REVIEW

The Fibroblast Landscape in Stomach Carcinogenesis

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SUMMARY

Single cell analyses have defined fibroblast populations present during stomach carcinogenesis. We discuss major genes expressed and the categorization of these fibroblast populations into 4 major subpopulations. Fibroblasts in the precancerous mucosa may drive progression of metaplastic lineages into cancer.

Numerous recent studies using single cell RNA sequencing and spatial transcriptomics have shown the vast cell heterogeneity, including epithelial, immune, and stromal cells, present in the normal human stomach and at different stages of gastric carcinogenesis. Fibroblasts within the metaplastic and dysplastic mucosal stroma represent key contributors to the carcinogenic microenvironment in the stomach. The heterogeneity of fibroblast populations is present in the normal stomach, but plasticity within these populations underlies their alterations in association with both metaplasia and dysplasia. In this review, we summarize and discuss efforts over the past several years to study the fibroblast components in human stomach from normal to metaplasia, dysplasia, and cancer. In the stomach, myofibroblast populations increase during late phase carcinogenesis and are a source of matrix proteins. PDGFRA-expressing telocyte-like cells are present in normal stomach and expand during metaplasia and dysplasia in close proximity with epithelial lineages, likely providing support for both normal and metaplastic progenitor niches. The alterations in fibroblast transcriptional signatures across the stomach carcinogenesis process indicate that fibroblast populations are likely as plastic as epithelial populations during the evolution of carcinogenesis. *(Cell Mol Gastroenterol Hepatol 2024;17:671–678; https://doi.org/10.1016/j.jcmgh.2024.02.001)*

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Epithelial alterations during the induction of metaplasia in the stomach have received considerable attention recently, and other studies have noted the association of these mucosal changes with the influence of M2-macrophages and type 2-innate lymphoid cells.[1–6] The intestinal type of gastric cancer develops within a field of oxyntic atrophy and metaplasia,[7] and recent studies have redefined a sequence of metaplastic changes initiated by pyloric metaplasia in response to parietal cell loss.[5] Continued inflammation leads to the progression of pyloric metaplasia into incomplete intestinal metaplasia, which is most associated with the development of dysplasia and adenocarcinoma.[8–11] Linked with alterations in mucosal lineages, there is a considerable expansion of stromal elements, but relatively less is known about the changes in fibroblast populations in the metaplastic and dysplastic mucosa. In this article, we will discuss recent investigations related to fibroblast populations in the stomach under normal conditions and during gastric carcinogenesis (Table 1).

Fibroblasts in Normal Human Gastric Mucosa

Stromal cells represent mesenchymal lineages found in the interstitial lamina propria of major organs and connective tissues.[19] Stromal cells consist of multiple cell types, including fibroblasts, myofibroblasts, and pericytes, and have distinguishing features of elongated cytoplasmic projections and spindle-shaped nuclei.[20] Fibroblasts produce extracellular matrix, including collagen, proteoglycans, and fibronectin.[21] In gastrointestinal organs, fibroblasts are generally known to maintain epithelial homeostasis and respond to environmental stimuli from mucosal infection or injury and are thought to support the proliferative niche with secretion of growth factors.[22,23] However, current knowledge of fibroblast functions and characteristics in the normal stomach tissue is not extensive and relies on recent investigations using single cell techniques. Both the normal rodent and human gastric mucosa present rather sparse fibroblast populations. Sigal et al[24] found that stromal cells located in the base of stomach antral glands secrete R-spondin (Rspo). Using different mouse models and fluorescence in situ hybridization, they demonstrated that fibroblasts near the base of antral glands expressed both α-smooth muscle actin (aSMA, *ACTA2* gene) and RSPO3. This finding was confirmed in in vitro culture of human primary antral myofibroblasts through quantitative polymerase

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Table 1. Diverse Fibroblast Populations Found Across the Normal, Metaplastic, and Dysplastic/Cancerous Human Stomach Using scRNA Sequencing

Fibroblast subtypes	Fibroblast defining markers	Additional markers	Study
PDGFRA+ telocyte-like fibroblasts	PDGFRA*hi*	POSTN, BMP4, CXCL14, and TGFBI	Lee et al[12]
Inflammatory fibroblasts	FBLN2*hi*	DCN, CFD, FBLN1, RSPO3 and IGFBP6	
Myofibroblasts	ACTA2hi and PDGFRBlo	ADIRF, MYL9, TAGLN, and TPM2	
Pericytes	ACTA2hi and PDGFRBhi	RGS5, NDUFA4L2, CSPG4, NOTCH3, and ENPEP	
Kruppel-like factor cells	KLF	KLF4, SFRP1, SFRP2, and PI16	Tsubosaka et al[13]
CCL11+ fibroblasts	CCL11	CCL11, ABCA8, APOE, and ADAM28	
PDGFRA+ fibroblasts	PDGFRA	PLAT, POSTN, BMP4, and WNT5A	
Fibroblasts that express fibroblastic and smooth muscle markers	ACTG2	HHIP, MYLK, and BARX1	
Pericyte-like	RGS5	TAGLN and CD36	
Pericytes with smooth muscle markers	ADIRF	RERGL, MYH11, and TAGLN	
Inflammatory fibroblasts	STC1	IL6, IL11, IL24, CXCL1, CXCL2, CXCL5, CXCL6, MMP1, MMP3, and MMP10	Kim et al[14]
Myofibroblasts	TAGLN	TPM1, TPM2, MYL9, and EGR1	
Intermediate CAFs	TGFβ	PDGFRA, POSTN, ID1, and ID3	
PDGFRA+ fibroblasts	PDGFRAhi	PLAT, POSTN, and PDGFRA	Huang et al[15]
HHIP+ myofibroblasts	HHIPhi	HHIP, ACTA2, and TAGLN	
Fibroblasts that express immune cell recruitment factors	PDGFRAhi, PDPNhi, and CD34hi	CXCL12, CFD, C3, C1S, CFH	Nowicki-Osuch et al[16]
Fibroblasts that express extracellular matrix components	PDGFRAhi, PDPNhi, and CD34lo	CXCL14, POSTN, COL6A1, and COL6A2	
Myofibroblasts	ACTA2	MYL9 and ACTG2	
Pericyte-like	CSPG4hi	PDGFA, ASPN, and S100A4	Kumar et al[17]
CAF-like	FAPhi	COL8A1, THBS2, and CTHRC1	
Myofibroblasts	ACTA2hi	THY1, DCN, COL4A1, FAP	Sathe et al[18]
Pericytes	PDGFRBhi	RSG5, PDGFRB	

chain reaction and immunoblotting, suggesting that human antral myofibroblasts also secrete RSPO3.[24] Moreover, they demonstrated that RSPO3 is a critical niche-specific regulator in coordinating the homeostasis and proliferation of the epithelial stem cells located at the base of mouse antral glands.

Pastula et al[25] demonstrated that co-culture of myofibroblasts with gastric organoids supported the growth of the organoids and suggested that fibroblasts release niche factors crucial for the proliferation of epithelial stem cells. In accordance with these findings, our recent study[12] described 4 distinctive fibroblast populations in the normal human stomach. ACTA2-expressing myofibroblasts population represented the major population in the normal stomach mucosa, even with gastritis. The studies by Pastula et al and Sigal et al[24] did not involve single cell analysis, and so the assignment of populations as myofibroblasts based on aSMA immunostaining or ACTA2 expression alone may be overcategorizing fibroblasts as myofibroblasts. Nevertheless, all these studies suggest that fibroblasts with a transcription profile aligned with myofibroblasts and high expression of ACTA2 (aSMA) might represent the major population in the stromal compartment that oversees the homeostasis of stomach glands under normal circumstances.

A recent study by Tsubosaka et al[13] used single cell RNA sequencing (scRNA-seq) and spatial transcriptomics to profile cell lineages of the human stomach with normal and intestinal metaplasia areas from a total of 32 sample patients. In the normal stomach mucosa, they identified a population with high expression of myofibroblast-related markers including ACTG2, HHIP, MYLK, and BARX1. BARX1 is a stomach-specific transcription factor and is involved in stomach development.[26] RNA in situ hybridization confirmed the presence of BARX1-expressing fibroblasts in the lamina propria of corpus and antral mucosa, suggesting an interaction between BARX1-expressing myofibroblasts and normal gastric epithelial cells.[13] Although myofibroblast populations are predominant in the normal stomach mucosa, 3 other fibroblast populations were also identified in our studies, indicating that heterogenous fibroblast populations are present in the normal mucosal milieu.[12]

Fibroblasts Associated With Human Stomach Metaplasia

Stomach metaplasia develops initially as a reparative mechanism after significant gastric damage.[5,27] Pyloric metaplasia represents the first metaplastic gland structure in injured mucosa, with the presence of a metaplastic cell lineage, spasmolytic polypeptide-expressing metaplasia (SPEM) cells, at the base and foveolar hyperplasia toward the lumen.[6,28,29] This alteration in glandular cell lineages

leads to the emergence of a zone with proliferative SPEM cells at the bases of pyloric metaplasia glands distinct from the isthmal progenitor cell zone in the upper third of normal corpus glands.[11] Pyloric metaplasia can then give rise to incomplete intestinal metaplasia glands, which show SPEM cells toward the bottom of glands.[11] These findings suggest that the process of metaplasia development alters the location of proliferative cells. Because of this restructuring of gland composition and spatial location of cells, it would seem likely that stromal changes must be involved in the reestablishment of major proliferating cell niche in the metaplastic glands. Initial studies in mice[30] demonstrated that *Helicobacter felis* infection increased myofibroblasts in the mouse stomach, in part through derivation from bone marrow cells and mesenchymal stem cells. Shibata et al[31] found that stromal myofibroblasts expand in the gastric corpus mucosa after up-regulation of SDF-1, a chemokine ligand for CXCR4, after *Helicobacter* infection. These studies suggested changes in myofibroblasts attendant with induction of oxyntic atrophy and metaplasia.

Other studies reported the presence of a pericryptal fibroblast sheath (PCFS)[32] in mouse and human stomachs with intestinal metaplasia. The PCFS surrounded glands in mouse and human stomach areas with CDX2-expressing intestinal metaplasia but were absent in normal stomach tissues. Liu et al[33] reported similar findings in a series of gastric mucosa tissues with normal, intestinal metaplasia, dysplasia, and gastric cancer sections. More recently, researchers have detailed a specific fibroblast lineage expressing *FoxL1* and *Pdgfra* as telocytes present within the PCFS in the small intestine.[34] Telocytes, fibroblast cells with elongated cytoplasmic processes, represent a distinctive stromal cell type.[35] The exact role of telocytes in maintaining the proliferative niche in normal or metaplastic stomach has not been evaluated.

Our recent investigations identified 4 distinctive fibroblast populations present in the human stomach stroma (Figure 1*A*)[12]: one with high *PDGFRA* (*PDGFRA*hi) expression and enriched in genes related to extracellular matrix organization and cell motility (telocyte-like fibroblasts), one with high *FBLN2* (*FBLN2*hi) expression and enriched in genes related to inflammatory pathways (inflammatory fibroblasts), one with high *ACTA2* (*ACTA2*hi) and low *PDGFRB* (*PDGFRB*lo) expression and enriched in genes related to myofibroblasts (myofibroblasts), and one with *ACTA2*Lo, *PDGFRB*hi expression and enriched in genes related to pericytes. All 4 populations were present in stomach with inflamed normal, metaplastic, and dysplastic/cancerous areas. As previous studies have reported, fibroblasts with *ACTA2*hi represented a major population in normal stomach mucosa. Of note, *PDGFRA*hi fibroblasts and *FBLN2*hi fibroblasts were significantly expanded in metaplastic tissues, and *PDGFRA*hi fibroblasts were also prominent in dysplastic/cancerous tissues. In addition, *PDGFRA*hi fibroblasts were observed in the isthmus region of corpus glands in normal stomach epithelia, where progenitor cells are usually located (Figure 1*B*). In metaplastic mucosa, *PDGFRA*hi fibroblasts were observed in close proximity with SPEM cells with extended morphology wrapping around gland bases, consistent with the properties of telocytes.[12]

Although several studies have noted the geographic association of fibroblasts with metaplastic or cancerous epithelia, few studies sought to address how fibroblasts might be influencing the behavior of metaplastic cells. Importantly, we compared the ability of different fibroblast populations to influence the phenotypes of gastroids with a metaplastic phenotype dominated by SPEM cells.[12] In Air-Liquid Interface co-cultures examining direct interaction of fibroblasts with metaplastic cells, fibroblasts isolated from both metaplasia-bearing and dysplasia/cancer-bearing mucosa induced loss of metaplasia markers and up-regulation of dysplasia markers as well as generation of polypoid morphologies (Figure 2).[12] No changes in metaplastic cell markers were observed in co-culture with fibroblasts isolated from normal gastric mucosa (Figure 2). These studies demonstrated for the first time that fibroblasts directly promote dysplastic transition in metaplastic cell lineages.

In the intestine, telocytes are located in submucosal regions near stem cells and are important for epithelial integrity because of their functional release of BMP and WNT ligands.[34,36,37] According to our single cell transcriptomic profile,[12] *PDGFRA*hi fibroblasts uniquely express *WNT4*, *WNT5A*, *BMP2*, and *BMP4*, suggesting that production of critical niche factors is a major function for telocyte-like cells in the stomach. Furthermore, because of their location in the isthmus regions of normal corpus glands in the stomach, it is also likely that *PDGFRA*-positive fibroblasts are important for maintaining normal progenitor/stem cell niche in the corpus. In addition, because of the presence and immediate proximity to metaplastic and dysplastic cell lineages,[12] *PDGFRA*-positive fibroblasts likely support the establishment of an alternative proliferative cell zone in metaplastic glands.

Using both scRNA-seq and spatial transcriptomics information, Tsubosaka et al[13] described 6 populations of fibroblasts in the human stomach. One of these populations demonstrated a unique high expression of PDGFRA, BMP4, WNT5A, and POSTN similar to the expression pattern in *PDGFRA*hi fibroblasts observed in our study.[12] Further investigation using RNA in situ hybridization in the PDGFRA and BMP4 co-expressing fibroblasts revealed that they were infrequently present in areas with normal mucosa but prominently observed surrounding and in close proximity to intestinal metaplasia lineages.[13] These results were confirmed with spatial transcriptomic assays. Moreover, BMP4-expressing fibroblasts increased from normal gastric mucosa to intestinal metaplasia, suggesting that BMP4 increases in fibroblasts promote pyloric metaplasia progression to intestinal metaplasia. Additional gene-regulatory network analysis of PDGFRA-expressing fibroblasts revealed that the FOXL1 transcription factor was up-regulated, suggesting that the PDGFRA-expressing cells likely represent a major telocyte population in the stomach, as we have observed.[12]

In addition, recent studies[14–16] described the presence of major fibroblast populations in precancerous lesions of human stomach. After performing scRNA-seq of patient biopsies, Kim et al[14] defined in silico a telocyte-like population with high *PDGFRA* expression, mostly associated with
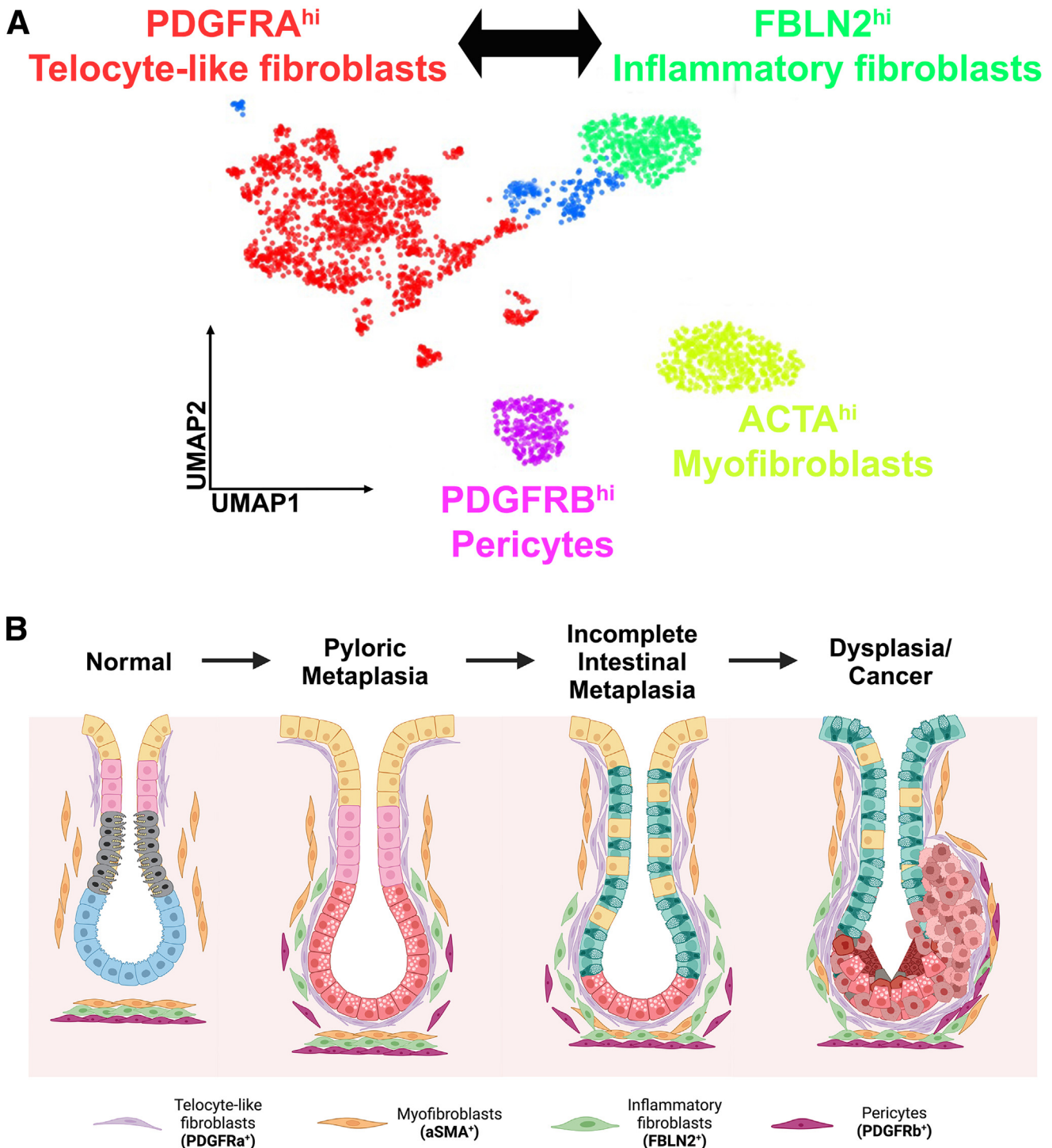
A

PDGFRAhi
Telocyte-like fibroblasts

FBLN2hi
Inflammatory fibroblasts

UMAP2

UMAP1

ACTAhi
Myofibroblasts

PDGFRBhi
Pericytes

B

Normal → **Pyloric Metaplasia** → **Incomplete Intestinal Metaplasia** → **Dysplasia/Cancer**

Telocyte-like fibroblasts (PDGFRa+)

Myofibroblasts (aSMA+)

Inflammatory fibroblasts (FBLN2+)

Pericytes (PDGFRb+)

Figure 1. Fibroblasts populations observed in human stomach carcinogenesis. (*A*) Single-cell RNA sequencing from different studies described a consensus of 4 major populations of fibroblasts in the human stomach: PDGFRA+ telocyte-like fibroblasts, FBLN2+ inflammatory fibroblasts, ACTA2+ myofibroblasts, and PDGFRB+ pericyte-like fibroblasts. (*B*) This illustration depicts the geographic location of fibroblasts at different stages in the process of gastric carcinogenesis from normal to pyloric metaplasia to incomplete intestinal metaplasia to dysplasia/cancer. PDGFRA-expressing telocyte-like fibroblasts are located closest to the epithelial cell lineages, with myofibroblasts tending to be more distant.

intestinal metaplasia. These observations corroborate previous findings of a major telocyte population in the stomach.[12] Similarly, Huang et al[15] analyzed a large patient cohort with intestinal metaplasia using spatial single-cell
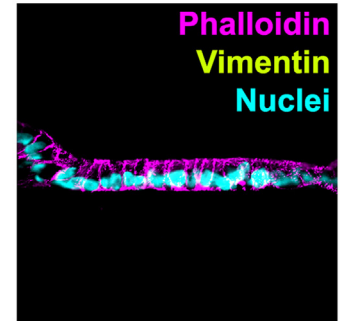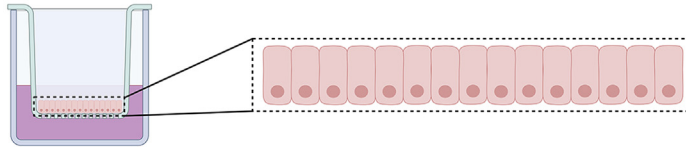
transcriptomics. They defined 2 fibroblast populations in human intestinal metaplasia samples. One population was PDGFRA-positive and also expressed POSTN, consistent with the telocyte-like population we identified.[12] A second
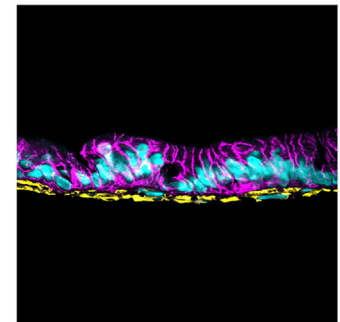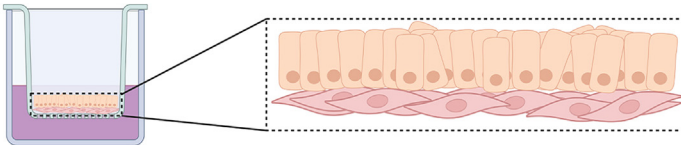
14 days of ALI culture
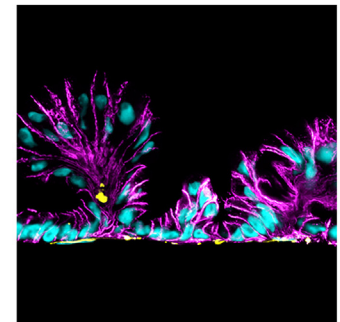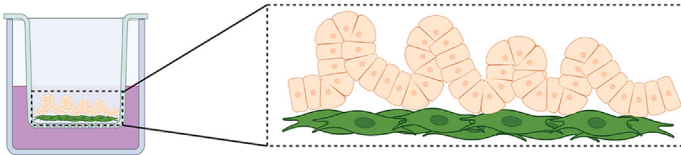
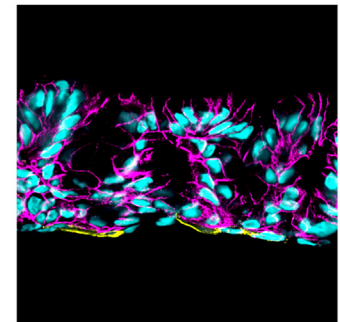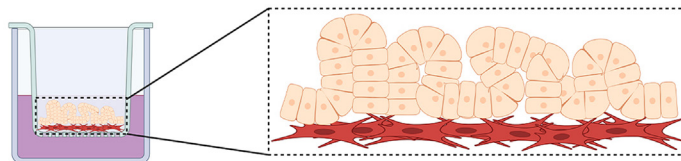**Figure 2. Co-culture of metaplastic human gastroid cells with fibroblasts using Air Liquid (ALI) Interface promoted metaplasia transition toward dysplasia.** In vitro Transwell culture of metaplastic gastroid cells alone (*A*) or directly on top of fibroblasts derived from inflamed normal (*B*), metaplasia (*C*), and dysplasia-bearing mucosa (*D*) was performed using the ALI technique. After 14 days of ALI culture, metaplasia- and cancer-derived fibroblasts triggered progression into dysplasia that was observed by polypoid morphologic changes (*C* and *D*) in association with up-regulation of dysplasia-related markers (TROP2 and CEACAM5) and the loss of metaplasia-related markers (CD44v9).[26] None of these changes were observed in metaplastic gastroid cells grown alone or on top of inflamed normal-derived fibroblasts (*A* and *B*).

fibroblast population was described as a myofibroblast population positive for *ACTA2*, *HHIP*, and *TAGLN*.[15] Nowicki-Osuch et al[16] analyzed commonalities between esophageal and gastric intestinal metaplasia using scRNA-seq and observed 3 fibroblast populations. One major population showed high expression of *PDGFRA* and *PDPN* with *POSTN*, correlating with our findings of a telocyte-like population.[12] The second major population was characterized by expression of *ACTA2*, *MYL9*, and *ACTG2* with a transcriptional signature similar to myofibroblasts. By immunostaining, they also reported an expansion of POSTN-positive and SMA-positive fibroblasts in samples with intestinal metaplasia.[35]As reflected by these studies, single-cell analytical methods have augmented our knowledge of the heterogeneity and diversity of fibroblast populations in the stomach.[12,13,14–16] Present studies reach a consensus on the existence of a major fibroblast population expressing PDGFRA that is expanded in areas with metaplasia in immediate proximity to epithelial cells (Table 1). This population might represent the major telocyte-like population in the stomach, with functional roles in the maintenance of progenitor cells in normal stomach and, most importantly, progression of metaplasia into dysplasia/cancer in transitioning zones.[12] There is likely even greater heterogeneity within the PDGFRA-expressing fibroblast population, and true telocytes expressing FOXL1 may represent a subpopulation of this cell type. At the same time, multiple studies have noted the presence of myofibroblasts in normal and metaplastic tissues. Although these myofibroblasts identified by aSMA staining may be a source of RSPO3, our scRNA-seq data showed that inflammatory fibroblasts were the predominant source of RSPO3 in the human stomach. In addition, myofibroblasts generally do not show the same proximity to the metaplastic and dysplastic cell lineages as the telocyte-like populations.

Fibroblasts in Human Stomach Cancer

In almost all solid tumors, fibroblast-like cells are an important component of the tumor microenvironment.[38–40] The term *cancer-associated fibroblasts* (CAF) refers to stromal cells that can promote progression of precancerous stages and promote tumorigenesis and tumor cell growth.[41] Studies in different types of cancer have identified at least 2 major types designated as myofibroblast CAF or inflammatory CAF.[42–45] More recently, thanks to improvements in scRNA-seq and spatial transcriptomic technologies, the heterogeneity within CAF and their geographic diversity in different tumors are becoming more evident.[46]

In gastric cancer, little is known about the origin, specific regulation pathways, and heterogeneity of fibroblasts, in part because of limited mouse models of gastric cancer mimicking the carcinogenic cascade seen in human patients. Kumar et al[17] found distinct tumor fibroblast populations in patient samples with gastric cancer. Notably, one population highly co-expressed INHBA and FAP, in comparison with fibroblasts from normal tissue, and were associated with poor prognosis. Further in vitro analysis demonstrated that INHBA is a positive regulator of FAP in gastric cancer fibroblasts. Another population strongly co-expressed both endothelial and fibroblast-

related markers, suggesting expansion of pericytes. In our recent study,[12] we observed that PDGFRA^hi telocyte-like fibroblasts were significantly expanded and wrapped around epithelial-containing glands but in a more disorganized fashion compared with metaplastic glands. Furthermore, we observed frequent co-expression of PDGFRA and PDGFRB in the fibroblasts from these tissues. The myofibroblast population (ACTA2^hi and PDGFRB^lo) was also present but mostly located in submucosal areas away from the epithelial compartment. Moreover, some dysplastic/cancerous tissue samples presented a significant expansion of the pericyte population (ACTA2^lo and PDGFRB^hi).[12] Sathe et al[18] also performed scRNA-seq and detected tumor-specific myofibroblasts enriched for extracellular matrix–related transcripts and prominent expression of *ACTA2* when compared with normal samples. These tumor-associated myofibroblasts also showed high expression of *RSPO3* and *EGR2*, a gene known to influence fibrosis. Thus, multiple different fibroblast populations are expanded within the cancer-bearing milieu.

Table 1 summarizes the markers that characterize commonly identified subclasses in human stomach. These include a class of telocyte-like fibroblasts that express high levels of PDGFRA with low expression of ACTA2. A second class of inflammatory fibroblasts expresses FBLN2, FBLN1, and RSPO3. Myofibroblasts demonstrate high expression of ACTA2 and minimal expression of PDGFRA, whereas pericytes express high levels of PDGFRB with low but significant levels of ACTA2. Although not all of these groups were described in all of the studies, most studies support these 4 fibroblast subsets in both normal and pathologic human stomach (Figure 1*A*). A recent investigation examined fibroblasts with high or low expression *Pdgfra* (*Pdgfra*^hi or *Pdgfra*^lo) in the mouse stomach.[47] *Pdgfra*^hi fibroblasts appear to be similar to the telocyte-like fibroblasts seen in human stomach. Moreover, they described *Pdgfra*^lo CD55^+ fibroblasts located at the base of corpus glands showing higher expression of *Grem1* and *Rspo3*. When we compare the results in mice with the human fibroblast scRNA-seq data from our studies, *Pdgfra*^lo CD55^+ cells appear to correlate with inflammatory fibroblast populations in the human stomach. Thus, diverse fibroblast subpopulations are present in the mouse and human stomach in homeostatic conditions.

Conclusions and Cell Biological Questions That Remain

In the human stomach, fibroblast populations display extensive heterogeneity, which appears to be more pronounced during carcinogenesis. Nevertheless, representatives of fibroblast populations are present throughout the spectrum from normal to metaplasia to cancer-bearing mucosa. Alterations in fibroblasts align more with changes in the relative abundance of populations and more importantly their expression and secretion of regulators that can affect mucosal cell behaviors. Thus, it appears that a simple term CAF is not appropriate for evaluating the dynamic scenarios in play within the carcinogenic milieu. It would seem more logical to specify relationships of specific populations within the precancerous and cancerous milieu with

promotion of carcinogenesis. This approach will also facilitate analysis of 2 critical processes within fibroblast populations: First, it is unclear how much plasticity exists within fibroblast subpopulations. In our examination of scRNA-seq data in the human stomach, we observed a connection between PDGFRA-expressing telocyte-like fibroblasts and FBLN2-expressing inflammatory fibroblasts[12] (Figure 1A). Nevertheless, these populations were distinct from and without connection to myofibroblasts. These results support the concept that there is plasticity between the telocyte-like and inflammatory fibroblasts. In contrast, there is less support for plasticity between myofibroblasts and either telocyte-like or inflammatory fibroblasts. Further studies are clearly needed to assess the interconversion among fibroblast populations and the influence of epithelial cell lineages on this process.

Second, it remains unclear how individual populations of fibroblasts alter their expression patterns, especially for secreted factors that may strongly influence the behavior of epithelial cells. We determined that conditioned media from fibroblast culture isolated from both metaplasia and dysplasia-bearing mucosa induced dysplastic cell lineage transition in metaplastic cells.[12] However, conditioned media from fibroblasts isolated from the normal stomach did not elicit these changes. Thus, fibroblasts derived from either metaplastic mucosa or dysplastic mucosa may secrete key factors that can strongly influence the carcinogenesis paradigm. How these factors are up-regulated and in which fibroblast populations they are expressed remain obscure.

Finally, fibroblast populations involved in carcinogenesis may be tissue specific. Whereas studies in pancreas and breast cancers have emphasized that myofibroblasts are the major driver of carcinogenesis,[41,48] that is clearly not the case in the stomach. Some of this discordance could reflect the stage evaluated in these different studies. Fibroblast populations that promote metaplasia and dysplasia progression may differ from those that promote adenocarcinoma lineage survival and metastasis. The interaction of multiple fibroblast populations, eg, myofibroblasts, inflammatory fibroblasts, and telocytes, acting in concert may determine the ultimate influence of the stroma on epithelial cells. Again, more detailed characterization of fibroblasts participating at different points in the carcinogenesis cascade in different organs is needed to clarify common and tissue-specific mechanisms. In the future, definition of fibroblasts must rely on detailed expression analysis and multiple lineage markers correlated with geographical associations between fibroblast populations and epithelial lineages.

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