Leftover embryonic cells connect gastric reflux and cancer

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The ultimate source of some cancers is embryonic cells. Research published in the June 24th *Cell*, a Cell Press publication, traces the precursor of deadly esophageal cancers to leftover embryonic cells found in all adults.

Some people with gastric reflux disease have a greater risk of developing esophageal cancer. These patients often have Barrett's esophagus, a condition in which intestinal-like cells appear in the esophagus. Esophageal cancers are difficult to treat and, together with gastric adenocarcinomas, kill more than a million people each year.

"A lot of cancers you can do little about, and new drugs are approved based on their ability to extend life by one or two months," said the senior author of this study, Frank McKeon of Harvard Medical School and the Genome Institute of Singapore. "Focus on the precursors of cancer may be our best hope for medicine. Here, we are looking at a precursor of a cancer precursor that is present in all of us."

"It's not clear that the embryonic stem cell precursors have any real purpose," says study author Wa Xian. "Methods to rid the body of those cells may therefore be the easiest and most cost-effective way to stop the disease before it even starts, particularly for those at the greatest risk."

The prevailing theory has been that the abnormal cells seen in Barrett's esophagus arise as the normal squamous stem cells "transcommit" in response to acid-reflux to a new, intestine-like fate. Using a mouse

model of chronic acid-reflux disease, , Xian and McKeon now show that, even as embryos, the animals showed a vast expanse of intestine-like cells in their esophaguses with gene expression profiles very similar to those seen in Barrett's.

"The metaplasia developed very quickly, in a matter of days," Xian said. "This was shocking to us as we generally consider cancer precursors taking multiple genetic 'hits' and years to develop."

The speedy development suggested that the precancerous condition wasn't related to the slow accumulation of mutations. Their findings also argue against the idea that the normal stem cells were undergoing a change of fate.

The mice under study lack a gene called p63 that is required for the self-renewal of stem cells in all stratified epithelial tissues. Because of their genetic defect, the mice are born without the squamous epithelium that normally lines the esophagus. "Without p63, the stem cells run out of gas and cease to exist," McKeon said. "You can't transcommit a cell that isn't there."

The gene profiles of those cells were also very different from cells of the intestine, despite their intestine-like appearance. "It's not a transcommitment," Xian said. "The Barrett's structure has its own cellular origin."

The researchers also generated mouse models in which the esophageal tissue could be damaged at precise times, revealing that this damage triggers a rapid mobilization of embryonic cells that would otherwise be resting. Those cells take up the newly freed space in a process that might mimic the evolution of Barrett's. Again, the speed with which those cells were activated seemed to rule out mutations as an explanation in favor of competition between normal cells and the minority embryonic

population.

"The dim prognosis for esophageal adenocarcinoma has driven therapeutic strategies aimed at destroying Barrett's esophagus, including Radio Frequency Ablation (RFA), before it progresses to aggressive cancer," McKeon said. "While RFA appears to be exceedingly effective in the short term, there are hints that Barrett's might be fairly resilient and poised for recurrence."

The new findings suggest it may be more effective to go after the precursor cells instead. To do that, Xian says they "will have to clone the stem cell for Barrett's and the Barrett's precursor cell in the junction to find the targets needed to eradicate them."

In a final note, McKeon and Xian say that they suspect an additional subset of cancers, especially those linked to inflammation and tissue damage, might arise from precursors derived in a manner similar to Barrett's. "If so, we anticipate rapid progress into a group of particularly aggressive cancers that typically outwit the best treatments we have."

Provided by Cell Press