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Isthmus Stem Cells Are the Origins of Metaplasia in the Gastric Corpus

The acquisition of genetic/epigenetic mutations in long-lived gastrointestinal stem cells leads to the development of cancer, as well as precancerous lesions such as metaplasia and dysplasia. In the proximal stomach corpus, this model of progression from stem cells has been supported by studies in mice and human beings, showing abundant proliferation in the isthmus and clonal expansion of mutated cells from the stem cell region. An alternative theory proposes that gastric metaplasia arises from mature differentiated chief cells. Despite reports of low levels of proliferation in chief cells in acute injury models, there is little evidence for reprogramming of chief cells into long-lived stem cells that continuously supply progeny over time. Critical flaws in the chief cell transdifferentiation theory include the definition of acute SPEM, the chief cell-damaging effect of chemical reagents, and the specificity of chief cell lineage tracing. In contrast, there is now strong evidence regarding the stem cell origins of gastric metaplasia that refutes the transdifferentiation theory. Here, we briefly review the history and definition of gastric metaplasia, and outline in detail the evidence that supports the stem cell origin of metaplasia. *(Cell Mol Gastroenterol Hepatol 2017;4:89–94; http://dx.doi.org/10.1016/j.jcmgh.2017.02.009)*

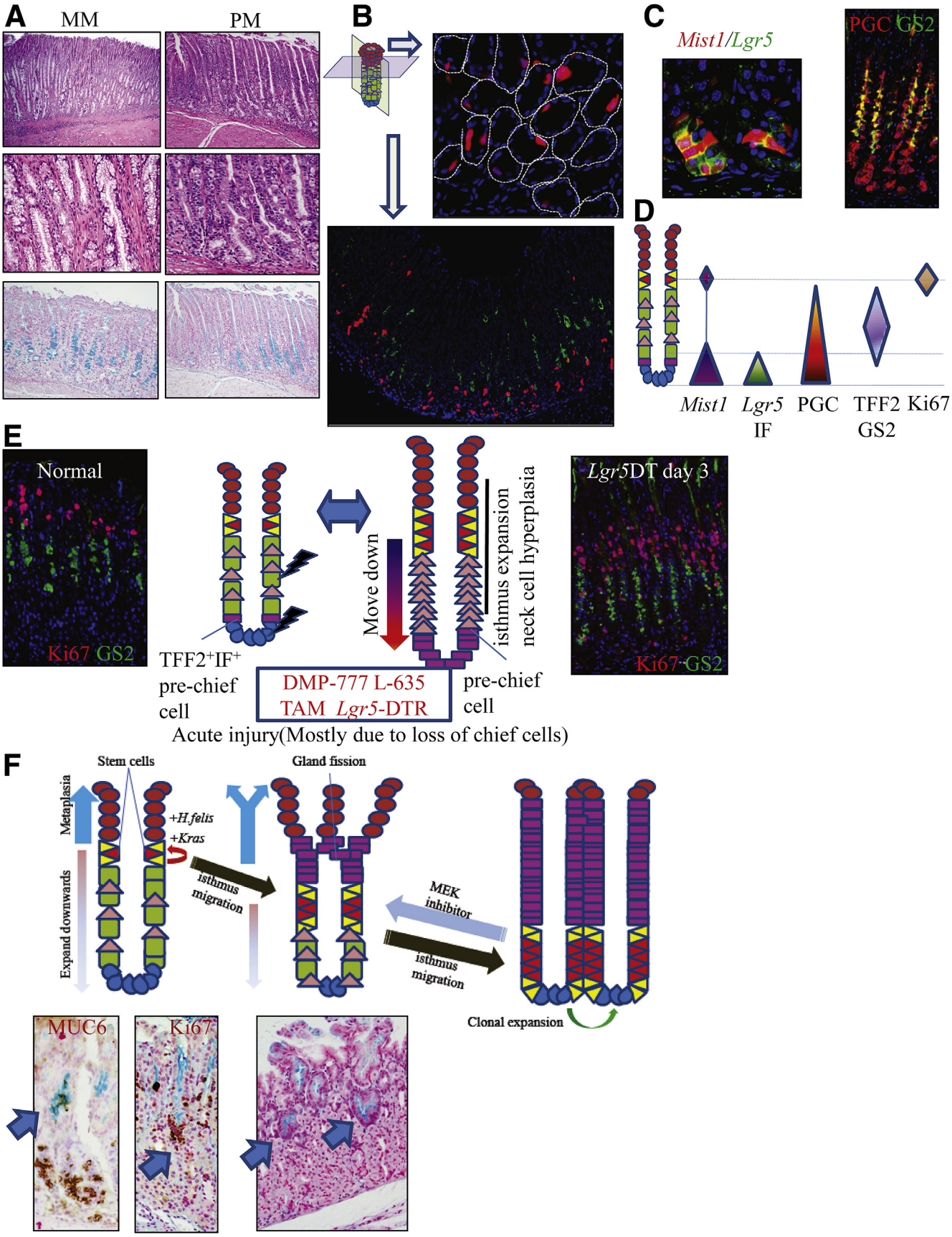
Metaplasia of the stomach gained increasing recognition when a link to gastric adenocarcinoma was noted and the Correa pathway was proposed. Although classic intestinal metaplasia (IM) with goblet cell differentiation initially received most of the attention, spasmolytic polypeptide-expressing metaplasia (SPEM) recently has attracted greater interest. SPEM was first characterized by "a marked expansion of an aberrant gastric mucous cell lineage that stained positive for spasmolytic polypeptide" in *Helicobacter felis*–infected mice (spasmolytic polypeptide was the original name given to trefoil factor family 2 [TFF2]).[1]

Helicobacter species induce a variety of histopathologic changes in mice, including oxyntic atrophy (loss of corpus chief and parietal cells), surface mucous pit-cell hyperplasia, mucous metaplasia (MM), and pseudopyloric metaplasia (PM).[2] In this process, chief cell disappearance precedes parietal cell loss and the development of SPEM.[2] Both MM and PM are classified as SPEM that expresses neck cell markers TFF2, gastric mucin-6 (MUC6), and Griffonia simplicifolia leaf lectin II (GS2), but they need to be distinguished. SPEM-MM is characterized by large, foamy $TFF2^{+}$ cells that secrete neutral and acid mucins and replace lost parietal and chief cells (Figure 1*A*). In addition to morphologic differences from normal mucous neck cells, SPEM-MM expresses unique markers (CD44 and Sox9) that are absent in normal neck cells. Thus, MM is clearly a form of metaplasia and not simply neck cell hyperplasia. In contrast, SPEM-PM occurs later and includes less differentiated cell types that resemble the pyloric antrum. Dysplasia emerges after SPEM-PM is established.[2]

An entity similar to TFF2-expressing PM in mice was recognized in human gastric tissue in 1999 and the name SPEM formally was proposed to encompass TFF2-expressing metaplasia. SPEM development was linked to mucosal injury associated with parietal and chief cell loss, particularly in chronic *Helicobacter* species infection. Although initial studies pointed to SPEM as a preneoplastic lesion, knockout of the signature peptide, TFF2, in mice accelerated gastric inflammation and carcinogenesis, suggesting a possible role for TFF2 as a tumor suppressor.[2]

Observations in Patients Indicate a Stem Cell Link

Analysis of resected gastric specimens showed the frequent co-existence of SPEM and IM in the same compound glands. This raised the question of whether SPEM originated from tissue resident stem cells or from another source. The stability and durability of IM and SPEM suggests that they are maintained by a self-renewing stem cell. Although there was an implicit assumption that metaplasia arises from epigenetic changes in multipotent gastric stem cells, more recent studies[3] have shown that metaplastic gastric glands are clonal, maintained by multiple stem cells, and can form large patches that spread by glandular fission.


A
MM
PM
B
C
Mist1/Lgr5
PGC GS2
D
Mist1
Lgr5 IF
PGC
TFF2 GS2
Ki67
E
Normal
Ki67 GS2
Move down
isthmus expansion
neck cell hyperplasia
Lgr5DT day 3
Ki67 GS2
TFF2+IF+ pre-chief cell
DMP-777 L-635
TAM Lgr5-DTR
pre-chief cell
Acute injury(Mostly due to loss of chief cells)
F
Stem cells
Gland fission
Metaplasia
Expand downwards
+H.felis
+Kras
isthmus migration
MEK inhibitor
isthmus migration
Clonal expansion
MUC6
Ki67