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Investigating the Stem Cell Dynamics of Gastric Intestinal Metaplasia in Vivo

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Purpose of study: There is an urgent need to develop spatiotemporal models of early cancer progression through quantifying the in vivo stem cell dynamics of precursor lesions. A detailed understanding of stem cell evolution of intestinal metaplasia may facilitate gastric cancer risk stratification and targeted intervention.

Methods: 3{micro}m serial sections of gastric mucosa were cut from gastric sleeve bariatric resection specimens, which were embedded en face. The tissue was labelled with immunohistochemistry for the transcription factor CDX-2 - a specific marker of the intestinal lineage. Serial sections were scanned and analysed using the digital pathology software QuPath. Analysis centred on gastric glands that were partially metaplastic, calculating the proportion of CDX-2 positive nuclei for each partially metaplastic gland, and the change in proportion through successive levels. This was used as a proxy measure of competition and the fitness of the metaplastic phenotypic change.

Summary of Results: Partially metaplastic glands were rare in bariatric resection specimens (mean frequency 2.54 glands x10-4 (range 2.21-3.12 x10-4)). The results from eight partially metaplastic gastric glands indicate that metaplasia achieves fixation through neutral drift, with a mean change in clone size between sections of 0.21 (p value = 0.09). This indicates that metaplastic clones do not have a competitive advantage over their neighbouring lineages, even in the setting of chronic inflammation. 3D reconstruction of the origin of metaplastic clones suggests that each tubule of a gastric gland is an independent stem cell unit. Finally, we find that metaplastic clones uniquely derived from the isthmus region of the gastric oxyntic gland, not from the basal region.

Conclusion: This study provides quantitative data on how the metaplastic phenotype achieves clonal fixation and may clarify the location of the stem cell zone in human gastric oxyntic glands.