DISEASE MECHANISMS

Out with the old, in with the new

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PHOTODISC

Barrett's oesophagus, a precursor of oesophageal adenocarcinoma, is thought to be induced by acid reflux. One hallmark of this disease is a change from the stratified (layered) squamous oesophageal epithelium to a columnar, intestinal-like epithelium, a process known as metaplasia. How and why this occurs is an area of debate, and new research proposes that this metaplasia is caused by an opportunist population of embryonic cells that repopulate the acid-reflux-damaged oesophagus.

Because p63 is required for the development of stratified epithelia, Frank McKeon, Wa Xian and colleagues investigated whether the absence of p63 might contribute to Barrett's metaplasia. *Trp63*$^{-/-}$ mouse embryos displayed a columnar epithelium characteristic of Barrett's metaplasia in place of the normal squamous epithelium of the oesophagus and forestomach. (In humans the squamocolumnar junction (SCJ) between squamous and columnar tissues is anatomically at the oesophagus–stomach junction, whereas in mice the SCJ is located midway through the stomach.) This metaplastic tissue resembled human Barrett's metaplasia both histologically and by gene expression analysis.

So what is the origin of these metaplastic cells? The authors used markers, such as carbonic anhydrase 4 (CAR4), to trace the origin of these cells in younger embryos and located them in a columnar monolayer lining the stomach. A comparison of *Trp63*$^{-/-}$ versus wild-type embryogenesis revealed that these cells are retained in bulk only in *Trp63*$^{-/-}$ embryos. Normally, CAR4-positive columnar cells lose a competitive colonization battle with p63-expressing squamous cells in the mouse stomach. However, even in wild-type adult mice, these CAR4-expressing cells persisted as a small population at the SCJ. Thus, these primitive cells could be poised to replace damaged squamous tissue in adults, as occurs during acid reflux. Indeed, the systemic ablation of stratified epithelia in adult mice resulted in the proliferation and migration of cells at the SCJ to repopulate the niche left by the squamous cell ablation, although these cells are yet to be confirmed as CAR4-positive.

An alternative mechanistic hypothesis for Barrett's metaplasia is the transdifferentiation of mature oesophageal squamous epithelial cells to columnar epithelial cells, which is linked to the overexpression of the transcription factor caudal-type homeobox 2 (CDX2). However, the metaplastic tissue in the *Trp63*$^{-/-}$ embryos did not express CDX2, a result that, coupled with the lineage tracing of the embryonic cells, implies that this transdifferentiation is not required for Barrett's metaplasia.

It will be interesting to see whether the competitive repopulation model proposed in this paper underlies most cases of human Barrett's metaplasia.

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ORIGINAL RESEARCH PAPER Wang, X. *et al.* Residual embryonic cells as precursors of a Barrett's-like metaplasia. *Cell* **145**, 1023–1035 (2011)