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Review

Diffuse gastric cancer: Emerging mechanisms of tumor initiation and progression

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ABSTRACT

Gastric cancer is globally the fourth leading cause of cancer-related deaths. Patients with diffuse-type gastric cancer (DGC) particularly have a poor prognosis that only marginally improved over the last decades, as conventional chemotherapies are frequently ineffective and specific therapies are unavailable. Early-stage DGC is characterized by intramucosal lesions of discohesive cells, which can be present for many years before the emergence of advanced DGC consisting of highly proliferative and invasive cells. The mechanisms underlying the key steps of DGC development and transition to aggressive tumors are starting to emerge. Novel mouse and organoid models for DGC, together with multi-omic analyses of DGC tumors, revealed contributions of both tumor cell-intrinsic alterations and gradual changes in the tumor microenvironment to DGC progression. In this review, we will discuss how these recent findings are leading towards an understanding of the cellular and molecular mechanisms responsible for DGC initiation and malignancy, which may provide opportunities for targeted therapies.

1. Introduction

Gastric cancer is the fourth leading cause of cancer-associated deaths worldwide, with over a million new cases and 760.000 deaths in 2020 [1]. Gastric cancer historically has been divided into three major subtypes based on histological characteristics: intestinal-, diffuse- and a mixed-type [2], although other (sub-)classification systems are in use (described in [3–8]). While the incidence of the intestinal-type has gradually declined over the last decades, the number of diffuse-type gastric cancer (DGC) cases has remained relatively constant [9,10]. Individuals diagnosed with DGC have a low survival rate (on average 18 months) that has only marginally improved over the last decades [10]. This poor prognosis is due to diagnosis usually being at a late tumor stage, and conventional treatments are frequently ineffective or result in resistance [11,12]. Early-stage DGC is asymptomatic and difficult to detect with current imaging modalities [13], and the turn-over point to aggressive advanced-stage DGC is poorly understood. The current clinical guideline for individuals with a genetic predisposition to develop hereditary DGC (HDGC) is therefore prophylactic removal of their stomachs [14]. Although DGC differs vastly from other gastric cancers in molecular basis and disease progression, patients usually are treated with the same chemotherapeutics that are non-specific for the mechanisms that drive their development [15]. An increased understanding of the mechanisms driving transition through the different stages of DGC progression could direct the development of more sensitive diagnostics and targeted treatments to enhance the prospects of DGC patients. In this review, we will provide an overview of the molecular and cellular processes underlying key steps of DGC development and discuss the current understanding as well as emerging concepts of the mechanisms responsible for DGC progression into aggressive tumors.

1.1. Clinical and histological stages of sporadic and hereditary DGC

In early-stage DGC, mutant cells delaminate from the gastric

Abbreviations: DGC, diffuse-type gastric cancer; HDGC, hereditary diffuse-type gastric cancer; SRC, signet ring cell; BM, basement membrane; MMP, matrix metalloprotease; EMT, epithelial-to-mesenchymal transition; CAF, cancer-associated fibroblast.

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epithelium and form small lesions within the mucosa (pT1a, Fig. 1) [14,16,17]. These intramucosal lesions contain diffusely spread signet ring cells (SRCs), which are characterized as mucin-filled cells with displaced, crescent-shaped nuclei [18,19]. Additionally, a small fraction of morphologically less differentiated cells is typically present at the base of these SRC lesions [19–21]. SRC lesions predominantly reside in the mesenchyme of the lamina propria (pT1a) but incidentally are observed to be confined within the basement membrane (BM) of epithelial glands (pTis, Fig. 1), which potentially represents the initial stage of DGC development [21–24]. Early-stage DGC is primarily detected in prophylactic resected stomachs of HDGC patients, who develop SRC lesions throughout their stomachs already from a young age [16,17]. The ratio of SRCs and poorly differentiated cells can vary between individual intramucosal lesions, and the increased abundance of poorly differentiated cells may be an early step of DGC progression (pT1a+, Fig. 1) [14]. Despite the presence of many early lesions, HDGC patients typically only develop a single advanced tumor over the course of years or decades, which is larger in size and has penetrated the submucosa and deeper tissue layers (≥pT2, Fig. 1) [14,19]. These malignant tumors largely consist of poorly differentiated cells that become highly migratory and can form metastases in the peritoneum, bone, lung and liver [19,25,26]. Sporadic DGC tumors are principally indistinguishable from advanced HDGC tumors by histological analysis and are therefore expected to follow a similar progression pattern. The step-wise appearance of more advanced-stage tumors in HDGC patients implies a progressive development of DGC, yet its remains to be answered whether advanced DGC originates from malignant transition of an early lesion or constitutes an independent event. In this review, we will outline the current understanding of the development of the different stages of DGC and factors that might facilitate the transition between stages.

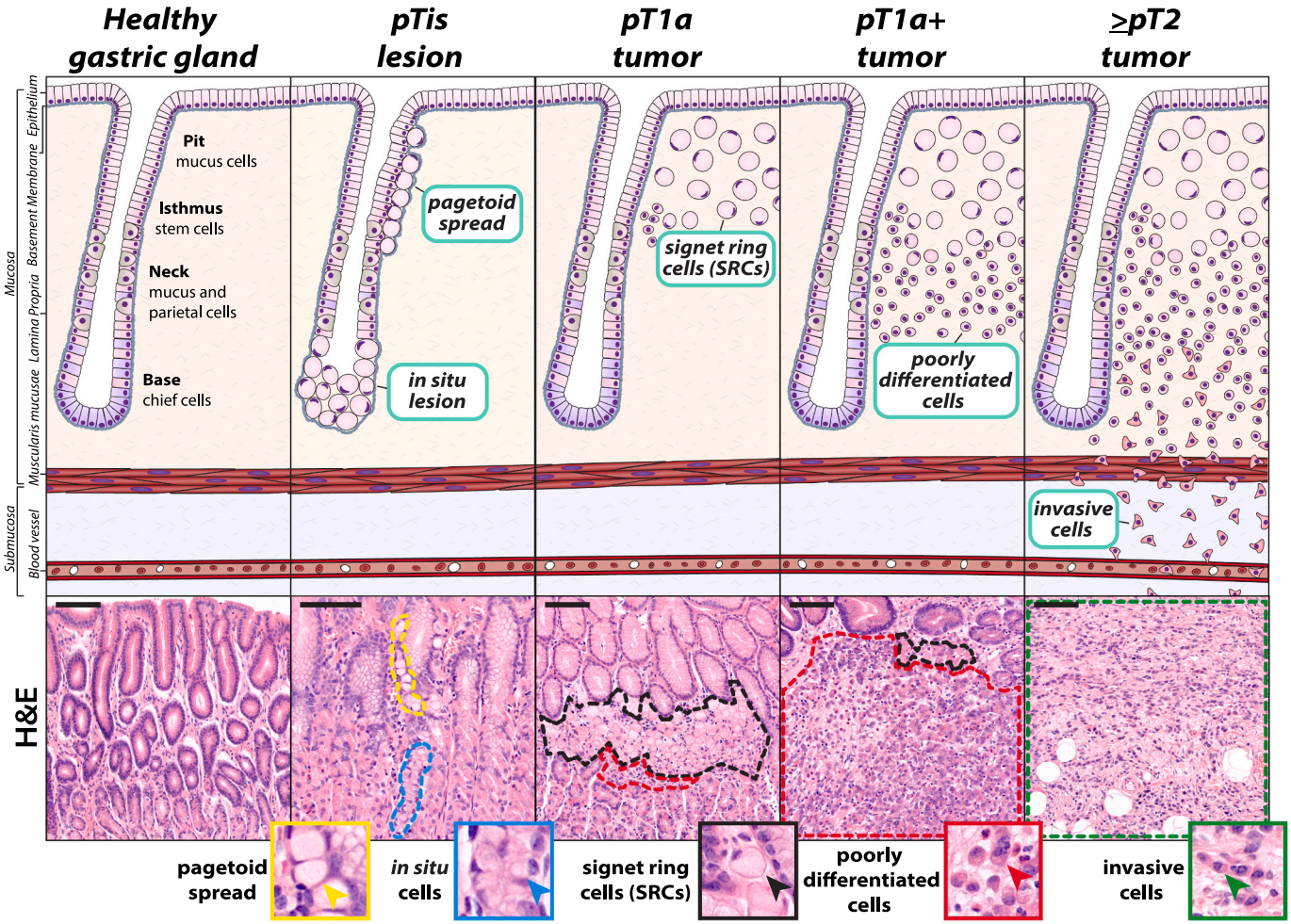

Fig. 1. Histological characterization of diffuse-type gastric cancer (DGC) progression.
Schematic images (top) and representative H&E examples (bottom, with individual tumor cells highlighted with arrows in the insets) that show the healthy gastric gland and the progressive infiltration of tumor cells into deeper layers of the stomach during DGC development. The gastric gland epithelium can be divided into different regions based on distinct cell populations (left panel).
During pT1a stage of DGC (3rd panel), tumor cells are restricted to the lamina propria and the lesion includes a high proportion of mucin-filled signet ring cells (SRCs; black outline in H&E staining) that increase in size towards the gastric lumen. The characteristic shape of SRCs is attributed to accumulation of mucin that pushes the nucleus aside, which results in a peripheral, crescent-shaped nucleus. At the base of a pT1a lesion there is typically a small proportion of poorly differentiated cells that lack accumulation of mucin (red outline in H&E staining). SRCs are also occasionally found within the epithelial glands and confined by the basement membrane (pTis, 2nd panel), which may represent an initial stage prior to the formation of intramucosal lesions (although it is uncertain whether all lesions go through this stage). These intraepithelial lesions are classified either as *in situ* lesions (blue outline in H&E staining) or pagetoid spread (yellow outline in H&E staining), with cells accumulating and replacing the healthy epithelium or migrating underneath it, respectively [16]. As DGC progresses into a pT1a+ lesion (4th panel), the proportion of poorly differentiated cells increases while the lesion is still restricted to the lamina propria. In advanced stages of DGC (≥pT2; 5th panel) a subset of poorly differentiated cells acquires migratory properties and reaches layers beneath the mucosa, as these cells diffusely spread into the submucosa (green outline in H&E staining) and the underlying muscle layers. All scale bars represent 250 μm.

1.2. Mutational basis of DGC development: A central role for alterations in E-cadherin adhesions and the actomyosin network

Multiple studies have been conducted to identify the genetic alterations associated with DGC (Appendix A) [4,27,28]. The best-established alteration linked to DGC development is loss of a functional *CDH1* gene, encoding for the adherens junction protein E-cadherin. *CDH1* is mutated in 12 - 38% of sporadic DGC tumors [15], and germline mutations in *CDH1* are responsible for up to 40% of DGC cases with familial clustering [16]. In tumors of DGC patients, the remaining wildtype *CDH1* allele is typically inactivated by somatic mutations, promoter hypermethylation or chromosomal rearrangements [24,29–32]. As a consequence, E-cadherin shows an altered distribution or is completely absent in DGC lesions, even in tumors lacking mutations in the *CDH1* gene [16,19,21,23,32–35]. *CDH1*-deficiency in mouse models similarly results in the formation of early-stage, intramucosal DGC lesions, supporting the central role of *CDH1* alterations in DGC (Table 1) [36,37]. Importantly, whereas attenuated function of E-cadherin is a key step in the initiation of DGC development, additional factors are required to drive transformation into advanced-stage DGC.

E-cadherin mediates cohesion between epithelial cells through homotypic interactions via its extracellular domain, while its cytosolic tail connects to the actin cytoskeleton through β- and α-catenin to mechanically connect the actomyosin cytoskeletons of neighboring cells (Fig. 2a) [38]. The cadherin-catenin complex also serves as a signaling platform through association with numerous additional proteins, including growth factor receptors and other signaling molecules [39]. Adherens junctions thereby regulate a vast number of intracellular signaling pathways as well as the organization of the actomyosin cytoskeleton [40–42]. Loss of E-cadherin will thus not only impact cell-cell adhesion, but also many other cellular processes that may contribute to DGC progression.

Other genetic alterations may influence the function of adherens junctions and thus the function of E-cadherin in tumors with wildtype *CDH1* (Box 1); for instance, germline mutations in *CTNNA1* encoding α-catenin are identified in HDGC patients [43]. In addition to loss of functional adherens junctions, components of the actomyosin network are also frequently attenuated in DGC (Box 1), most prominently due to mutations in *RHOA* and gene fusions of the RhoGAP ARHGAP26 (*CLDN18-ARHGAP26*) [4,27,28,44,45]. As a member of the Rho family of small GTPases, RhoA is a well-established regulator of the actin cytoskeleton (reviewed in [46]). There is no clear consensus on the functional consequences of DGC-associated *RHOA* mutations, as these have been described to both induce and inhibit RhoA activity [27,28,47,48]. This discrepancy may in part be explained by mutations differentially affecting the binding of individual downstream effector proteins of RhoA, as demonstrated for the RhoA Y42C mutant [48]. Because adherens junctions and the actomyosin network are strongly interconnected and can regulate each other's organization [49–51], both are potentially compromised in tumor cells harboring mutations in either. Although this suggests a role for actomyosin dysregulation during the early stages of DGC development, *RHOA* mutations are predominantly found in advanced DGC and exert an additive effect to the malignancy of DGC tumors harboring mutations in *CDH1* [27,28,48,52]. Despite loss of cell-cell adhesion and alterations of the actomyosin network being hallmarks of DGC, it remains unclear if and how these alterations mechanistically contribute to DGC initiation and subsequent tumor progression.

Several well-known tumor suppressors that are recurrently altered in other epithelial cancers are also among the most frequently mutated genes in DGC (Box 1). This includes genes encoding for P53 and ARID1A [4,27,28], which exert a wide variety of biological functions in cells, including regulation of the cell cycle and gene transcription [53,54]. In addition, both proteins are important in the regulation of DNA repair [53,54]. Disrupted function of these proteins could thus promote DGC development, in part, by accelerating the acquisition of additional

Table 1
Mouse models of diffuse-type gastric cancer (DGC).

Specificity	Genetic alterations	Pathology	Ref
Ubiquitous	*CDH1*$^{-/+}$	- Mainly cancer-free (8 mo) - One SRCC (1/20)	[24,198,199]
	CDH1$^{-/+}$ +MNU	- Intramucosal SRCCs	[24]
Atp4b-Cre: (pre-) parietal cells	*CDH1*$^{fl/+}$ *TP53*$^{fl/fl}$	- Cancer-free (12 mo)	[106]
	CDH1$^{fl/fl}$	- Intramucosal SRCCs	[36]
	CDH1$^{fl/fl}$ *TP53*$^{fl/fl}$	- Advanced DGC - Lymph node metastases - SRCs & poorly differentiated cells	[106,200]
	CDH1$^{fl/+}$ *TP53*$^{fl/fl}$ *KRAS*$^{LSL-G12D}$	- Two mixed gastric carcinomas - Not invasive	[200]
	CDH1$^{fl/fl}$ *TP53*$^{fl/fl}$ *KRAS*$^{LSL-G12D}$	- Intestinal, diffuse & mixed carcinomas - Lymph node, lung & liver metastases	[200]
Pdx-1-Cre: endocrine & isthmus cells	*TP53*$^{fl/fl}$	- Cancer-free (12 mo)	[201]
	SMAD4$^{fl/fl}$	- Cancer-free (12 mo)	[201]
	TP53$^{fl/fl}$ *SMAD4*$^{fl/fl}$	- Mainly cancer-free (9 mo) - One adenocarcinoma (1/28)	[107]
	CDH1$^{fl/+}$ *TP53*$^{fl/fl}$	- Cancer-free (9 mo)	[107]
	CDH1$^{fl/fl}$	- Intramucosal SRCCs	[201]
	CDH1$^{fl/fl}$ *TP53*$^{fl/fl}$	- Advanced DGC - Lymph node metastases - SRCs & poorly differentiated cells	[107]
	CDH1$^{fl/fl}$ *TP53*$^{fl/fl}$ *SMAD4*$^{fl/fl}$	- Advanced DGC - Lymph node & lung metastases	[107]
Tff1-Cre: pit cells; subset of isthmus, chief & parietal cells	*CDH1*$^{fl/fl}$	- Intramucosal SRCCs	[202]
Anxa10-Cre-ERT2: gastric epithelium	*CDH1*$^{fl/fl}$ *KRAS*$^{LSL-G12D}$ *SMAD4*$^{fl/fl}$	- Advanced DGC - Lung & peritoneal metastases - SRCs & poorly differentiated cells	[114]
	CDH1$^{fl/fl}$ *KRAS*$^{LSL-G12D}$ *APC*$^{fl/fl}$	- Intestinal gastric cancer - Serrated tooth-like morphology	[114]
Mist1-Cre-ERT2: chief & stem cells *(single tamoxifen pulse)*	*CDH1*$^{fl/fl}$	- Non-persistent SRC lesions - Arise after 10 days, disappear after 6 mo	[37]
	CDH1$^{fl/fl}$ +*H. felis*	- Persistent (>12 mo), large SRC lesions	[37]
	CDH1$^{fl/fl}$ *TP53*$^{LSL-R172H}$ +*H. felis*	- Advanced DGC	[37]
Mist1-Cre-ERT2: chief & stem cells *(+ tamoxifen)*	*CDH1*$^{fl/fl}$	- Cancer-free (14 mo) - SRC lesion n.d.	[48]
	RHOA$^{LSL-Y42C}$	- Cancer-free (14 mo) - SRC lesion n.d.	[48]
	CDH1$^{fl/fl}$ *RHOA*$^{LSL-Y42C}$	- Advanced DGC - Organoid allografts derived from this mouse metastasized to lung & liver - SRCs & poorly differentiated cells	[48]

Genetically engineered mouse models used to study DGC development, through either ubiquitous or cell type selective gene alterations, as indicated. Cell type-specific alterations are established by expression of Cre recombinase driven by a cell type-specific promoter, targeting genes flanked by LoxP (fl) sites (gene

deletion) or preceded by a LoxP-stop-LoxP (LSL) cassette (gene activation). Tamoxifen-inducible Cre expression (Cre-ERT2) further enables temporal control of gene alterations (e.g. to prevent developmental defects or enable tracing of tumor growth over time). Abbreviations: DGC = diffuse-type gastric cancer; MNU = *N*-methyl-N-nitrosourea (carcinogen); mo = month(s); n.d. = not determined; SRC = singet ring cell; SRCC = signet ring cell carcinoma.

mutations that can further contribute to DGC progression.

2. Detachment of mutant cells from the gastric epithelium

Development of intramucosal SRC lesions and advanced DGC require the detachment of one or multiple cells from the gastric epithelium into the underlying mesenchyme. In both DGC patients and mouse models, the base of SRC lesions are found near the isthmus region of gastric glands that harbors a pool of gastric stem cells [19,24,36,37]. This spatial bias implies that DGC originates from these proliferative cells in the isthmus region. It is unclear whether this local origin of intramucosal lesions is due to cells selectively escaping from this part of the epithelium or only these cells being able to grow into intramucosal lesions. Moreover, it remains to be determined whether intramucosal lesions are formed by clonal expansion of a single delaminated cell, or whether multiple cells escape from the epithelium to continuously supply the lesion with additional cells. Loss of E-cadherin appears to be sufficient for cell detachment, as both DGC patients harboring *CDH1* mutations and mouse models with loss of both *CDH1* alleles develop many SRC lesions already at an early age (Table 1) [18,20,36,37]. How *CDH1* and other DGC-associated mutations induce detachment of mutant cells from the epithelium remains unanswered, although previously described functions of E-cadherin in epithelial organization provide insights into this (Fig. 2).

2.1. Basal cell extrusion by neighboring cells

The main function of E-cadherin is to establish cell-cell adhesions [40]. However, E-cadherin-deficient cells can still form intact gastric epithelia both in mice and organoids [36,37,48,55–57], due to the presence of other adhesion molecules [58]. It therefore appears unlikely that detachment of cells from the epithelium in DGC is simply a consequence of a complete loss of cell-cell cohesion. Nonetheless, this does not exclude a role of attenuated cell-cell adhesion in cell detachment from the gastric epithelium, because cell delamination might be induced when E-cadherin is selectively lost in individual cells within an otherwise healthy epithelial layer (Fig. 2b). This differential expression of E-

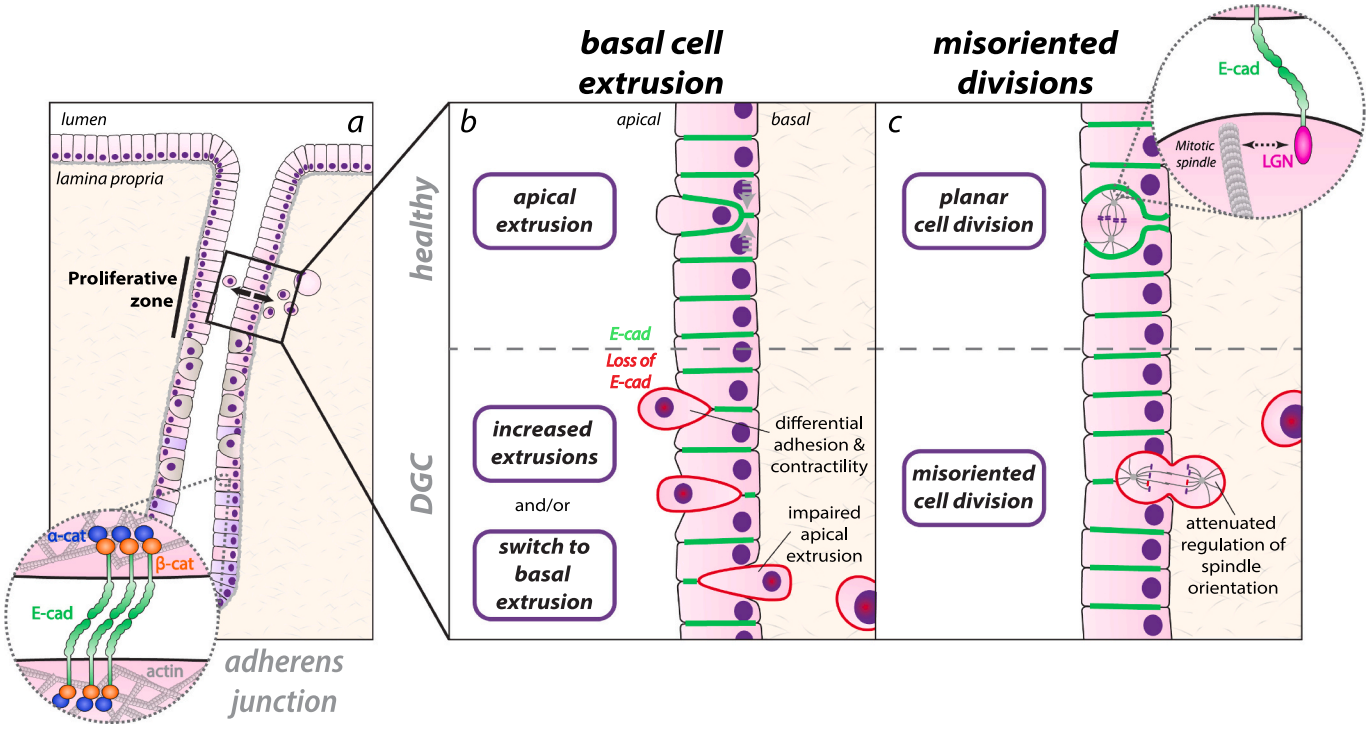

Fig. 2. Potential mechanisms of tumor cell delamination from the gastric epithelium into the lamina propria.
a. Diffuse-type gastric cancer (DGC) development is initiated by the delamination of tumor cells around the proliferative zone of the epithelium. While cells that delaminate from the apical side of the epithelium are lost in the lumen, basally delaminated cells can form lesions in the lamina propria. DGC initiation results from disruption of adherens junctions, in which *E*-cadherin (E-cad) connects neighboring cells by homotypic interactions of its extracellular domain and is coupled to the actin cytoskeleton through interaction with α-catenin (α-cat) and β-catenin (β-cat) (indicated in inset). Attenuated adherens junction function may result in basal cell delamination either by inducing cell extrusion by neighboring cells (b), or misoriented cell divisions (c).
b. In healthy epithelia (top), live and apoptotic cells are actively extruded from the epithelium into the lumen through contraction of a basal actomyosin ring surrounding the extruding cell that is formed in neighboring cells. The formation of this basal actomyosin ring is guided by E-cadherin (demonstrated thus far only for apoptotic cell extrusion). Loss of E-cadherin (indicated in red) could thereby hamper apical cell extrusion, which may result in cells exiting the epithelium from the basal side instead. In addition, when E-cadherin-deficient cells are surrounded by neighboring cells that retained E-cadherin this results in differential adhesive and contractile properties between these cells, which can trigger extrusion of the E-cadherin-deficient cell (apically and/or basally). In gastric epithelia, E-cadherin loss could thus potentially result in extrusion of cells into the lamina propria by *i*) promoting extrusion of E-cadherin-deficient cells by neighboring cells *ii*) and/or influencing the direction of extrusion (either of the former or of live cell extrusion that already takes place in healthy epithelia).
c. Single-layered epithelia maintain a monolayered architecture by orienting the mitotic spindle in plane of the epithelium to ensure planar cell divisions (top). This process is guided by a direct interaction of E-cadherin (green) with the adaptor protein LGN (magenta) that regulates the connection of astral microtubules of the mitotic spindle with the cell cortex (see inset). Loss of E-cadherin results in misoriented divisions of which daughter cells could end up outside the epithelium (either in the lumen or the lamina propia), which may underlie the intramucosal accumulation of tumor cells in DGC.

cadherin will result in differential adhesive capacity and actomyosin contractility between cells, which in other epithelial models has been shown to initiate active extrusion of cells from the epithelium by healthy neighboring cells [59–65]. In line with this, *in vitro* cultured cells with disrupted E-cadherin adhesions are extruded from the epithelial layer when surrounded by wildtype cells [66]. These findings suggest that individual cells with attenuated E-cadherin adhesion and/or actomyosin regulation might be actively extruded from the gastric epithelium by their healthy neighbors.

The formation of a DGC lesion requires cells to be extruded basally from the epithelial layer into the lamina propria, in contrast to apical extrusion that would result in their loss in the gastric lumen (Fig. 2b). Recent findings in epithelial cultures suggest that loss of functional E-cadherin potentially could, besides promoting cell extrusion, also bias extrusion to the basal side. Epithelial tissues contain intricate mechanisms that regulate extrusion of epithelial cells during homeostasis to eliminate cells from the epithelium (Fig. 2b) [67,68]. These mechanisms direct extrusion of cells specifically towards the apical side of the epithelium, relying on actomyosin-generated forces in neighboring cells. This process is guided by E-cadherin adhesions, and dysregulation of cadherin-mediated adhesion has been shown to block apical extrusion [61–63,66,69–73]. Compromised apical extrusion may instead lead to extrusion of cells basally from the epithelial layer (Fig. 2b), as has previously been proposed to be induced by several oncogenes [73–78]. These findings imply that loss of E-cadherin in DGC could both promote extrusions of mutant cells by their neighbors, and alter the orientation of extrusions to enable the escape of cells into the lamina propria. However, direct evidence for a role of misregulated cell extrusion in DGC is currently lacking.

2.2. Loss of planar cell divisions

An alternative explanation for detachment of cells from the gastric epithelium during DGC development is loss of control of the orientation of cell divisions (Fig. 2c). E-cadherin instructs the orientation of the mitotic spindle to ensure that cell divisions occur within the plane of the epithelium and thereby maintains the single-layered architecture of simple epithelia [79–84]. This involves a direct interaction of the cytosolic tail of E-cadherin with the adaptor protein LGN, a core component of the spindle orientation machinery (Fig. 2c) [83]. Loss of E-cadherin in DGC might therefore result in misoriented divisions of gastric isthmus cells after which daughter cells could end up outside the epithelial layer, either in the lumen or into the lamina propria. Randomization of division orientation in *Drosophila* wing disc epithelia has been shown to result in formation of tumor-like masses [85,86]. However, it remains to be determined whether loss of planar cell division contributes to the initiation of human cancers including DGC.

2.3. Breachment of the basement membrane

Delaminated cells must pass the BM that separates the epithelium and the underlying lamina propria to form intramucosal SRC lesions (Fig. 1). Incidentally, intraepithelial lesions (pTis) are found in close proximity of intramucosal SRCs [22,23], suggesting that intraepithelial lesions may represent an initial step of DGC development. However, because most intramucosal SRC lesions (pT1a) do not have a detectable intraepithelial lesion in their proximity, it is unclear whether all tumors go through this potentially short-lived stage.

While loss of E-cadherin is sufficient to form SRC lesions in the lamina propria, it is currently unknown how cells breach the BM in DGC. However, several mechanisms by which mutant cells pass the BM have been described (reviewed in [87,88]), which may be employed by mutant cells in DGC. In various human cancers, tumor cells upregulate and secrete factors (e.g. matrix metalloproteases, MMPs) that promote degradation of the BM over time [89]. Loss of E-cadherin has been linked to upregulation of MMPs in multiple cancer cell lines [90–94], and several MMPs are upregulated in both early and advanced DGC [6,95]. Furthermore, loss of polarity in E-cadherin-deficient gastric cells is proposed to result in basal secretion of proteases that are natively produced by these cells (e.g. pepsinogen) and normally secreted apically into the lumen [17], although it is unknown whether these factors can contribute to BM degradation. Mutant cells may also actively traverse the BM by protease-independent mechanisms. For instance, delamination from the epithelium (albeit through misoriented divisions or basal extrusion) will generate forces that could potentially be sufficient to physically breach the BM [88,96,97]. In model systems for other tumors, BM penetration of mutant cells is facilitated by pre-existing weakness of the BM [98,99]. The local strength of the BM might therefore influence the fate of delaminated cells, resulting either in luminal clearance, the formation of an intraepithelial lesion, or passage through the BM to form an intramucosal lesion.

3. Intramucosal lesions and the origin of advanced DGC

E-cadherin-deficient cells that have escaped from the epithelial glands into the lamina propria can develop into intramucosal lesions, which in early-stage DGC consist primarily of mucin-filled SRCs [19,21,52,100]. SRCs are differentiated, hypo-proliferative cells, and are therefore unlikely to directly contribute to the eventual malignancy of DGC [19,52]. A small fraction of less differentiated cells at the base of the SRC lesion remains proliferative and are thought to be progenitors of SRCs, akin to stem cells that differentiate into the mucus-producing cells normally present in the gastric gland [19,20]. The small number of these poorly differentiated cells (~5% of the total SRC lesion [19,52]) suggests that most delaminated cells accumulating in the lamina propria inherently undergo differentiation into SRCs. Intrinsic differentiation of delaminated cells will limit the growth of intramucosal lesions and could potentially also result in their dissipation over time. Indeed, tracing experiments in mice imply that SRC lesions are only short-lived, as transient depletion of E-cadherin in a sub-population of gastric epithelial cells results in the formation of SRC foci that gradually decline again over time (Table 1) [37]. It is unclear whether SRC lesions found in HDGC patients are more persistent or are also dynamically formed and dissipated.

Progression towards advanced DGC is accompanied by an increased abundance of poorly differentiated cells with proliferative capacity (pT1a+, Fig. 1) [14,19], also illustrated by the reduction of differentiation markers in advanced DGC [6,19]. This accommodates growth of the lesion as well as malignant behavior, as poorly differentiated cells can acquire migratory features and invade into deeper tissue layers and into blood- or lymphatic vessels over time (≥pT2, Fig. 1). Loss of only *CDH1* in mice stomachs results in development of indolent SRC lesions and not advanced DGC, and the latter is only induced upon introduction of additional mutations or environmental changes (Table 1). These changes impinge on survival of intramucosal cells that have escaped the epithelium and maintaining these cells in an undifferentiated, proliferative state, which together can promote the persistence and expansion of intramucosal lesions.

The progressive accumulation of poorly differentiated cells, as seen in pT1a+ and ≥pT2 tumors, suggests that gradual changes in early-stage lesions may drive their transition into advanced DGCs over time. In line with this, advanced DGC tumors frequently contain SRCs near the lumen that may indicate the former existence of an early lesion (personal observation, CvdP). Alternatively, the development of early-stage SRC lesions and advanced DGC may represent independent events, in which delaminated cells either form non-persistent SRC lesions or can form advanced tumors. In both models, the characteristics of the delaminated cell may determine its ability to maintain in an undifferentiated state and proliferate, relying on its (epi)genetic status and/or the specific type of cells (e.g. stem/progenitor cells). In addition, in both models the progression towards advanced tumors relies on the accumulation of poorly differentiated cells by genetic or epigenetic changes that

maintain intramucosal cells in an undifferentiated, proliferative state and promote their long-term survival, as outlined in the next sections.

4. Regulation of cell survival underlying SRC lesion persistency and DGC progression

Intramucosal DGC cells have to avert the induction of cell death and establish long-term survival to enable formation and growth of SRC lesions. In epithelial tissues, cells typically undergo apoptosis after their delamination from the epithelium into the mesenchyme [78,85,86,101]. This induction of cell death following epithelial detachment involves elevated actomyosin contractility that takes place when epithelial cells lose contact with their neighbors [101–103]. The initial survival of intramucosal DGC cells may be aided by the alteration of actomyosin contractility and induction of pro-survival pathways following E-cadherin loss [6,55,104,105]. However, additional transformation of intramucosal cells through genetic or epigenetic changes induced by environmental factors are likely essential to enable the long-term survival of intramucosal cells. Hereby these changes can contribute to the persistency and progression of DGC tumors.

In DGC the loss of E-cadherin frequently co-occurs with mutations in *TP53* encoding for P53, a central regulator of apoptosis (Box 1) [4,27,28]. The additional loss of *TP53* in *CDH1*$^{-/-}$ mouse models leads to both a significant increase in the presence of SRC foci in the stomach as well as development of more advanced tumors [106,107]. Mutations in other pathways that regulate cell survival, such as mutations found in the PI3K/AKT pathway (Box 1) [4,28], may similarly promote tumor persistency and growth. The induction of apoptosis could alternatively be hampered by mutations that directly impact the regulation of the actomyosin network [4,27,28,44,45,108]. Multiple studies demonstrated that mutations in *RHOA* enhance survival and outgrowth of single gastric cancer cells and promote the formation of advanced DGC tumors in mice [27,28,47,48,55]. Both mutations in *TP53* or *RHOA* strongly correlate with DGC progression and lower patient survival [48,109–111], indicating that alterations that enhance cell survival may contribute to DGC malignancy.

5. Accumulation of poorly differentiated cells during DGC progression

Expansion of the pool of poorly differentiated cells is essential for the growth and progression of DGC tumors and can be established by restricting the differentiation of intramucosal cells into SRCs. In the healthy stomach, proliferation and differentiation of the stem cells residing within the isthmus are regulated by several factors (e.g. Wnt) secreted by a subset of cells of the gastric gland and in the surrounding stroma (Fig. 3a, reviewed in [112,113]). Accumulating evidence indicates that these local niche factors also maintain delaminated intramucosal cells in an undifferentiated, proliferative state in early-stage DGC lesions. For instance, the absence of Wnt pathway ligands triggers differentiation of DGC organoids into SRC-like cells [56]. The mechanisms that regulate self-renewal and differentiation of stem cells in

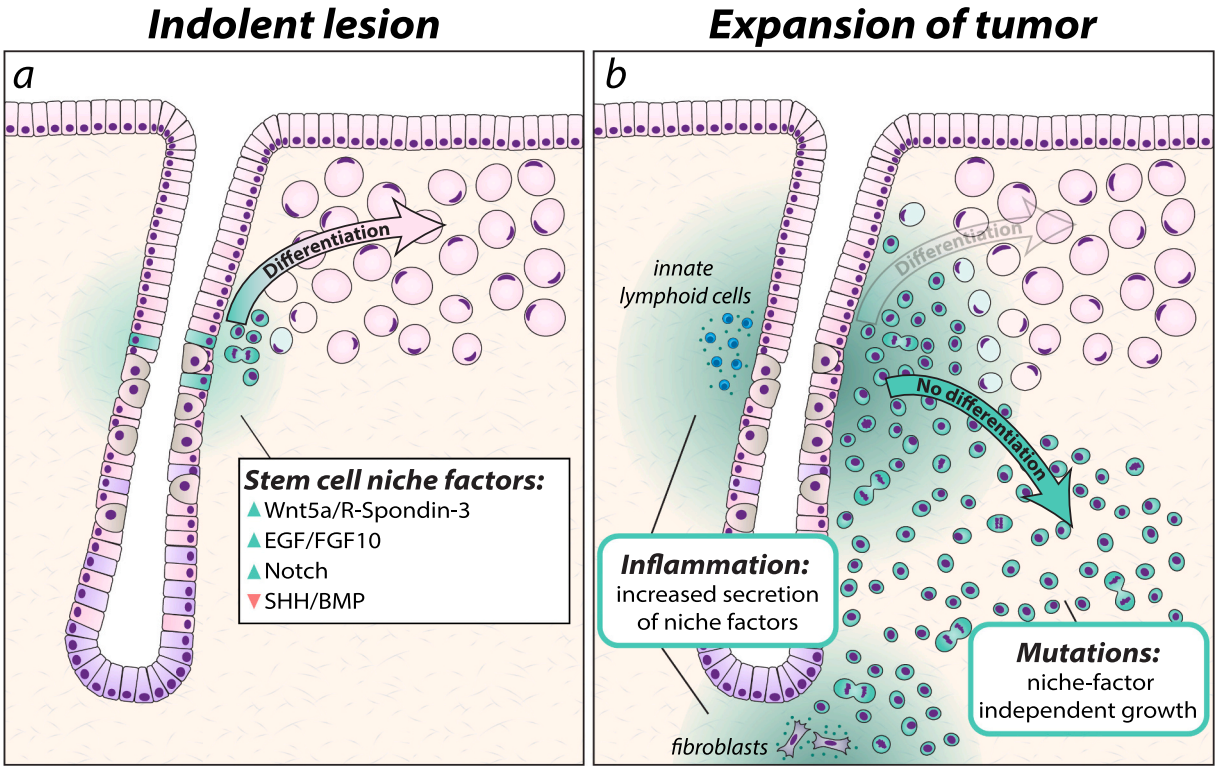

Fig. 3. Regulation of proliferation and differentiation of intramucosal diffuse-type gastric cancer (DGC) cells by niche factor signals.
a. Stem cells that reside within the isthmus region of the healthy gastric epithelium are maintained in an undifferentiated stem cell state due to local secretion of niche factors (as listed, visualized in green) by epithelial cells and surrounding stromal cells [113]. Although indolent DGC lesions consist mostly of differentiated signet ring cells (SRCs), cells at the base of these lesions that are in proximity to the isthmus remain in a more undifferentiated state. This might, at least in part, be attributed to the differentiation of tumor cells still being dependent on local stem cell niche factors. Note that niche factors may vary between anatomical regions of the stomach (e.g. Gastrin)[113], and also a (reserve) pool of stem cells is present at the base of gastric glands [112,113].
b. The expansion of undifferentiated cells in DGC lesions results from either genetic mutations or external factors (e.g. *Helicobacter pylori* infection) that both can prevent their differentiation into SRCs. Mutations (e.g. in *APC*) establish niche factor independency and thus enable tumor cells to remain undifferentiated outside of the stem cell niche region. Chronic inflammation of the stomach leads to increased niche factor secretion by stromal cells, for instance of Wnt5a by innate lymphoid cells surrounding the isthmus and R-spondin-3 by fibroblasts that are present in the muscularis mucosae. This increased abundance of niche factors can expand the region in which niche factor dependent DGC tumor cells maintain an undifferentiated and proliferative state.

healthy gastric epithelia thereby also play a central role in regulating the size of the pool of undifferentiated cells during DGC progression. As SRC lesions are formed in proximity to the stem cell region [19,24,36,37], the local presence of stem cell niche factors may enable delaminated cells to maintain in an undifferentiated state and thereby allow the formation of an initial lesion (Fig. 3a). The diffusion range of stem cell niche factors will be limited, which could explain the small number of undifferentiated cells that are restricted to the base of the lesion near the isthmus in SRC lesions. Therefore, for an early-stage DGC lesion to expand and progress, additional factors are required that allow intramucosal cells to overcome the dependency on local niche factors to remain in an undifferentiated and proliferative state.

5.1. Mutations can override niche factor dependency

Mutations that override the dependence on factors that regulate differentiation of stem- or progenitor cells, such as Wnt/R-Spondin and EGF/FGF10, are frequently found in advanced DGC [6,55,114]. These mutations can directly alter activity of niche factor-regulated signaling by affecting pathway components (e.g. *APC* mutation or amplification of *FGFR2*), but also affect these pathways indirectly [28,115,116]. For instance, constitutively active RhoA indirectly activates several signaling cascades including the Wnt pathway, which leads to the formation of highly invasive tumors [48]. Similarly, combined loss of *TP53* and *CDH1* enables gastric organoids to grow independently of the niche factor R-Spondin [55]. These data demonstrate that accumulation of additional mutations contribute to malignant progression of early lesions by establishing independency of locally secreted niche factors, thereby allowing the expansion of poorly differentiated cells throughout the lamina propria to promote tumor growth (Fig. 3b).

5.2. External factors increase local niche factor secretion and promote tumor growth

In addition to genetic alterations that can establish independency of niche factors, also changes within the tumor microenvironment can influence the ability of cells within intramucosal lesions to remain undifferentiated and proliferative outside of the local stem cell niche (Fig. 3b). Inflammation, for instance caused by *Helicobacter pylori* infections that are chronically prevalent in over half of the world population [117], and injury were both shown to promote the secretion of several niche factors by gastric epithelial as well as stromal cells [37,118–122]. Although *H. pylori* infections are mainly linked to intestinal-type gastric cancer, systemic *H. pylori* infections also increase the rate of DGC tumor cell proliferation and tumor progression [100,123]. Moreover, whereas mice lacking E-cadherin (in the absence of other genetic alterations) develop intramucosal lesions that are not persistent, persistent lesions are formed in the presence of chronic inflammation [37]. Chronic inflammation can accelerate DGC tumor outgrowth by increased secretion of Wnt5a from innate lymphoid cells, which enhances both cell survival and proliferation [37,118]. Inflammation is further found to increase R-spondin secretion by stromal fibroblasts located in the lower mucosa, which maintains DGC tumor cells in an proliferative and undifferentiated state (Fig. 3b) [56,119]. Altogether, these findings underscore that both external factors and genetic mutations influence niche factor regulation and dependency, which can lead to an increased abundance of poorly differentiated cells and consequently the progression towards an advanced DGC tumor.

6. Acquisition of migratory capacity during progression of DGC

A critical step in the malignant progression of DGC is the acquisition of invasive properties in a subset of poorly differentiated cells, which facilitates spreading into the submucosa and deeper layers (Fig. 1). In HDGC tumors, the population of poorly differentiated cells that invades the muscularis mucosae acquires a mesenchymal-like migratory morphology and shows activation of c-Src, FAK and STAT3 [17,19,24]. This mesenchymal morphology suggests that transcriptional reprogramming of tumor cells through an epithelial-to-mesenchymal transition (EMT) contributes to tumor progression. Indeed, transcriptional regulators of EMT (e.g. Twist1 and ZEB1) and mesenchymal markers (e.g. Vimentin and N-cadherin) are upregulated in advanced DGC and correlate with poor survival prospects for patients [106,107,124–128]. Although these data indicate that advanced DGC cells have undergone EMT, evidence for EMT underlying the initial transition towards invasiveness remains contradictory because the invasive poorly differentiated cells in early-stage DGC lack several classical markers of EMT [21]. FAK/Src signaling has been implicated in promoting this potential (partial) EMT during initiation of invasion, but may also directly promote gastric cancer cell invasion through activation of other pro-migratory pathways, e.g. through Rho-family GTPases [129,130]. Furthermore, increased FAK/Src signaling in DGC organoids induces activation of the transcriptional regulator YAP, which in turn promotes invasion and outgrowth of DGC tumor cells at metastatic sites [48,131,132]. Thus, while it has become apparent that a subset of poorly differentiated cells over time acquires migratory features, it remains unclear what initiates this transition. Several genomic alterations and changes in the tumor environment have been identified in advanced DGC tumors and correlate with increased aggressive features of DGC, which could potentially underlie the initiation of invasion in early-stage DGC.

6.1. Identification of genetic alterations contributing to DGC invasion and metastasis formation

The genomic alterations that are recurrent in advanced DGC tumors could potentially drive the transition towards invasive tumors. Thus far it has been difficult to delineate whether these mutations impact cell invasion or other processes that contribute to tumor malignancy (i.e. cell survival and differentiation). Nonetheless, mutant RhoA and P53 have both been implicated in the migratory behavior of various epithelial tumor cells (reviewed in [133,134]), and may directly contribute to the invasive potential of DGC in addition to their role in the outgrowth of intramucosal lesions. RhoA Y42C is shown to promote invasive behavior and tumor progression in DGC mouse models that also lack E-cadherin through activation of FAK [48]. This indicates that altered RhoA signaling could potentially promote the transition from poorly differentiated cells into invasive cells. However, as both RhoA and P53 impinge on many cellular processes, it remains unclear when and how loss of these components contributes to DGC progression.

To identify alterations that specifically contribute to invasion or aid metastasis and thereby underlie DGC progression into advanced tumors, several studies have compared the mutation and expression profiles of early and late stages of DGC (Fig. 4). Direct genomic comparison of a primary tumor with its metastasis within the same patient identified an inhibitory mutation in the TGF-β receptor II selectively in the metastatic lesion, implying a role for altered TGF-β signaling in tumor cells in DGC invasion and metastasis (Fig. 4a) [135]. TGF-β signaling is attenuated in up to 53% of DGC patients, mainly due to mutations in the receptor and the downstream effector SMAD4, and loss of either promotes metastasis formation in DGC mouse models [4,107,109,111,114,135,136]. Importantly, TGF-β signaling also fulfils a pro-oncogenic role, as TGF-β ligands are increasingly expressed in advanced DGC and this correlates with poor survival [124,136–138]. Secretion of TGF-β can promote DGC progression to invasive tumors, for instance, by modulating the tumor microenvironment and potentially through SMAD4-independent mechanisms in tumor cells [137,139–143]. Additional mutations that correlate with metastatic potential were identified by comparison of the genetic profiles of multiple highly metastatic with non-metastatic tumors in a cohort of DGC patients (Fig. 4b) [111]. This revealed the enrichment of several genomic alterations in metastatic DGC, including mutations in the non-canonical cadherin FAT4 that were shown to

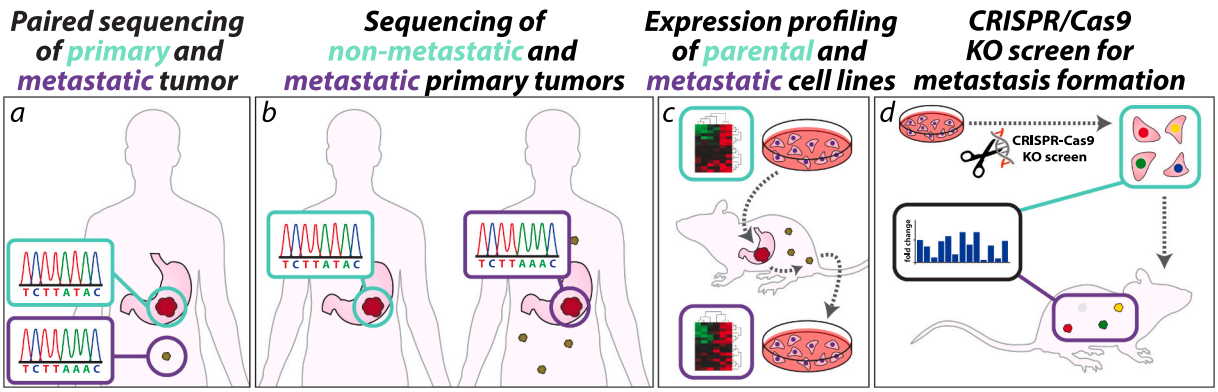

Fig. 4. Experimental approaches to identify factors involved in invasion and metastasis in diffuse-type gastric cancer (DGC).
Different approaches that have been employed to identify alterations that specifically contribute to DGC tumor cell invasion or metastasis formation:
a. Comparison of genetic profiles of a primary tumor (cyan) and its associated ovarian metastasis (magenta) that identified mutations that were selectively present in the metastatic tumor (i.e. in *TGFRBII*, Nadauld et al. 2014 [135]).
b. Comparison of the genetic profiles of primary tumors of different patients with (at least three) lymph node metastases (magenta) or no metastases (cyan), identifying mutations that are enriched in tumors with metastatic capacity (e.g. *FAT4*, Choi et al. 2018 [111]).
c. Comparison of gene expression profiles of parental cancer cell lines (cyan) with their counterparts (magenta) that were isolated from metastatic lesions following transplantation in mice, identifying signaling pathways associated with invasion and metastasis formation (e.g. DDR2 signaling, Wnt pathway). Kurashige et al. xenografted patient-derived cell lines into the gastric wall of mice and established new cell lines from ascites [148]. Park et al. allografted DGC tumor cell lines (derived from Pdx1-Cre, $TP53^{fl/fl}$, $CDH1^{fl/fl}$ mice) subcutaneously into mice and established new cell lines from lung metastases [147].
d.*In vivo* CRISPRCas9 knockout (KO) screen identifying genes essential for metastasis formation (An et al. 2021 [149]). Metastatic cells were treated with guide RNAs targeting candidate genes that show enriched expression in highly metastatic cell lines (see Fig. 4c) and were injected in mice spleens (cyan). Liver metastases (magenta) were subsequently analyzed for the presence of guide RNAs to determine which knocked-out genes were underrepresented (illustrated by blue cells, e.g. *Tmsb4x*) and therefore were required for metastasis formation.

increase proliferation and invasion of gastric cancer cell lines [144–146]. Characterization of cell lines generated from primary tumors and their metastatic counterparts further highlighted the importance of Wnt pathway activation, and identified collagen type I receptor tyrosine kinase DDR2 as a potential driver of metastasis (Fig. 4c) [147,148]. In parallel, CRISPRCas9 knockout screening for genes that are required for metastasis formation of tumor cells xenografted in mice uncovered a role for the actin regulator Tmsb4x in metastatic DGC (Fig. 4d) [149]. Together, these studies identified key molecular alterations that promote malignancy and metastasis formation of DGC. How these alterations mechanistically impact cellular behavior, and whether they impinge on the transition towards tumor invasion and/or other processes underlying DGC malignancy (e.g. colonization at the metastatic site), remain important questions for future investigations.

7. Alterations in the tumor microenvironment linked to DGC invasion

Accumulating evidence indicates that in addition to genomic alterations also alterations in the tumor microenvironment contribute to the transition towards invasion in DGC tumors. Progression from indolent SRC lesions to invasive DGC tumors coincides with gradual changes in the surrounding extracellular matrix (ECM) and in the composition of the tumor-associated cell population, which both are linked to DGC malignancy (Fig. 5).

7.1. Reorganization of the extracellular matrix

The ECM of the gastric mucosa is composed of a meshwork of matrix proteins that provides structure to the gastric tissue, such as fibronectin and collagen type I [150]. Advanced DGC tumors often show increased accumulation of ECM components in the mesenchyme compared to earlier stages of DGC and healthy tissue [6,151,152], which correlates with poor patient survival [137,153–155]. Remodeling of the ECM within DGC lesions is in part mediated by secretion of matrix proteins by tumor cells themselves, as well as by tumor-associated cells (Fig. 5) [156–158]. This results in an altered composition of the ECM, for instance due to deposition of matrix proteins that are lowly abundant in the healthy mesenchyme (e.g. collagen type XII and laminin γ) [6,124,153,155,158,159]. The structural organization and physical properties of the ECM network also gradually alter during DGC progression due to secretion of matrix remodeling enzymes, including MMPs that locally degrade matrix elements and LOXL2 that cross-links collagen fibers (Fig. 5) [6,155,160,161]. These structural changes of the ECM can facilitate invasion of tumor cells by providing space for cells to migrate through the ECM meshwork (Fig. 5) [162]. In addition, chemical and mechanical changes of the ECM network are sensed by cells through adhesion receptors, including integrins. These adhesion molecules engage with specific matrix proteins and trigger intracellular signaling cascades, dependent on the physical properties of the matrix (Fig. 5) [163,164]. Integrin-mediated signaling can lead to a diverse range of downstream effects that can contribute to tumor cell invasion, for instance through the activation of pro-migratory proteins YAP and FAK [163,164]. In addition to changes in ECM, also several specific integrin subtypes are upregulated in advanced DGC and correlate with poor prognosis, underscoring the contribution of altered integrin-dependent signaling to DGC malignancy [165–167]. Together, these findings indicate that progressive changes in the ECM and the downstream signaling pathways induced by the matrix receptors may promote a migratory phenotype in DGC tumors.

7.2. Cancer-associated fibroblasts and other tumor-associated cells

Cancer-associated fibroblasts (CAFs) represent a major constituent of the microenvironment of DGC lesions and are implicated in tumor progression and invasion. CAFs are highly abundant in DGC tumors compared to intestinal-type gastric cancer, particularly in invasive regions of tumors, and tumor infiltration of CAFs correlates with poor survival of gastric cancer patients [126,143,168]. Tumor cells can attract CAF precursors and stimulate their transition to pro-migratory CAFs, in part by secretion of TGF-β that is highly abundant in advanced DGC tumors (Fig. 5) [143,169–171]. CAFs are shown to enhance invasion of DGC cancer cell lines *in vitro* and in simultaneous orthotopic transplantations in mice [143,172,173]. DGC invasion may

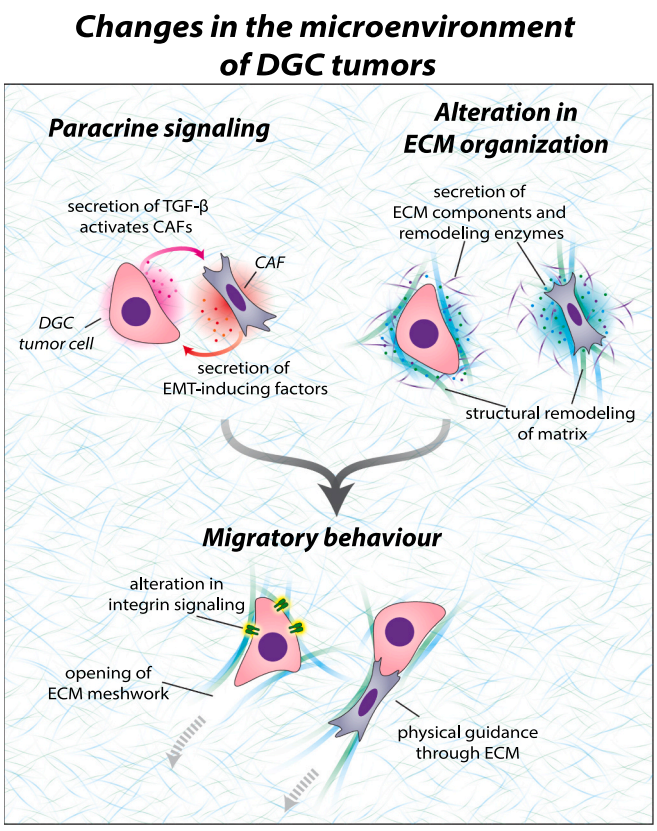

Fig. 5. Components of the diffuse-type gastric cancer (DGC) tumor microenvironment that promote tumor cell migration.
Progression of DGC towards an advanced stage coincides with several changes in the tumor microenvironment.
Top left: DGC cells recruit and activate cancer-associated fibroblasts (CAFs), chiefly by secretion of TGF-β ligands (magenta). In turn, CAFs promote tumor cell invasion by secretion of several factors that change the invasive potential of tumor cells, among which epithelial-to-mesenchymal transition (EMT)-inducing factors (red).
Top right: secretion of extracellular matrix (ECM) components by CAFs and tumor cells themselves alters the composition of the ECM. In addition, the organization of the ECM is altered by secretion of matrix remodeling enzymes (e.g. resulting in cross-linking and bundling of ECM fibers) as well as physical interactions of CAFs with the ECM.
Bottom: the changes in matrix composition and organization promote migratory behavior of DGC cells via alteration of integrin signaling that can induce pro-migratory pathways (e.g. through FAK/Src or YAP). In addition, the physical reorganization of the ECM creates a pathway in the meshwork for tumor cells to migrate through. Finally, direct interaction of CAFs with tumor cells has been proposed to guide DGC cell invasion.

rely on several different mechanisms by which CAFs can stimulate DGC cell migratory behavior, including the secretion of EMT-inducing factors (Fig. 5) [143,154,171,174]. In addition, CAFs are demonstrated to enhance migration of DGC cells by influencing the organization of the ECM, both by secretion of matrix (remodeling) proteins and by physically interacting with ECM components that leads to reorganization the ECM network (Fig. 5) [143,157,175,176]. Lastly, CAFs have been observed to directly interact with gastric tumor cells, and CAF-tumor cell interactions are proposed to physically guide tumor cells through the ECM (Fig. 5) [157,172,175,177]. Next to CAFs, other stromal cells including reprogrammed endothelial cells and tumor-associated neutrophils are similarly able to promote EMT and facilitate DGC intravasation and invasion [178,179]. M2-macrophages stimulate proliferation and invasion of gastric cancer cell lines in *in vitro* co-cultures and promote the formation of metastases in mice [180,181]. In addition, many stromal cells including CAFs and immune cells are implicated in forming an immune-repressive environment in DGC that can facilitate tumor progression [6,171,182–185]. Altogether, these data show that changes in the tumor microenvironment contribute to the migratory capacity of DGC cancer cells and may be key determinants of invasiveness in DGC tumors.

8. Conclusions and future perspectives

Genomic and transcriptomic analyses of DGC tumors, supported with different mouse and organoid models, have greatly advanced our understanding of the molecular changes underlying DGC development. Identification of the cellular functions of the proteins associated with DGC provided further insights into the mechanisms that drive DGC initiation and progression. Dysfunctional E-cadherin adhesions can trigger the delamination of cells into the mucosa, although E-cadherin loss on its own is insufficient for the formation of advanced DGC. It remains to be determined whether compromised function of the cadherin complex also influences later stages of DGC progression (e.g. cell survival). These effects of mutant E-cadherin may, in part, be ascribed to resulting changes in the organization of the actomyosin cytoskeleton or gain-of-function of components released from the adherens junction complex (e.g. p120-catenin [186]). The formation of intramucosal lesions following E-cadherin loss implies that the absence of E-cadherin in the gastric epithelium is not compensated by other types of cadherin proteins. Altered expression of other cadherins (e.g. upregulation of N-cadherin during EMT [106,126–128] or genomic inactivation of *FAT4* [111,146]) may contribute to further DGC progression, although it is unclear whether and which specific functions of these other cadherins underlie this. Patients with germline *CDH1* mutations are selectively predisposed to DGC as well as lobular breast cancer [187]. Uncovering why loss of E-cadherin is more detrimental in the stomach and breast (e.g. due to the distinct ability to survive in the mesenchyme across tissues) could help to further unravel the mechanisms by which DGC develops.

Although E-cadherin deficiency is sufficient for the formation of early-stage DGC lesions, additional alterations are required for intramucosal lesions to expand and develop into invasive and metastatic tumors. These alterations include both additional genetic mutations as well as changes in the tumor microenvironment, and act on different steps of DGC progression; *i)* promoting survival of delaminated cells within the mesenchyme; *ii*) enabling tumor cells to maintain an undifferentiated state outside of the local stem cell niche to promote tumor expansion; and *iii*) inducing a highly migratory state of tumor cells and promoting their invasion into the surrounding tissue. Nonetheless, we are only beginning to understand why despite the presence of many SRC foci typically only a single advanced tumor develops, and many important questions remain to be answered. For instance, does the fate of intramucosal cells depend on the specific cell type delaminating from the epithelium (e.g. mesenchymal outgrowth may be restricted to cells with stem cell capacity) and is this fate influenced by the anatomical region of the stomach (i.e. the corpus or antrum that differ in cellular composition and abundance of niche factors)? The appearance of several distinct tumor cell populations is clearly linked to DGC progression; however, it remains elusive how each of these populations is regulated and contributes to eventual malignancy. As such, does the accumulation of poorly differentiated cells that underlies expansion of advanced tumors originate from cells present in early lesions, or represent a distinct pool of cells that is separately delaminating from the epithelium? And does lesion formation involve a single delamination event, or could accumulation of poorly differentiated cells also be fueled by additional supply of mutant cells delaminating from the epithelium? Finally, as SRCs are hypo-proliferative, it remains elusive whether these cells are truly non-malignant or, for instance, exhibit plasticity and thereby still contribute to tumor progression. Monitoring the evolution of DGC tumors over time, for example, by lineage tracing of tumors or by multi-omic analyses of the different sub-populations of tumor cells, could help to provide answers to these outstanding questions.

Knowledge of the molecular and cellular mechanisms that drive DGC progression will help to identify targets for specific therapies. Therapeutic intervention may aim to eliminate early SRC lesions. Synthetic lethality screens have already identified the selective sensitivity of E-cadherin-deficient cells to inhibition of several signaling pathways, including PI3K/AKT/mTOR- and EGFR signaling [57,104,105,188–191]. Restraining the impact of external factors that are linked to persistency and/or expansion of early DGC lesions may aid to halt their progression. As such, inflammation inhibitors were shown to diminish SRC lesion formation in E-cadherin-deficient mouse models [37]. Although HDGC patients could potentially benefit from targeting early lesions, sporadic DGC tumors are typically diagnosed at an advanced tumor stage. For these advanced tumors, therapeutic interventions impinging on growth-promoting and pro-migratory pathways that are essential for DGC progression may be effective. For instance, combined inhibition of PI3K and YAP in DGC allografts in mice successfully decreased tumor growth [48]. Importantly, DGC tumors in individual patients will harbor different molecular alterations that will result in distinct responses to specific therapies. Stratification of DGC tumors based on their molecular characteristics has proven to be predictive of clinical outcomes and can identify effective drug targets to enhance treatment efficacy [4–7,192–196]. Subclassification of DGC tumors based on their proteomic expression profiles identified a subclass that was least sensitive to conventional therapeutics, but potentially vulnerable to immunotherapy [6]. The recent advancements in patient-derived tumor organoids enable preclinical screening of drug responses for individual tumors, which together with genomic and proteomic screening of these tumors could further improve treatment efficacy in the future [197].

Ethics declarations

The authors declare no competing interests.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbcan.2022.188719.

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