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# Metaplasia: tissue injury adaptation and a precursor to the dysplasia–cancer sequence

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## Abstract

Metaplasia is the replacement of one differentiated somatic cell type with another differentiated somatic cell type in the same tissue. Typically, metaplasia is triggered by environmental stimuli, which may act in concert with the deleterious effects of microorganisms and inflammation. The cell of origin for intestinal metaplasia in the oesophagus and stomach and for pancreatic acinar–ductal metaplasia has been posited through genetic mouse models and lineage tracing but has not been identified in other types of metaplasia, such as squamous metaplasia. A hallmark of metaplasia is a change in cellular identity, and this process can be regulated by transcription factors that initiate and/or maintain cellular identity, perhaps in concert with epigenetic reprogramming. Universally, metaplasia is a precursor to low-grade dysplasia, which can culminate in high-grade dysplasia and carcinoma. Improved clinical screening for and surveillance of metaplasia might lead to better prevention or early detection of dysplasia and cancer.

Metaplasia is the replacement of one differentiated cell type with another mature differentiated cell type that is not normally present in a specific tissue[1]. It is important to distinguish metaplasia from transdifferentiation. Transdifferentiation is a process in which one differentiated cell type converts into a completely different cell type present in the tissue[2]. Although the change from one type of cell to another in metaplasia might be a part of the normal adult maturation processes, as will be discussed later, it is not known to occur during embryonic development[3]. Metaplasia may be induced or accelerated by some sort of abnormal stimulus (for example, acid or base, and hence a change in pH; hormones; cigarette smoke; and alcohol)[4]. In the context of an abnormal stimulus, the original cells adapt to the environmental stress by changing identity. If the stimulus that caused metaplasia is removed, it is not clear whether the tissues can return to their normal pattern of differentiation. However, if the condition promoting metaplasia persists, metaplasia can progress to dysplasia and occasionally malignancy, as will be discussed later (for example, in the oesophagus)[5]. It is not realistically possible to determine the prevalence or incidence of tissue metaplasia of any type in the general population, as that information would require

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comprehensive and longitudinal monitoring, but one can glean some information about metaplasia and progression to dysplasia and cancer in the oesophagus, which has been studied more than metaplasia in other tissues. It is estimated that oesophageal intestinal metaplasia, termed Barrett oesophagus, will progress to cancer in 1 in 860 (0.12%) individuals with the condition[6].

The progression of metaplasia to dysplasia may be viewed as an 'oncogenic' phase, in contrast to the initial development of metaplasia, which is viewed as an 'adaptive' phase that occurs in response to environmental stress. While insights into the mechanisms leading to metaplasia are key to understanding tissue homeostasis as well as adaptation to stress, studying metaplasia progression to low-grade dysplasia and high-grade dysplasia can reveal major contributors to malignancy at early stages. Given the wide prevalence of tissue metaplasia and the limited progression to dysplasia and cancer, there is tremendous intersection of this topic with cancer prevention, early detection, risk stratification, prognosis and therapy. This Review focuses on the types of metaplasia, the potential cellular origins of metaplasia, the ways to model certain types of metaplasia and the potential opportunities for intervention to either reverse or arrest it.

## Tissue metaplasia

Metaplasia tends to occur in tissues constantly exposed to environmental agents, which are often injurious in nature. For example, the pulmonary system (lungs and trachea) and the gastrointestinal tract are common sites of metaplasia owing to their contacts with air and food, respectively. As a result, the tissue epithelial structure adapts through metaplasia, with definitive morphological changes. The type of metaplasia depends upon the resident tissue. Metaplasia may be categorized broadly as squamous metaplasia, intestinal metaplasia or acinar–ductal metaplasia (ADM) (TABLE 1).

### Squamous metaplasia

Lung squamous metaplasia can occur in either the alveolar epithelium or the airway epithelium. Metaplasia of the alveolar epithelium features the replacement of alveolar cells (normally a unilayer of cuboidal or columnar cells) with squamous epithelium, whereas metaplasia of the airway epithelium features the replacement of bronchiolar or bronchial epithelium with squamous epithelium[7] (FIG. 1). Squamous metaplasia comprises multiple layers of cells and is believed to be resistant to injury compared with metaplasia of the alveolar, bronchial or bronchiolar epithelium. As a result of exposure to injury, squamous metaplasia may be accompanied by varying grades of inflammation, fibrosis and necrosis. The lung neoplasias that can emerge from squamous metaplasia include cystic keratinizing epithelioma and squamous cell carcinoma[8].

Another illustration of squamous metaplasia is observed in the cervix. The endocervix comprises a simple columnar (glandular) epithelium. By contrast, the ectocervix is composed of stratified squamous epithelium, forming a squamocolumnar junction between the endocervix and the ectocervix. During puberty, the endocervix reconfigures (everts) to the ectocervix, resulting in exposure of the ectocervix to an acidic milieu[9]. This environment triggers a metaplastic response, which is initially patchy in the crypts and culminates in total

replacement by squamous epithelium[10]. Human papillomavirus (HPV) infection of metaplastic squamous epithelium can result in dysplasia and squamous cell cancer[11]. HPV is associated with nearly all cervical dysplastic and cancer tissues[12,13].

Other types of squamous metaplasia are rare. Breast squamous metaplasia may be observed in fibroadenomas, cysts, abscesses and chronic inflammation, and is almost always benign[14,15]. It is rare for breast squamous metaplasia to progress to breast squamous cell carcinoma, although this cancer accounts for only <1% of all breast malignancies[16,17]. Skin squamous metaplasia can be observed in the setting of ulcers or scars and may be a precursor to squamous cell carcinoma[18,19]. Similarly, squamous metaplasia has been noted in sebaceous glands in the skin and other issues[19].

## Intestinal metaplasia

The second major tissue metaplastic subtype is intestinal metaplasia, which is found in the distal oesophagus at the gastro-oesophageal junction or in the glandular stomach (TABLE 1). In the case of Barrett oesophagus, admixture of acid and bile is believed to result in mucosal injury, inflammation, cellular oxidative stress and the production of reactive oxygen species (ROS), thereby creating a milieu permissive for metaplasia[20–24] (FIG. 2). Acid reflux alone or with bile salts can increase ROS in models of Barrett oesophagus[25]. In the setting of chronic inflammation, long-term exposure to ROS can damage proteins, lipids, mitochondria and DNA[26]. This damage can lead to dysfunctional mitochondria, altered gene expression patterns, induction of metaplasia and transformation of the epithelium. Barrett oesophagus can progress to low-grade dysplasia and high-grade dysplasia and culminate in oesophageal adenocarcinoma (EAC)[27,28]. Ablative approaches, such as radiofrequency ablation and endoscopic mucosal resection, are employed in dysplastic states[29,30] and result in diminished progression to EAC. Interestingly, even after ablation, there is a risk of recurrence of Barrett oesophagus[31,32]. One might speculate that all abnormal tissue was not ablated successfully, allowing expansion of residual Barrett oesophageal tissue, and/or that squamous progenitor cells have been reprogrammed to an intestinal metaplasia fate.

In the case of the glandular stomach, chronic *Helicobacter pylori* infection, which is highly prevalent globally, can lead to the loss of acid-secreting parietal cells in some patients[33]. Pathologists refer to the condition in which parietal and chief cells are lost as chronic atrophic gastritis. Although the most histologically obvious change that occurs in atrophic gastritis is the loss of parietal cells, it should be noted that the digestive-enzyme-secreting chief cells are also no longer present. As parietal cells die, metaplastic cells that express abundant spasmolytic polypeptide (SP, also known as TFF2) emerge; thus, this type of metaplasia is referred to as spasmolytic polypeptide-expressing metaplasia (SPEM)[34]. Of note, parietal cell apoptosis is insufficient to induce metaplasia[35].

The factors that contribute to the emergence of gastric intestinal metaplasia include but are not limited to ongoing *H. pylori* infection, bile reflux, cigarette smoking, alcohol consumption and a diet low in fruit, vegetable and vitamin C intake and high in salt intake[36]. Autoimmune gastritis can also cause atrophic gastritis, SPEM and intestinal metaplasia[34,37]. The foci of gastric intestinal metaplasia tend to appear initially at the antrum–corpus junction. Over time, the foci enlarge and converge, involving the antrum and the corpus[38].

Complete gastric intestinal metaplasia resembles the small intestinal epithelium, with evidence of all small intestinal cell lineages and full expression of brush border enzymes[38].

Incomplete gastric intestinal metaplasia resembles the colonic epithelium, with incomplete mucin expression and the absence of a mature brush border (similar to in Barrett oesophagus)[38]. Dysplastic foci may eventually appear within areas of intestinal metaplasia. Reminiscent of intestinal metaplasia in the oesophagus, intestinal metaplasia in the stomach can also progress to low-grade dysplasia and high-grade dysplasia and culminate in gastric adenocarcinoma[36]. The true frequency of progression to adenocarcinoma in the stomach is difficult to discern, given the large surface area of the gastric mucosa (which cannot be easily covered with random tissue sampling), the lack of imaging modalities to guide targeted tissue sampling during endoscopy, and the fact that the susceptible populations in Asia, Africa, Central America and South America are too large for uniform and standardized approaches to screening and surveillance[39]. Nevertheless, clinical progress is being made with population-based approaches in countries such as Japan, Korea and Colombia[40–42].

### ADM

The third major example of metaplasia is ADM in the pancreas (FIG. 3; TABLE 1). In mice, ADM is associated with acute or chronic inflammation[43]. In humans, ADM may be found in chronic pancreatitis[44]. ADM is reversible in mouse models, where resolution of the acute inflammatory stimulus leads to reversion to the original acinar and ductal cell lineages[45]. Chronic inflammation in the pancreas may also yield some permanent ADM lesions. In mice, ADM is a well-defined precursor to pancreatic intraepithelial neoplasia (PanIN), and eventually, PanIN lesions may progress to pancreatic ductal adenocarcinoma[46,47]. Lineage tracing in mice reveals that ADM occurs *in vivo* and that these ADM lesions can progress to PanIN[48]. Epithelial explants from the exocrine pancreas lose acinar cells in culture, with subsequent expansion of ductal cells[49–52]. Human acinar cells also undergo ADM, as observed by *in vitro* lineage tracing[53].

### Other tissue ADM

ADM has been observed infrequently in salivary glands and mammary glands (TABLE 1); although the meaning of this phenomenon is unclear, there is much overlap in morphological features among the pancreas, the salivary gland and the mammary gland. ADM in the mouse salivary gland is a result of the loss of p120-catenin (also known as catenin-δ1), and mice lacking p120-catenin in the salivary glands die postnatally, likely because the disruptions to salivary secretion affect digestion[54]. E-cadherin is stabilized by p120-catenin at the cell membrane as part of adherens junctions[55,56], and the loss of p120-catenin creates an environment for cell–cell disaggregation and local inflammation and is a likely stimulus for salivary ADM.

## Cell of origin

### Barrett oesophagus

In tissue metaplasia, the epithelium often contains a mixture of resident and ectopic cells. Therefore, the cell of origin for the metaplastic cells becomes ambiguous and sometimes

controversial. Barrett oesophagus has garnered attention in this context[57–60]. Studies in transgenic mice have revealed that the interleukin-1β (IL-1β)–IL-6 signalling cascade and Delta-like protein 1 (DLL1)-dependent Notch signalling cause Barrett oesophagus[61]. Lineage tracing indicates that these lesions arise from leucine-rich repeat-containing G-protein coupled receptor 5 $(LGR5)^+$ gastric cardia stem cells[61].

Another study in mice observed that *Trp63* (which encodes the transcription factor p63)-null embryos rapidly develop intestine-like metaplasia at the squamocolumnar junction of the oesophagus and stomach[62]. Of note, *Trp63*-knockout mice die at birth and also have truncation of the limbs and striking absence of epidermal, prostate, breast and urothelial tissues, findings suggestive of the loss of ectodermal stem cells[63]. When *Trp63* is deleted, the simple columnar epithelium expands into the stratified squamous epithelial territory and demonstrates certain intestinal-like epithelial characteristics (for example, Alcian blue-positive staining). The authors of this study further hypothesized that the *Trp63*-null embryonic columnar epithelium persists in the adult squamocolumnar junction[62]. When the neighbouring squamous epithelium is damaged, the residual *Trp63*-null columnar cells can expand and thereby resemble Barrett metaplasia[62].

Insights have also emerged from human studies of Barrett oesophagus through the use of techniques such as microdissection, gene mutation analysis (for example, of mutations in mitochondrial DNA (mtDNA)), gene expression analysis of lineage-specific genes, immunohistochemistry and, occasionally, *in situ* hybridization. Some of these studies reveal that Barrett glands have features in common with gastric glands, resulting in the conclusion that Barrett oesophagus originates from potential stem cells in the gastric cardia[64]. As an extension of this logic, through the use of markers of proliferation and specific markers of Barrett glands, it has been suggested that Barrett glands may have properties overlapping those of pyloric gastric glands, which are located in the distal antrum and not near the squamocolumnar junction[65].

While these studies suggest that the cellular origin of Barrett oesophagus is in the gastric cardia region of the squamocolumnar junction, studies with 3D organotypic cultures have revealed a possible cellular origin in oesophageal basal cells[66]. Here, Barrett metaplasia development may depend upon the coordinated actions of MYC, the transcription factor caudal type homeobox 2 (CDX2) and the inhibition of Notch signalling[66]. Active Notch signalling may be important in the maintenance of the columnar cell lineage in Barrett oesophagus[61]. Mechanistically, gastro-oesophageal reflux may induce cellular reprogramming of the oesophageal squamous epithelium as a basis for metaplasia[67]. Presumably, this reprogramming could occur in oesophageal stem or progenitor cells or even in differentiated cells. As a separate consideration, bone marrow progenitor cells were putatively shown to act as a cell of origin for oesophageal metaplasia in a rat model, but it is not clear in what physiological context this might occur[68]. To date, there is a lack of *in vivo* evidence in genetic mouse models that proves that oesophageal stem or progenitor cells are the source of Barrett oesophagus.

Another possible cell of origin for Barrett oesophagus is from the oesophageal submucosal glands. DNA sequencing has revealed that human Barrett oesophagus and the neighbouring

submucosal gland epithelium share the same mutations and loss of heterozygosity in the tumour suppressors cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and *TP53* (which encodes p53) (REF. 69). Histological analysis has revealed an association of human ductal metaplastic oesophageal submucosal glands with Barrett high-grade dysplasia and EAC[70]. In a porcine model, radiofrequency ablation of the oesophageal epithelium resulted in the conversion of oesophageal submucosal glands to a ductal phenotype with expression of the SRY-box 9 (SOX9) transcription factor, a ductal marker[71]. Overall, it is intriguing that ADM may represent a possible underpinning of Barrett oesophagus if a cell of origin resides in the oesophageal submucosal glands, as the same type of metaplasia is found in the pancreas. Studies in mice are not feasible, as mice lack oesophageal submucosal glands.

How can one reconcile the seemingly divergent studies that implicate different sources for the cell or cells of origin? Some aspects are related to differences in model systems (from mouse to pig to human), experimental approaches (non-genetic to genetic) and nomenclature of what constitutes a stem cell versus a progenitor cell. Although there has been a tendency to conclude that the cell of origin resides in only one tissue compartment, it is tempting to speculate that more than one cellular origin may exist for the initiation of Barrett oesophagus. The cell of origin may depend upon context-specific cell-autonomous and non-cell-autonomous cues.

## Gastric intestinal metaplasia

Gastric intestinal metaplasia in the glandular stomach arises in the setting of atrophic gastritis. There are two competing models for the origin of gastric metaplasia, and they will both be summarized. Intestinal metaplasia may arise from SPEM[72] (FIG. 4) or perhaps directly from chief cells[73,74] or gastric isthmus stem cells[75]. SPEM is associated with the development of dysplasia in *H. pylori*-infected mouse models and is also observed in association with human gastric cancer[73,76]. Is there a specific subset of cells within chief cells that trigger SPEM or cancer? It is known that $LGR5^+$ cells with properties of self-renewal are located in the gastric antrum and yield long-lived gastric units *in vitro*[77]. Furthermore, reserve $LGR5^+$ cells have now been identified within mouse and human chief cells and can catalyse epithelial regeneration after injury *in vitro*[78]. Although $LGR5^+$ cells do not appear to give rise to either SPEM[79] or intestinal metaplasia, they have been found to give rise to early gastric cancer[78].

Other studies advocate that the cell of origin for gastric intestinal metaplasia resides in the gastric isthmus[80]. For instance, MIST1 (also known as $BHLHA15)^+$ stem cells in the gastric isthmus display clonal expansion in the setting of $Kras^{G12D}$ mutation, resulting in gastric intestinal metaplasia[75,81]. Through the use of genetic mouse models and lineage tracing over time to determine the source of proliferation, one compelling study found that metaplastic cells are long-lived, suggesting that reprogramming occurs in long-lived stem cells and does not involve transdifferentiation[75]. Furthermore, ablating the stem cells blocked metaplasia and cancer.

### Other types of metaplasia

From the viewpoint of cervical squamous metaplasia, endocervical crypts may be seen deep to the surface epithelium. One might speculate that such crypts are a potential morphological origin of squamous metaplasia, but this claim has not yet been substantiated through genetic *in vivo* lineage-tracing experiments. Other types of tissue metaplasia are described in pathology specimens, and the dearth of studies does not permit conclusions about the cell(s) of origin.

## Expansion of metaplastic clones

Lineage tracing in humans, by following certain mutations in mtDNA, has demonstrated that the expanded metaplastic epithelia share the same mtDNA point mutations as those in human Barrett oesophagus and gastric intestinal metaplasia. These findings support the premise that Barrett oesophagus and gastric intestinal metaplasia are clonally evolved[64,82–84] and raise the possibility that metaplasia in these tissues initially occurs in stem cells and that subsequent gland fission promotes the spread of intestinal metaplasia[85]. The true identity of the original cells remains to be established; alternatively, gene reprogramming might be occurring in progenitor cells, or possibly in differentiated cells, as rare events that trigger metaplasia. Notably, long-lived stem cells have been identified in both human and mouse oesophagus and stomach[86–89], with compelling evidence obtained in the oesophagus from lineage tracing in a genetic mouse model in which keratin 15 $(KRT15)^+$ oesophageal basal cells are long-lived and contribute to tissue regeneration after radiation injury.

## Regulation of metaplasia

### Transcription factors in metaplasia: p63 and SOX2

Some drivers of tissue metaplasia have been identified and revolve around transcription factors whose functions contribute to cellular identity and plasticity during metaplasia. For example, the transcription factor SOX2 plays a critical role in the generation of the stratified squamous epithelium lining the oesophagus and the anterior portion of the stomach in mice (forestomach; a part of the stomach that is present in mice but not humans)[90]. Significant reductions in SOX2 protein levels lead to the formation of simple columnar epithelium in place of stratified squamous cells[90]. Moreover, the metaplastic cells secrete mucins, similar to the secretion of mucins by columnar cells in the glandular stomach and small intestine. Interestingly, mesenchymal transcription factors can also modulate squamous cell specification. Deletion of the gene encoding homeobox protein BarH-like 1 (BARX1), a transcription factor enriched in the mesenchyme, also results in the presence of secretory columnar cells in the squamous cell region of the mouse oesophagus and forestomach[91]. The metaplastic epithelium ectopically expresses mucin 5AC (MUC5AC)[91]. These findings suggest that both epithelial (for example, SOX2 and p63) and mesenchymal (BARX1) factors are required to establish squamous cell identity in the upper gastrointestinal tract.

In the adult lung, the presence of squamous metaplasia is characterized by an expansion of $p63^+$ $SOX2^+$ cells in the proximal lung airways[92]. Although both p63 and SOX2 are

expressed exclusively in the basal progenitor cells of the oesophagus and trachea, the latter is lined by a simple columnar epithelium in adults. Therefore, the presence of abundant $p63^+$ $SOX2^+$ basal cells in the lung metaplastic squamous epithelium suggests the adoption of an oesophageal basal cell lineage[93,94].

## Transcription factors in metaplasia: CDX2

Intestinal metaplasia identity may be fostered by the transcription factor CDX2, which is overexpressed in both Barrett oesophagus and gastric intestinal metaplasia[95,96]. Indeed, transgenic mice with *Cdx2* expression targeted to the glandular stomach develop intestinal metaplasia[97]. Provocatively, conditional knockout of *Cdx2* in the mouse intestine yields squamous metaplasia accompanied by the ectopic presence of $p63^+$ $SOX2^+$ basal cells[98]. CDX2 controls chromatin access for interactions with other transcription factors to modulate cell cycle progression, proliferation and differentiation[99,100].

## Transcription factors in ADM: PTF1A and MIST1

Pancreatic ADM is driven by the loss of acinar-lineage-specific transcription factors, such as pancreas transcription factor 1 subunit α (PTF1A), and the induction of the paired mesoderm homeobox protein 1 (PRRX1)–SOX9 axis[101–104]. The molecular basis of ADM involves transforming growth factor-α (TGFα) and epidermal growth factor receptor (EGFR) signalling[43]. Transgenic mice with *Tgfa* overexpression in the exocrine pancreas show evidence of duct-like cells[49]. Acinar-specific expression of activated KRAS in mice (*LSL-Kras*$^{G12D/+}$*;Ptf1a*$^{Cre/+}$ mice) results in ADM[105]. These metaplastic structures are proliferative and express Notch target genes[106–108]. Transgenic expression of pancreatic and duodenal homeobox 1 (*Pdx1*) in the *Ptf1a* locus[109] results in the transition of acinar cells to duct-like cells and is regulated through signal transducer and activator of transcription 3 (STAT3) activation[110]. Pancreatic ADM lesions are associated with inflammation with a concomitant increase in MEK–ERK signalling[111]. In human pancreatic sections, the close juxtaposition of ADM and PanIN suggests but does not prove progression of ADM to PanIN[112].

MIST1 is a global regulator of secretory cell architecture in multiple professional secretory cells, such as the acinar cells of the pancreas and salivary gland and the chief cells of the stomach[113]. During metaplasia in the stomach, salivary gland and pancreas, *Mist1* is one of the first genes whose expression is decreased as cells scale down their secretion[114], and forced expression or loss of MIST1 interferes with the induction of and recovery from metaplasia, respectively[115–117]. Specifically, deletion of *Mist1* leads to reduced levels of amylase, an enzyme specifically produced by mature exocrine pancreatic cells. Lineage tracing with cells expressing *lacZ* in the *Mist1* locus (*Mist1*$^-$ *lacZ*$^+$ cells) has demonstrated that these cells express ductal genes (for example, keratin 20 (*Krt20*)), suggesting that a cell-fate switch occurs in differentiated exocrine cells[102]. Of note is that the same *Mist1*$^-$ *lacZ*$^+$ cells also maintain moderate levels of nuclear protein transcription regulator 1 (*Nupr1*)[118] and regenerating islet-derived 1 (*Reg1*)[119], genes that are expressed in embryonic pancreatic cells.

Deletion of *Mist1* also blocks the differentiation of chief cells in the base of gastric glandular units[120]. Consequently, uncommitted epithelial cells accumulate along the pathway where the derivatives of isthmus progenitor cells migrate[120]. More importantly, SPEM occurs in the glandular stomach of *Mist1*$^{-/-}$ mice upon treatment with the protonophore DMP-777 or its analogue L635, which induces the loss of parietal cells and inflammation[121]. These findings suggest that MIST1 is critical for the maturation of epithelial progenitor cells in the developing pancreas and glandular stomach. In both organs, blocking the differentiation process seems to facilitate the incidence of metaplasia. It will be interesting to determine whether conditional deletion of *Mist1* in the adult also interferes with epithelial differentiation and facilitates metaplasia.

## Epigenetic and genomic considerations

It is conceivable that these transcription factors, in specific tissues, function in a coordinated fashion with epigenetic regulators that fuel chromatin remodelling to permit the binding of genomic loci by the transcription factors to create a cellular framework for metaplasia. This type of regulation has yet to be definitively identified in tissue metaplasia but has been suggested to occur in Barrett oesophagus[122,123].

Ideally, genomic analysis of metaplasia across tissue types might reveal common processes, but anatomic location often serves as a barrier to obtaining tissues for analysis. In the case of Barrett oesophagus, tissue is accessible via upper endoscopy. To that end, whole and paired exomic sequencing of normal and Barrett oesophagus has unravelled a crucial role for mutations of *TP53* and *CDKN2A*[124–126]. Although the exact consequences of *TP53* mutations in the development of Barrett oesophagus remain to be elucidated, it is possible that such mutations might serve as a gatekeeper for the maintenance of metaplasia and/or drive the conversion of metaplasia to low-grade dysplasia in the oesophagus[124] and perhaps the stomach as well[127]. Loss of *CDKN2A* results in enhanced cell cycle progression. Additionally, mutations of other transcription factors have been detected in Barrett oesophagus, for example, *GATA6* amplification and *SMAD4* deletion[125]. Specifically, *SMAD4* deletion could foster a pro-proliferative environment, and *GATA6* amplification might also have oncogenic properties. It will be interesting in the future to determine the role of these transcription factors in the development of Barrett oesophagus and gastric intestinal metaplasia.

Although EAC is highly aneuploid, with multiple high-level gains and losses, Barrett oesophagus is typically copy number neutral (99.7%, range 62.8–100%, of genomes had a copy number of 2)[126]. Regarding specific alterations, recurrent loss of 9p heterozygosity was found in 11 of 23 (48%) samples, and no high-level amplifications were observed. The number of focal deletions was found to increase with increasing stage from non-dysplastic Barrett oesophagus to dysplastic Barrett oesophagus to EAC[125]. These deletions in Barrett oesophagus were often not shared with the patients' paired EAC tissues, suggesting that they may not be important in progression to cancer. Focal amplifications seemed to be observed almost exclusively in EAC, with rare examples of these changes in samples of high-grade dysplasia[125]. Genome doubling events were also commonly identified in EAC and only rarely identified in high-grade dysplasia. No genome doubling was seen in low-grade

dysplasia or non-dysplastic Barrett oesophagus[125]. Taken together, these studies suggest a pattern where there is acquisition of a small number of copy number changes in non-dysplastic Barrett oesophagus and low-grade dysplasia[125,126]. Many of these changes seem to be present in both patients who progress to higher-stage disease and those who have stable non-progressive disease. However, around the time of development of high-grade dysplasia and then EAC, there is a dramatic rise in the number of copy number changes found throughout the genome[125,126].

## Pathogens, inflammation and immune cells are key factors in metaplasia

The non-epithelial actions (effects on immune cells, inflammatory cells and fibroblasts) of acid and/or bile, pathogens, cigarette smoke, alcohol and nutritional deficiencies conspire to foster a stressful environment in which epithelial cells are forced to change identity and lineage specification. Interestingly, microorganisms may find these shifts in environmental cues very attractive. For example, chronic infection with *H. pylori*, especially virulent strains, results in loss of parietal cells and in acid production, which are key drivers of gastric intestinal metaplasia[33]. These environmental changes may be mediated in part through the local recruitment of lymphocytes and the secretion of cytokines. Invariably, HPV oncogenic strains are associated with cervical squamous metaplasia and facilitate the development of squamous dysplasia[13]. Indeed, there may be a role for communities of microorganisms in oesophageal intestinal metaplasia[128] and, by extension, possibly in lung squamous metaplasia and skin squamous metaplasia.

Pro-inflammatory and immunological cues influence epithelial cell signalling and the induction of metaplasia. This mechanism has been established for the IL-6–STAT3 pathway in Barrett oesophagus[61] and pancreatic ADM[129]. Pancreatic ADM lesions are commonly associated with inflammation[111]. Immune cells in the microenvironment play important roles in metaplasia. For example, depletion of macrophages in L635-induced gastric SPEM prevents its development[130]. Macrophage-secreted inflammatory cytokines, such as tumour necrosis factor (TNF) and CC motif chemokine 5 (CCL5), play roles in pancreatic ADM, with contributions from macrophage-released matrix metalloproteinases (MMPs), such as MMP9, as well[131,132]. Recently, it was demonstrated that IL-13 alters macrophage populations from an inflammatory macrophage subpopulation to an alternatively activated macrophage subpopulation in ADM[133]. The development of Barrett-like metaplasia in the mouse requires the suppression of $CD8^+$ T cell-dependent apoptosis of epithelial cells, which is probably mediated by $CD11b^+$ $GR1^+$ immature myeloid cells or myeloid-derived suppressor cells[134].

Activated fibroblasts interplay with epithelial cells in the development of metaplasia through aberrant sonic hedgehog (SHH) signalling[135–138]. In the context of Barrett oesophagus, it has been proposed that epithelial cells induce SHH expression, which in turn promotes stromal expression of SHH target genes such as patched 1 (*PTCH1*) and bone morphogenetic protein 4 (*BMP4*), and may result in the expression of epithelial *SOX9* and cytokeratins[137]. Similarly, it has been shown that in the pancreas, genetic ablation of smoothened (*Smo*), which mediates SHH signalling, in fibroblasts results in the activation of AKT and the transcription factor GLI2 and increased ADM[135,139]. Another factor in the

stroma is the transcription factor ETS2. Stromal ETS2 in the mouse pancreas driven by *Kras*$^{G12D}$-induced ADM has been shown to be important for the recruitment of chemokines and immune cells, such as T regulatory cells, myeloid-derived suppressor cells and mature macrophages[140].

Cell intrinsic events also appear to be of functional relevance in tissue metaplasia. To that end, mutant KRAS signalling is critical for pancreatic ADM[141,142]. Similarly, mutant KRAS in gastric chief cells results in gastric SPEM[143]. MYC, which is downstream of mutant KRAS, is associated with intestinal metaplasia in the oesophagus and stomach and with squamous metaplasia in the lung[144–146].

## Future translational directions

Each type of metaplasia is identified through characteristic morphology, histopathology and lineage-specific markers (including transcription factors). However, the roles of aetiological factors (such as acid, bile and cigarette smoke) are different in each type of metaplasia. The initiation and/or maintenance of oesophageal and gastric intestinal metaplasia and pancreatic ADM may share certain principles: activation of common cell signalling pathways (including mutant KRAS) and the roles of pro-inflammatory cells, immune cells and fibroblasts, which may act in concert to promote metaplasia.

Intestinal metaplasia, whether in the oesophagus or stomach, is a *bona fide* precursor to a continuum of low-grade dysplasia to high-grade dysplasia to adenocarcinoma[82,87,147]. Squamous metaplasia, likewise, can progress to dysplasia and squamous cell carcinoma[8]. Pancreatic ADM, at least in mice, is a precursor to PanIN and pancreatic ductal adenocarcinoma[148]. Considering that metaplasia is a precursor to dysplasia and cancer, there is still a need to elucidate further the entire spectrum of events that are responsible in this continuum.

Screening for metaplasia and the metaplasia-dysplasia continuum is possible when tissue access is possible. This is the case in the oesophagus and stomach, which may be assessed by upper endoscopy, and in the cervix, which may be assessed by Pap smear. In each tissue, the finding of low-grade dysplasia requires closer evaluation by the pathologist and closer monitoring by the clinician. The identification of patient groups at risk of dysplasia and cancer enables the use of more elaborate screening and surveillance strategies. Examples include genomic and transcriptome analyses that may be helpful in different tissue metaplastic states, as has been done in Barrett oesophagus. Furthermore, cell-free DNA and circulating epithelial and tumour cells may provide further information for subtyping patients in the future. Circulating materials might identify those patients who are likely to progress to dysplasia or who harbour dysplastic cells. Another at-risk population group comprises individuals with an inherited genetic predisposition to cancer. It does not appear that most cancers in inherited genetic syndromes evolve through metaplasia. However, a small subset of Barrett oesophagus cases may be heritable[149,150].

From a therapeutic viewpoint, ablation through mechanical and chemical modalities in the cervix, bladder and skin is an approach to eradicating metaplastic lesions. It is difficult to

estimate how many cancers would be averted with ablative strategies, as population-based calculations are lacking in almost all tissue metaplasia-dysplasia-cancer states, with the possible exception of the progression of Barrett oesophageal dysplasia to cancer. For the progression of Barrett oesophagus, one would imagine a reduction of the observed 0.12% frequency of progression[6] if all patients could be captured; however, ablation is recommended only for low-grade and high-grade dysplasia and not for metaplasia. Gastric intestinal metaplasia with low-grade dysplasia requires close monitoring, and high-grade dysplasia requires endoscopic or surgical resection[151].

Future research in metaplasia should continue to focus or elaborate upon determining cell or cells of origin, carrying out new or expanded genomic analyses, developing more model systems (for example, 3D cultures) and applying this knowledge to prevention and therapy. Furthermore, given the nature of tissue metaplasia, the identification of common mechanisms and pathways in different tissues may alleviate the barriers to prevention and therapy.

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## Glossary

**Dysplasia**
A condition in which cells have abnormal cellular architecture, with nuclear atypia, nuclear hyperchromasia and loss of cell polarity.

**Glandular stomach**
The part of stomach that is responsible for normal physiological functions.

**Parietal cells**
Also known as oxyntic cells, these are the acid-producing cells in the stomach epithelium.

**Chief cells**
Pepsinogen- and chymosin-producing cells in the stomach epithelium.

**Atrophic gastritis**
Loss of segments of the gastric mucosa in the setting of inflammation.

**Spasmolytic polypeptide-expressing metaplasia**
(SPEM). Metaplastic cells that are marked by spasmolytic polypeptide expression in the stomach epithelium.

**Brush border**
The small intestinal epithelial microvilli-covered surface that expresses brush border enzymes that mediate the transport of micronutrients from the lumen to within the epithelium.

**Exocrine pancreas**

Compartments of acinar and ductal cells that secrete and transport digestive enzymes.

**Gastric cardia**

The small region that constitutes the first part of the stomach and is composed of columnar cells.

**Oesophageal submucosal glands**

Distinct structures below the oesophageal epithelium that have secretory functions.

**Foveolar hyperplasia**

A characteristic of reactive gastritis observed in the gastric antrum and body.

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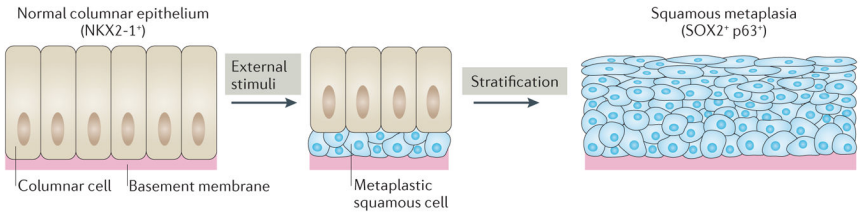


**Figure 1. Squamous metaplasia**

In tissue columnar cells (for example, in the lung or cervix), external stimuli (for example, low vaginal pH in the cervix and cigarette smoke in the lung) promote the conversion to metaplastic squamous cells, which stratify. In the lung, columnar cells are identified by the expression of homeobox protein Nkx2.1 (NKX2-1), and squamous cells are enriched for p63 and SRY-box 2 (SOX2), similar to oesophageal basal cells and their marked expression of p63 and SOX2.

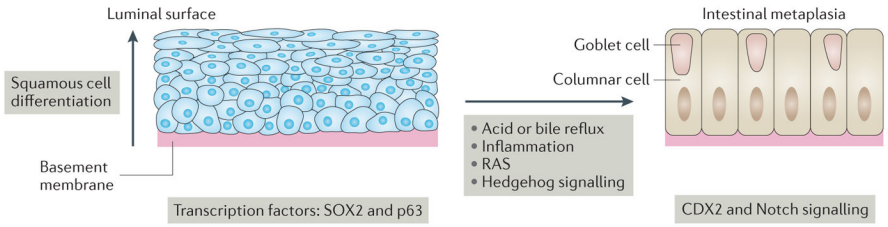


**Figure 2. Intestinal metaplasia in the oesophagus**

The normal oesophageal squamous epithelial proliferative basal cells ($p63^+$ and SRY-box 2 $(SOX2)^+$) undergo early and terminal differentiation as they migrate towards the luminal surface. In concert with acid or bile reflux and pro-inflammatory stimuli (for example, interleukin 6 (IL-6)–signal transducer and activator of transcription 3 (STAT3)), incomplete intestinal metaplasia (presence of columnar cells and goblet cells and absence of Paneth cells and enteroendocrine cells) appears. Goblet cells produce mucins, which are cytoprotective. Mesenchymal homeobox protein BarH-like 1 (BARX1) and bone morphogenetic protein 4 (BMP4) (induced by epithelial sonic hedgehog (SHH)) are critical for the transition from the squamous cell lineage to the intestinal (columnar) cell lineage. Caudal type homeobox 2 (CDX2) is critical for the induction of columnar cells, and Notch signalling is a key pathway for the maintenance of the columnar cell lineage. Genomic studies have revealed that *TP53* mutation is important in the earliest dysplastic clones. In this figure, the underlying premise is on the morphological and molecular changes that occur, but the cell of origin is not implied.

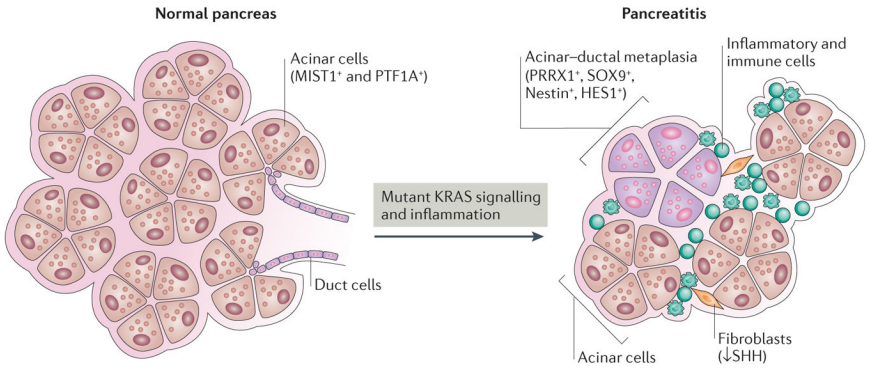


**Figure 3. Acinar–ductal metaplasia**

Normal pancreatic acinar cells, which compose the bulk of the pancreatic parenchyma and express pancreas transcription factor 1 subunit α (PTF1A) and MIST1, can convert into a ductal-cell-like state, which is referred to as acinar–ductal metaplasia (ADM). Pro-inflammatory stimuli from T cells, macrophages and myeloid-derived suppressor cells (MDSCs) and mutant KRAS are critical for the appearance of ADM lesions. These lesions are enriched for paired mesoderm homeobox protein 1 (PRRX1) and SRY-box 9 (SOX9) transcription factors, as well as for $Nestin^+$ and the transcription factor $HES1^+$ cells, the latter owing to active Notch signalling. Pancreatic fibroblasts are a source of sonic hedgehog (SHH), which slows ADM formation.

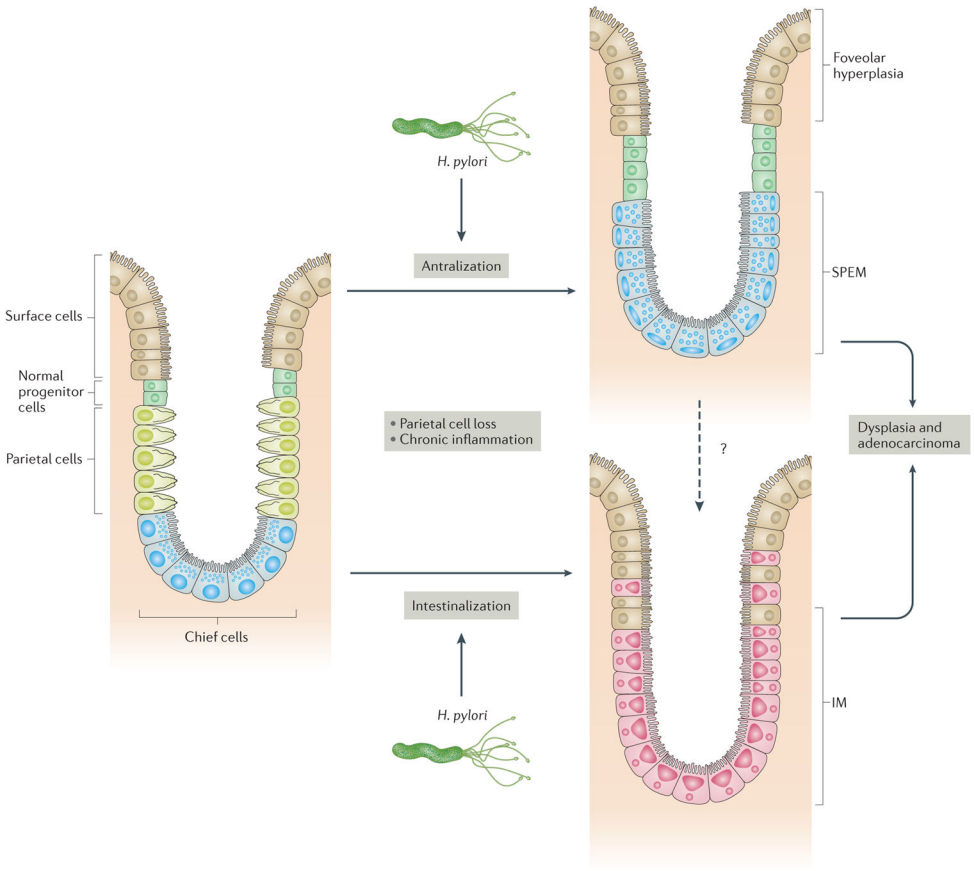


**Figure 4. Spasmolytic polypeptide-expressing metaplasia and gastric intestinal metaplasia**

The gastric epithelium harbours chief cells at the base, underneath acid-producing parietal cells, progenitor cells (or stem cells) and surface cells. In the face of *Helicobacter pylori* infection, there is parietal cell loss and chronic inflammation. One pathway results in foveolar hyperplasia and spasmolytic polypeptide-expressing metaplasia (SPEM), which might be a precursor to intestinal metaplasia (IM, indicated by the dashed arrow). Another pathway leads directly to IM. Both SPEM and IM are precursors to dysplasia and later adenocarcinoma. Please refer to the main text for a discussion of cell of origin.

## Table 1

Types of tissue metaplasia and environmental stimuli

| Type of metaplasia | Stimulus | Transition in cell lineage | Precancerous |
|---|---|---|---|
| *Squamous metaplasia* | | | |
| Lung airway | Cigarette smoke | Columnar to squamous | Yes |
| Cervix | Low vaginal pH, human papillomavirus | Columnar to squamous | Yes |
| Mammary gland * | Inflammation, infection | ? | Yes |
| Sebaceous gland * | Inflammation | ? | Unclear |
| Skin * | Inflammation | Squamous (maintained) | Unclear |
| *Intestinal metaplasia* | | | |
| Oesophagus‡ | Acid and/or bile, obesity | Squamous to intestinal | Yes |
| Stomach | High salt intake, low vegetable and fruit intake, low vitamin C intake, *Helicobacter pylori* infection, autoimmune gastritis | Columnar (stomach) to intestinal | Yes |
| *Acinar–ductal metaplasia* | | | |
| Pancreas | Inflammation | Acinar to ductal | Yes |
| Mammary gland * | Inflammation | Acinar to ductal | Unclear |
| Salivary gland * | Inflammation | Acinar to ductal | Unclear |

* Much less investigated and inferred from descriptive pathology reports.

‡ Barrett oesophagus.