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EDITORIAL

Mystery Solving: Acid Reflux and Cell Mobility in Barrett's Esophagus and Esophageal Adenocarcinoma

Gastroesophageal reflux disease is remarkably common and usually benign, and yet it is a risk factor for Barrett's esophagus (BE), the precursor of potentially lethal esophageal adenocarcinoma (EAC). Many efforts have yielded exciting insights into how BE, as the archetypal precursor lesion, undergoes a mutational maturation and clonal competition to become more dangerous entities such as dysplasia and EAC.[1,2]

Phipps et al[3] instead focus on the next and more pathogenic stage of this evolution, in particular how dysplasia and EAC mobilize for metastatic spread. Using high-content imaging, they screen large small interfering RNA (siRNA) libraries for one that impacts cell shape and cell motility as a proxy for spreading activities. They then hypothesize that low pH conditions accompanying acid reflux or intratumor conditions might suppress some of the same genes whose suppression led to shape/motility changes and set about to address the impact of low pH in the 2 cell lines. Remarkably, there was an intersection in the 2 datasets, and multiple downstream experiments support the concept that this intersecting gene set could lead to hypermigratory and epithelial-mesenchymal transition (EMT) phenotypes that could be relevant to both 2-dimensional spread by dysplastic BE or 3-dimensional, metastatic spread by EAC cells.

The authors start by binning the siRNA-treated cells into 12 morphology categories and then simplifying to 6 categories, with 6 genes representing those with the highest z-scores for the combined categories. Scratch assays showed gain-of-function in wound closure times for 3 genes (GPS1, SPRY1, and MOY9B), with the first 2 showing no obvious effects on proliferation or cell cycle. GPS1 knockdown cells showed a distinct ameboid phenotype marked by leading edge F-actin and appropriate tubulin association. The dynamic analyses of GPS1-knockdown cells are superb and sure to draw much attention to this effect. An ameboid phenotype is of obvious interest to those pondering why BE spreads through the squamous epithelium or why EAC transits a basement membrane to distant sites. Interestingly, treating the dysplastic BE or EAC cell lines with low pH also caused an immediate and yet transient drop in the GPS1 transcript.

A second gene highlighted in this study was a subunit of ribonucleotide reductase, RRM2, whose knockdown put it into the EMT bin marked by spindly cells, decreased E-cadherin, and increased vimentin. The loss of RRM2 on low pH is delayed, although finally it is more dramatic than that of GPS1, and occurs with an almost compensating increase in RRM2B expression, a subunit linked to hypoxic conditions. Although the cell cycle alteration in the RRM2 knockdown cells precludes any good analysis of wound healing, the link between RRM2 and EMT will attract much interest in the field.

The strengths of this article are the remarkably detailed forward-genetics and high-content analysis, which have highlighted the ability of single genes to effect morphologic changes that would favor the dynamic behavior attributed to EAC and precursor lesions. That GPS1 and RRM2 are also suppressed by acid exposure is a hint that environmental factors could trigger similar morphologic changes, with low pH being invoked by gastric acid reflux, as well as a condition of intratumor hypoxia. It would be impossible to fully mimic the respective acid challenges that are operating via different mechanisms, likely at different pHs (the authors allude to different pH challenges), and over months and even decades. Because different pHs are likely to impact many of these genes implicated in discrete morphologic states differently, one could imagine that the same cell could be converted to an ameboid state by one pH challenge and another at a different challenge.

Although it is exciting to speculate on directions of the datasets generated in this study and what the overall approach has enabled, it is critical to highlight the necessity of applying the pipeline to more patient-derived cells. Future endeavors will likely focus on the validation of the key genes identified in this study and efforts to further tease out the complexity of local environmental influences on epithelial cells during the etiology and progression of the disease.

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Conflicts of interest
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