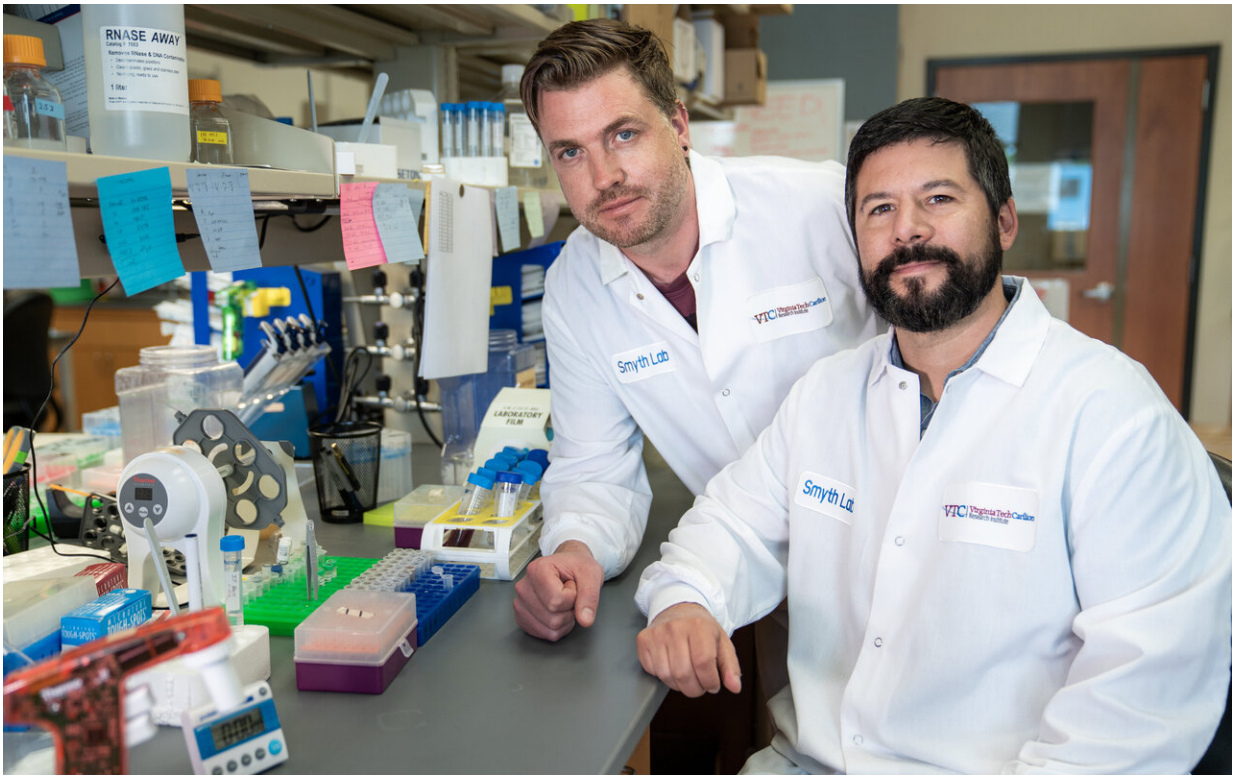
Lost in translation: The medium is the message for a healthy heartbeat

May 28 2019



James Smyth (left), an assistant professor with the Fralin Biomedical Research Institute's Center for Heart and Reparative Medicine Research, and research scientist Michael Zeitz worked with colleagues to reveal how a genetic message to produce healthy heart tissue is altered in the body during stress and aging. Credit: Virginia Tech

Researchers at the Fralin Biomedical Research Institute at Virginia Tech

Carilion have revealed how a genetic message to produce healthy heart tissue is altered in the body during stress and aging to contribute to sudden cardiac death.

The discovery published in today's *Cell Reports* centers on communication between heart cells and allows for the potential of developing targeted therapies to help people at risk of arrhythmias and heart attacks.

Led by senior author James Smyth, an assistant professor with the Fralin Biomedical Research Institute's Center for Heart and Reparative Medicine Research, scientists focused on how generally overlooked, untranslated regions of RNA that flank the genetic code become shorter during aging or while under stressful conditions.

The slight change influences how the cell reads a genetic message to make proteins and build important cellular structures including channels that electrically couple the cells of the heart together to allow for coordinated contractions and the resultant efficient pumping of blood.

"Typical understanding of the biology used to be as straightforward as 'here's the message, make a protein,'" said Smyth, who is also an assistant professor in the Department of Biological Sciences of the College of Science. "We know it is not that simple anymore. It's actually dynamically regulated. If the cell is stressed, that message will be read differently."

"Using traditional means of detecting levels of message or levels of RNA in cells during stress or aging, you wouldn't see the changes we saw," Smyth said. "We focused on how this untranslated region could be changed during stress and how that could influence how the cell reads the message."

During stress, such as conditions of oxygen deprivation that occur during ischemic heart disease or stroke, the untranslated regions become shorter, which changes how the cell synthesizes the encoded protein products and limits intercellular communication in heart cells.

Researchers focused on a gene called GJA1, which provides instructions to make Connexin 43, the gap junction protein.

Gap junctions directly couple the contents of adjacent cells and are essential to normal heart function, where they enable the rapid and organized spread of electrical impulses between cells that cause contractions of the heart muscle.

Malfunctions in this electrical communication can cause signals in the heart to become disorganized and lead to irregularities that can lead to sudden cardiac death.

"The more we identify these molecular, very fundamental mechanisms, the sharper we're going to get in therapeutics," Smyth said. "By manipulating this biology, we are figuring out the downstream factors acting on the DNA or RNA. Hopefully we have found a powerful angle to develop therapeutics, such as small molecules for precise, safer treatments."

Researchers studied cardiac cells, mouse cell lines, and aged mouse heart tissue where they found increases in the major GJA1-encoded protein—which should spell healthier conditions between heart cells—but they also observed increased, but truncated, untranslated regions of RNA that shut down synthesis of other GJA1-encoded proteins that modulate gap junction formation.

Scientists also exposed cardiac cells derived from human-induced pluripotent stem cells to reduced oxygen, which also revealed an increase

in truncated, untranslated regions, demonstrating that this is a common response of untranslated regions of RNA to physiological stress that is conserved across species.

The response also takes place in a variety of cells.

"This activity occurs in cancer, heart, and brain cells," Smyth said. "When we saw that, we knew it was a powerful piece of biology, because it was happening everywhere."

The study is the latest resulting from more than four years of work by members of the Smyth lab and others at Fralin Biomedical, a university-level research institute of Virginia Tech.

More information: *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.04.114 , www.cell.com/cell-reports/full … 2211-1247(19)30604-7

Provided by Virginia Tech