of the same region. Selectively deleting the small RNAs embedded in the region's non-coding portion shut down the cell death pathway and solved the puzzle: a mutation in this region protects the cells because it eliminates the small RNAs, not because it eliminates the protein. The three small nucleolar RNAs function together not only to promote cell death from nutrient excess, but also to promote more general mechanisms of cell death in diseased tissues.

"It has taken us a long time to understand this surprising finding," Schaffer says. "But it has been a fun story to pursue. Often it's the results you don't expect that are the most exciting."

As a cardiologist who treats patients at Barnes-Jewish Hospital, Schaffer says a multifaceted approach is necessary to manage the complexities of metabolic diseases like diabetes and obesity. Encouraging patients to reduce the amount of fat and sugar in the diet might be a primary strategy for treatment, but when that becomes ineffective, it would be

helpful to have other ways to reduce cellular damage from excess fats in the muscles, heart, pancreas, liver and other organs. In that instance, manipulating amounts of these small RNA molecules presents one avenue to pursue in the search for possible treatments.

"We have a genetically modified mouse that does not make these three RNAs," Schaffer says. "So will that mouse somehow be protected against cellular damage from diabetes complications? That's a very interesting question, and it's where our future work is headed."

More information: Michel CI, Holley CL, Scruggs BS, Sidhu R, Brookheart RT, Listenberger LL, Behlke MA, Ory DS, Schaffer JE. Small nucleolar RNAs U32a, U33 and U35a are critical mediators of metabolic stress. *Cell Metabolism*. July 2011. www.sciencedirect.com/science/ … ii/S1550413111002099

Provided by Washington University School of Medicine

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