UT SOUTHWESTERN MEDICAL CENTER NEWS

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Investigators uncover intriguing clues to why persistent acid reflux sometimes turns into cancer

DALLAS – Aug. 10, 2007 – New research from scientists at UT Southwestern Medical Center and the Dallas Veterans Affairs Medical Center underscores the importance of preventing recurring acid reflux while also uncovering tantalizing clues on how typical acid reflux can turn potentially cancerous.

In research published in July and August, scientists discovered that people with acid reflux disease, particularly those with a complication of acid reflux called Barrett's esophagus, have altered cells in their esophagus containing shortened telomeres, the ending sequences in DNA strands. Combined with related research to be published this month, the findings indicate that the shortened sequences might allow other cells more prone to cancer to take over.

"The research supports why it is important to prevent reflux, because the more reflux you have and the longer you have it, the more it might predispose you to getting Barrett's esophagus. So you want to suppress that reflux," said Dr. Rhonda Souza, associate professor of internal medicine at UT Southwestern and lead author of the paper which appears in the July issue of the *American Journal of Physiology – Gastrointestinal and Liver Physiology*.

Heartburn occurs when acid splashes back up from the stomach into the esophagus, the long feeding tube that connects the stomach and throat, causing a burning sensation.

Over time, the persistent acid bath can cause normal skin-like cells in the esophagus to change into tougher, more acid-resistant cells of the type found in the stomach and intestine, a condition called Barrett's esophagus, explained Dr. Stuart Spechler, professor of internal medicine and senior author of the paper. "Unfortunately, those acid-resistant cells are also more prone to cancer," Dr. Spechler said.

Adenocarcinoma of the esophagus, the cancer that is especially associated with Barrett's esophagus, is currently the most rapidly rising cancer in the U.S., with a sixfold increase in cases during the past 30 years, according to the National Cancer Institute.

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Understanding how and why the cells change in some cases and not others has been a major challenge for investigators.

Researchers compared telomere length and telomerase activity in biopsy specimens from 38 patients with GERD and 16 control patients. This new line of research suggests that the continuous acid bath affecting esophageal cells causes them to divide more frequently in order to regenerate the damaged lining. However, each time the cells divide, the telomeres at the end of DNA become shorter. When they become too short, the aging cell can no longer divide, Dr. Souza said.

Scientists suspect that when cells can no longer divide, other cells might infiltrate the area to make up for the loss. And those cells may be more likely to generate the acid-resistance that makes them more likely to turn cancerous.

"If the telomeres get short enough, maybe the cells can't regenerate any more and maybe that's why you start to see this change," said Dr. Spechler. "Perhaps the esophagus can't regenerate the normal skin-like squamous cells, and instead, it has to recruit cells from somewhere else and that's why you start getting these changes to intestinal-like cells."

Other studies by this group of UT Southwestern digestive disease specialists suggest the alternate cells that eventually take over might be bone-marrow cells.

"There could be cells circulating from the bone marrow that wouldn't ordinarily end up in the esophagus. But if you shorten the telomeres enough and the esophagus can't regenerate anymore, perhaps these bone-marrow cells might have to replace that tissue, and bone-marrow cells can turn into intestinal tissue," Dr. Spechler said. "This hasn't been proven, but we have some data that supports that."

In research available online prior to printing this month in *Diseases of the Esophagus*, Drs. Souza, Spechler and colleagues demonstrate that bone-marrow cells come into play to regenerate the esophageal lining in rats that have heavy reflux.

"So the first paper shows that the telomeres are short, suggesting that the normal squamous cells might not be able to divide anymore, so they die out," Dr. Spechler said. "The second paper suggests that the bone-marrow cells may then come and take their place, giving rise to the intestinal

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cells instead of the normal, skin-like cells."

Further research will be needed to confirm that hypothesis, Dr. Souza said.

"It's an interesting series of experiments," she said. "None of them absolutely prove that this is what's going on, but it's an interesting concept, and it certainly supports the theory that your normal cells poop out and eventually they can't replace the damaged ones, and maybe that's why you get Barrett's esophagus."

If confirmed, the research might also help scientists find a way to prevent the bone-marrow cells from invading or to identify markers that would allow an earlier diagnosis for Barrett's esophagus, which doesn't usually have symptoms.

Other UT Southwestern researchers involved in the studies are Dr. Jerry Shay, vice chairman of cell biology, and Dr. Geri Brown, associate professor of internal medicine. In addition, researchers from the University of Florida, Texas Tech University Health Science Center in El Paso and the Mayo Clinic also participated.

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