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Opinion

Cancer progression as the chronic stabilization of invasive growth

Dogus M. Altintas [1,*] and Paolo M. Comoglio[2,*]

'Invasive growth' is a coordinated biological program that enables tissues to adapt to environmental adversity. In cancer, tumor cells deploy adaptive behaviors including epithelial plasticity, migration, invasion, metastatic competence, and therapy persistence. Although these processes are often studied independently, single-cell and spatial analyses increasingly reveal coordinated cellular states in which they are co-deployed. We propose that invasive growth provides a unifying framework for interpreting these observations. Because invasive growth normally functions transiently during development, tissue repair, and regeneration, cancer progression may depend not simply on its activation but on its chronic stabilization. This opinion article shifts the central question from how invasive growth is activated to why it fails to resolve, providing a framework for understanding tumor progression and therapeutic intervention.

Significance

Cancer progression is commonly interpreted in terms of individual processes such as invasion, epithelial plasticity, stemness, or therapy resistance. This opinion article proposes that these behaviors can be viewed as coordinated manifestations of a conserved physiological program—'invasive growth'—that becomes chronically stabilized within tumor ecosystems. By shifting the focus from program activation to failed resolution, this framework offers a unifying perspective on cancer progression and identifies new conceptual opportunities for therapeutic intervention.

A unified framework for tumor progression

Cancer progression is commonly described through a collection of partially overlapping concepts, including protection from apoptosis, epithelial plasticity, invasion, stemness, microenvironmental remodeling, **metastatic competence** (see Glossary), and therapy resistance. Each framework captures an important aspect of tumor biology. However, tumor progression, metastatic dissemination, and treatment failure require tumor cells to coordinate multiple adaptive capabilities across diverse and changing microenvironments, rather than deploying each behavior in isolation [1]. Recent single-cell and spatial analyses have brought this coordination into sharper focus by revealing cellular states in which these behaviors are co-deployed within the same tumor cell populations and niches [2–5]. As a result, the boundaries separating invasion, plasticity, stemness, and therapy resistance are becoming increasingly blurred. This convergence suggests that understanding tumor progression may require stepping back from individual behaviors to consider the biological principles that orchestrate migration, survival, proliferation, and tissue remodeling into a coordinated biological response.

A concept that anticipated this emerging view is '**invasive growth**'. Originally defined as a coordinated biological program integrating cell dissociation, motility, survival, proliferation, **extracellular matrix (ECM)** remodeling, and **morphogenesis** [6–10], invasive growth requires these processes to act together. Individually, these activities are insufficient to support effective tissue colonization: proliferation without migration produces tissue expansion; migration without survival produces attrition; matrix degradation without polarity control produces tissue disruption. Invasive growth emerges when these processes become coordinated in space and time to support coherent tissue colonization and architectural remodeling. This program encompasses many of the cellular behaviors that are increasingly recognized as co-deployed during tumor progression, including plasticity, tissue invasion, microenvironmental remodeling, metastatic competence, and therapy resistance. It therefore provides a framework for asking whether the multidimensional cellular states

[1]Laboratoire de Biologie Tissulaire et Ingénierie Thérapeutique (LBTI), UMR CNRS 5305, Institut de Biologie et Chimie des Protéines, Université Claude Bernard Lyon 1, Lyon, France
[2]IFOM ETS – The AIRC Institute of Molecular Oncology, 20139 Milano, Italy

*Correspondence:
dogus.altintas@gmail.com (D.M. Altintas) and pcomoglio@gmail.com (P.M. Comoglio).

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revealed by recent technologies reflect the coordinated deployment of a common biological program. Importantly, invasive growth is not intrinsically pathological: during development, tissue repair, and regeneration, it normally operates transiently and resolves once **tissue homeostasis** has been restored [6,8,11]. Wounds heal. Regeneration ends. Could tumor progression reflect the chronic stabilization of invasive growth? We propose that tumor progression can be viewed through this lens: not simply as the activation of individual invasive behaviors but as the chronic stabilization of their coordinated deployment.

By integrating evidence that has largely been considered within separate fields, this synthesis highlights two features obscured when individual processes are considered in isolation: the functional coordination of invasive behaviors and their alternative trajectories toward resolution or stabilization.

In this opinion article, we first revisit the historical foundations, biological rationale, and evolutionary origins of invasive growth and define the functional modules and signaling principles that coordinate it. We then examine how studies of **tumor ecosystems**, cellular plasticity, stress adaptation, and metastatic progression support the coordinated deployment of these modules in cancer. Finally, we explore how a normally transient program may become chronically stabilized in cancer and consider the therapeutic implications of this perspective.

Historical foundations of invasive growth

From invasion to invasive growth

The ability of tumor cells to breach tissue boundaries is one of the most striking features of malignant disease. Historically, invasion was primarily regarded as a morphological hallmark of cancer, reflecting the capacity of tumor cells to infiltrate adjacent tissues and eventually colonize distant organs [12]. The term 'karkínos', used by Hippocrates to describe tumors with crab-like extensions and later Latinized as cancer, already conveyed the image of a lesion spreading into surrounding tissues [13]. As molecular insights into cancer accumulated, invasion became increasingly recognized as an active process involving cell motility, ECM remodeling, and survival mechanisms [14–16]. Nevertheless, these behaviors were largely interpreted as consequences of malignant transformation rather than components of a broader biological program.

During the late 1980s and 1990s, studies in cell and developmental biology showed that behaviors traditionally associated with tumor invasion also emerge transiently during physiological processes such as embryogenesis, branching morphogenesis, wound healing, and tissue repair [17–19]. These observations suggested that the biological program underlying invasion, 'invasive growth', extends far beyond cancer.

Biological and evolutionary roots of invasive growth

During development, epithelial cells transiently remodel polarity, adhesion, motility, and interactions with the ECM to colonize new territories and reorganize tissue architecture [20,21]. For instance, epithelial cells undergoing branching morphogenesis in the developing mammary gland, kidney, or lung invade the surrounding ECM while maintaining coordinated growth and survival [22–31]. Similarly, during gastrulation and neural crest delamination, cells transiently loosen epithelial junctions, reorganize their cytoskeleton, and dynamically remodel cell–matrix interactions to migrate collectively while preserving tissue-level coordination [32–34]. Similar behaviors also emerge in adult tissues during wound healing, tissue repair, and organ regeneration. Following tissue injury, epithelial and stromal cells remodel polarity, adhesion, cytoskeletal organization, and ECM interactions—frequently through partial **epithelial–mesenchymal transitions (EMTs)**—to restore tissue integrity and re-establish functional architecture

Glossary

Adaptive program: a coordinated set of cellular behaviors that is transiently deployed in response to physiological demands or environmental challenges. In this opinion article, invasive growth is proposed as an adaptive program that integrates migration, survival, proliferation, and tissue remodeling.
Cancer-associated fibroblasts: activated stromal cells that dynamically remodel the ECM and secrete paracrine factors that shape tumor progression and therapeutic resistance.
Environmental adversity: microenvironmental challenges—such as hypoxia, nutrient limitation, therapeutic injury, and mechanical stress—that trigger adaptive programs such as invasive growth.
Epithelial–mesenchymal transition (EMT): a spectrum of phenotypic plasticity in which epithelial cells acquire mesenchymal traits. Partial states maintain collective behavior and are critical for invasive growth.
Extracellular matrix (ECM): the noncellular, three-dimensional scaffold of structural proteins that provides mechanical support and biochemical cues to regulate tissue organization and cell fate.
Hepatocyte growth factor (HGF): a stromal-derived cytokine and MET ligand that orchestrates the invasive growth program during development, tissue repair, and cancer.
Hybrid epithelial–mesenchymal states: intermediate phenotypic states in which cells coexpress epithelial and mesenchymal markers, enabling collective migration and enhanced metastatic potential.
Integrated stress response (ISR): an evolutionarily conserved signaling network activated by environmental stress that reprograms translation to promote cellular adaptation and survival.
Invasive growth: a coordinated physiological program integrating epithelial plasticity, migration, survival, ECM remodeling, proliferation, and morphogenesis. Although physiologically transient, it is proposed here that it becomes chronically stabilized during cancer progression.
MET: a receptor tyrosine kinase activated by HGF that serves as a central coordinator of invasive growth by integrating multiple downstream signaling pathways controlling migration, survival, proliferation, and morphogenesis.

[35–37]. The defining feature of physiological invasive growth is its reversibility [35,38,39]. Once tissue architecture has been restored, the program resolves through repolarization and differentiation, restoring structural and functional homeostasis (Figure 1).

The evolutionary roots of invasive growth extend far beyond multicellular organisms (Figure 2). Organisms such as the ameba *Dictyostelium discoideum* and budding yeast *Saccharomyces cerevisiae* have been extensively used to study adaptive behaviors involving collective migration, polarity remodeling, environmental sensing, and stress adaptation [40–46]. In *S. cerevisiae*, nutrient deprivation induces filamentous and invasive growth associated with polarity remodeling and substrate penetration [44–46]. In *D. discoideum*, starvation triggers cAMP-guided aggregation, collective migration, and multicellular organization [40–43]. Although these behaviors are not equivalent to invasive growth in vertebrate tissues, they illustrate ancient adaptive modules that couple environmental sensing to coordinated changes in cell polarity, migration, and collective organization. The conservation of these adaptive modules across distant evolutionary lineages suggests that key components of invasive growth emerged long before the appearance of complex multicellular organisms and were subsequently repurposed during morphogenesis, tissue repair, and cancer progression.

Together, these observations suggest that cancer does not invent invasive growth *de novo*. Rather, malignant progression co-opts a physiological program that normally orchestrates tissue morphogenesis, repair, and regeneration under tight spatial and temporal control.

Functional modules of invasive growth

One key module involves the transient remodeling of epithelial cohesion through changes in adherens junctions, polarity complexes, and cell–cell adhesion systems, thereby increasing cellular plasticity while preserving tissue organization [21,35,47]. Importantly, these transitions do not necessarily correspond to complete epithelial-to-mesenchymal conversion. Instead, this module is frequently deployed through partial or hybrid epithelial–mesenchymal programs that preserve collective behavior and the capacity for recolonization [48–51].

A second module couples directional migration to environmental sensing. Coordinated remodeling of the actin cytoskeleton, focal adhesions, and integrin-dependent mechanotransduction pathways promotes the formation of migratory structures such as lamellipodia and invadopodia, enabling cells to continuously adapt their migration to the biochemical and mechanical properties of the surrounding tissue [52,53].

A third module remodels interactions with the ECM. Integrins dynamically reorganize adhesive contacts, while matrix metalloproteinases (MMP-2, MMP-9, and membrane type 1 matrix metalloproteinase (MT1-MMP)) degrade basement membranes and stromal matrices, facilitating tissue infiltration [52,54,55]. Migration through unfamiliar tissue environments exposes cells to detachment, oxidative stress, hypoxia, and nutrient limitation. Matrix remodeling must therefore be coupled to survival programs that prevent apoptosis and anoikis [56,57]. Successful tissue recolonization completes the invasive growth program, restoring functional tissue architecture during development and repair, or enabling metastatic outgrowth in cancer [8,58].

Molecular coordination of invasive growth

How are these diverse cellular behaviors synchronized at the molecular level? Many cytokines and growth factors can independently stimulate proliferation, migration, survival, or differentiation. Invasive growth, however, requires the spatiotemporal integration of these activities into a coherent adaptive response. This observation suggests that the signaling systems governing invasive

Metastatic competence: the acquired ability of disseminated tumor cells to survive, adapt, and ultimately colonize a distant tissue environment.
Morphogenesis: the biological process that generates, remodels, or restores organized three-dimensional tissue architecture.
Plexins: a family of transmembrane receptors for semaphorins that regulate cell adhesion, migration, and tissue morphogenesis.
RON: a receptor tyrosine kinase closely related to MET that cooperates with integrins and other membrane receptors to regulate invasive growth.
Therapy persistence: the capacity of a subpopulation of tumor cells to survive therapeutic insult by entering a highly adaptive state.
Tissue homeostasis: the steady-state equilibrium maintained by physiological processes, which is disrupted in cancer and chronic diseases.
Tumor ecosystem: the dynamic, multicellular network of cancer cells, stroma, immune cell populations, and ECM that collectively drives tumor evolution.

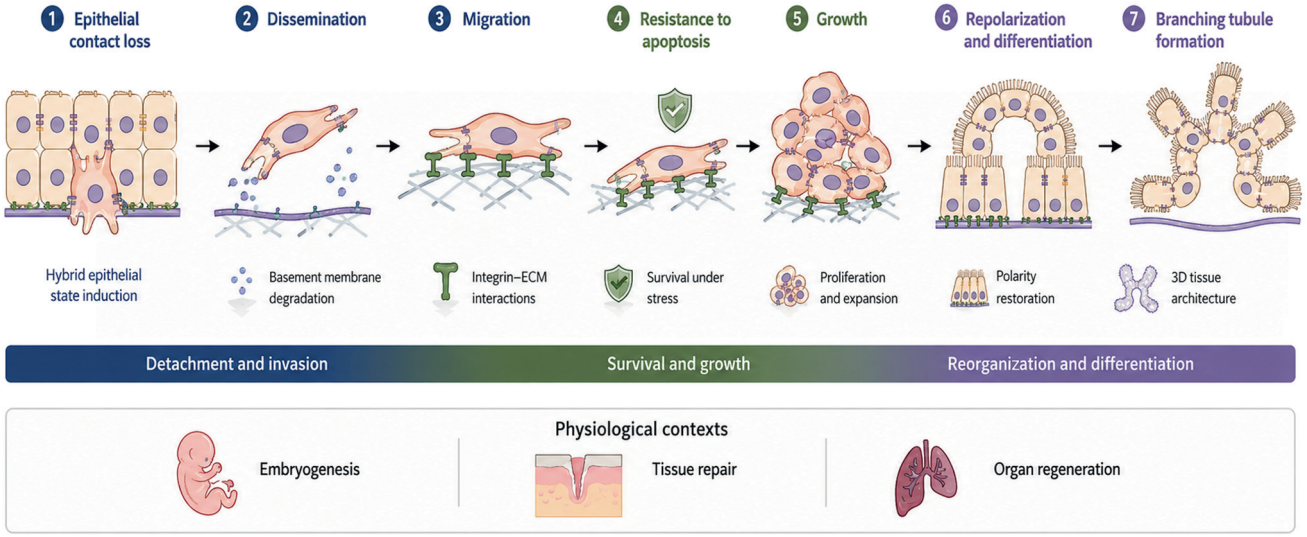


Figure 1. Invasive growth as a coordinated adaptive program. Invasive growth integrates epithelial plasticity, migration, survival, proliferation, and tissue organization in response to environmental cues. The schematic illustrates epithelial contact loss and acquisition of a hybrid epithelial state (1), followed by basement membrane degradation and dissemination (2), and migration through integrin–extracellular matrix (ECM) interactions (3). Resistance to apoptosis supports survival under stress (4), while proliferation enables cellular expansion (5). Repolarization and differentiation (6) support the formation of organized three-dimensional structures, illustrated here by branching tubules (7). The colored band groups these behaviors into three functional modules: detachment and invasion, survival and growth, and reorganization and differentiation. These activities can overlap rather than follow a strictly linear sequence. Physiological contexts include embryogenesis, tissue repair, and organ regeneration (bottom). This figure was created using BioRender (http://biorender.com/).

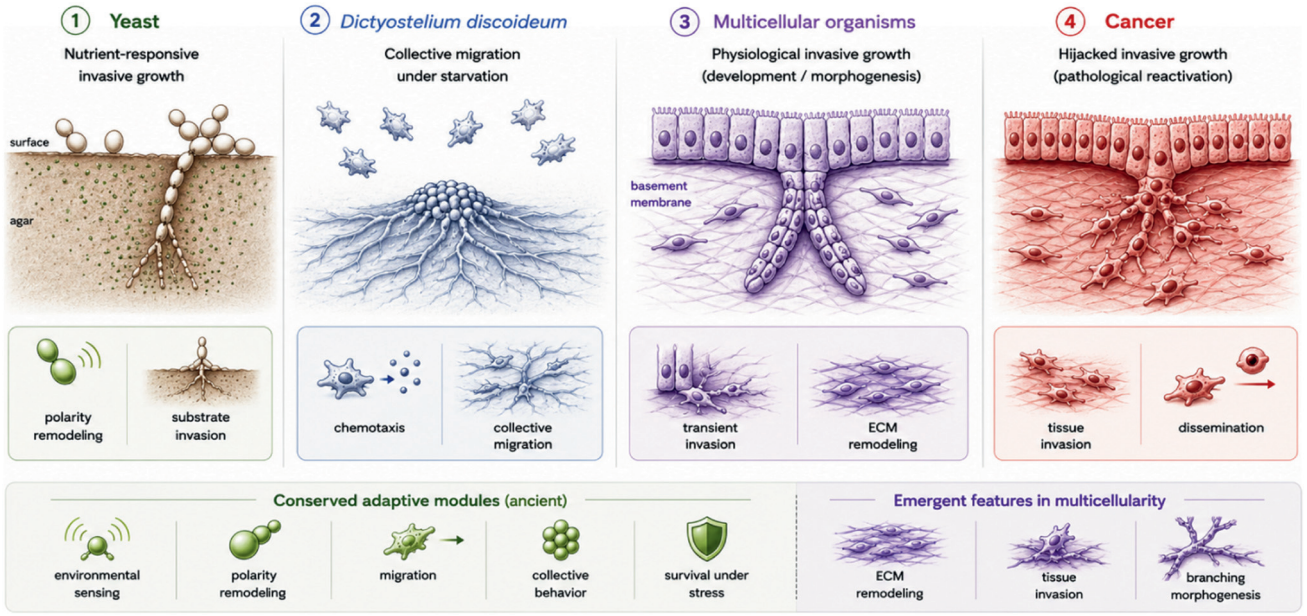


Figure 2. Evolutionary emergence of invasive growth modules. Conserved adaptive modules for environmental sensing, polarity remodeling, migration, and collective behavior emerged before multicellularity and were progressively integrated into the transient invasive growth program of developing and regenerating tissues. Cancer reactivates these conserved modules in pathological contexts. This figure was created using BioRender (http://biorender.com/). ECM: extracellular matrix.

growth must operate not simply as activators of individual cellular behaviors but also as coordinators of multiple biological outputs.

Developmental biology has provided some of the first evidence that complex cellular behaviors are coordinated through integrated signaling networks. Semaphorins, **plexins**, ephrins, netrins, and related guidance systems simultaneously regulate cell polarity, adhesion, migration, and tissue morphogenesis, demonstrating that tissue navigation relies on the integration of spatial and biochemical information rather than on isolated cellular responses [7,59–62].

Among the signaling systems implicated in invasive growth, studies on **hepatocyte growth factor (HGF)**, also known as scatter factor, and its receptor **MET** provided one of the first experimentally defined molecular frameworks linking epithelial dissociation, migration, survival, proliferation, and morphogenesis within a unified biological response [58,63–67]. Rather than activating a single downstream pathway, MET signaling coordinates multiple cellular outputs through multifunctional phosphotyrosine docking sites that recruit distinct signaling effectors [68,69]. Different downstream pathways preferentially regulate motility, survival, proliferation, morphogenesis, and ECM remodeling, while signaling specificity further depends on signal duration, cellular context, and interactions with membrane-associated receptors, including integrins, plexins, and related receptor tyrosine kinases such as **RON** [52,56,59,68–75]. Through this organization, a shared upstream signaling system couples complementary behaviors through distinct downstream effectors, coordinating their deployment without requiring them to occur simultaneously. Although MET provides a paradigmatic example, this biological logic extends beyond any single receptor system and reflects the broader integration of signaling networks coordinating coherent biological responses (Figure 3).

Invasive growth as a framework for cancer progression

The signaling systems described earlier provide a mechanistic basis for coordinating multiple cellular behaviors. In tumors, single-cell and spatial analyses increasingly identify cellular states combining plasticity, invasion, stress adaptation, and **therapy persistence** [2–5,50,76–81]. Their coexistence does not, by itself, establish that they share a common regulatory mechanism. It does, however, raise the question of whether signaling systems that coordinate physiological invasive growth also organize their joint deployment in cancer. Viewing these findings through the lens of invasive growth connects insights from processes often studied separately to examine how their functional cooperation supports tumor progression.

We examine epithelial plasticity and metastatic colonization as complementary examples. Epithelial plasticity illustrates how changes in cellular identity and adhesion are integrated with migration, survival, and collective organization. Metastatic colonization brings these capabilities together with proliferation and tissue remodeling to establish growing populations in a new environment. Together, these examples allow us to examine how plasticity, survival, and growth interact with ECM remodeling and tumor ecosystems.

Plasticity without full EMT

Among the concepts that have shaped our understanding of tumor progression, EMT occupies a central position. It provides a compelling framework for explaining how epithelial tumor cells acquire migratory and invasive properties. However, metastatic progression requires more than cellular plasticity alone. Successful dissemination also depends on the coordinated deployment of survival, proliferation, tissue adaptation, and recolonization programs. Consistent with this broader view, complete and stable epithelial-to-mesenchymal conversion is rarely observed in human tumors. Instead, tumor progression is predominantly associated with **hybrid**

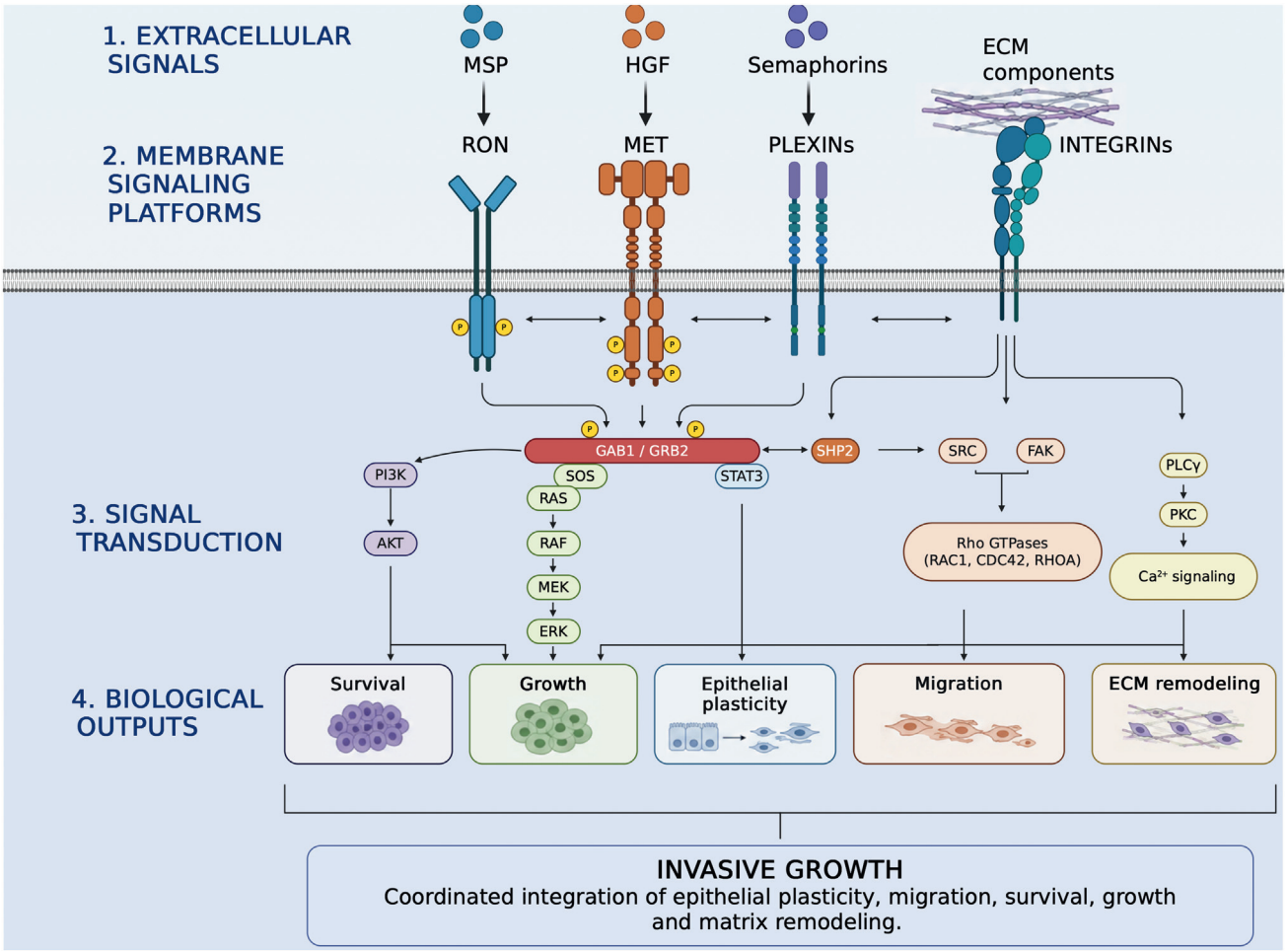


Figure 3. Molecular coordination of invasive growth. Multiple extracellular cues converge on interconnected membrane signaling platforms centered on MET, RON, plexins, and integrins. Rather than activating individual cellular behaviors independently, these signaling networks integrate distinct downstream pathways to coordinate epithelial plasticity, migration, survival, proliferation, and extracellular matrix remodeling. Invasive growth, therefore, emerges from the coordinated deployment of multiple biological outputs rather than activation of any single signaling pathway [52,58,59,68,75]. This figure was created using BioRender (http://biorender.com/). AKT: protein kinase B; CDC42: cell division control protein 42; ECM: extracellular matrix; ERK: extracellular signal-regulated kinase; FAK: focal adhesion kinase; GAB1: GRB2-associated-binding protein 1; GRB2: growth factor receptor-bound protein 2; GTPases: guanosine triphosphatases; HGF: hepatocyte growth factor; MEK: mitogen-activated protein kinase; MET: HGF receptor tyrosine kinase; MSP: macrophage-stimulating protein; P: phosphorylation; PI3K: phosphoinositide 3-kinase; PKC: protein kinase C; PLCγ: phospholipase C gamma; RAC1: Rac family small GTPase 1; RAF: RAF family serine/threonine kinases; RAS: RAS family small GTPases; RHOA: Ras homolog family member A; RON: receptor tyrosine kinase; SHP2: Src homology 2 domain-containing protein tyrosine phosphatase 2; SOS: Son of Sevenless guanine nucleotide exchange factor; SRC: Src family nonreceptor tyrosine kinase; STAT3: signal transducer and activator of transcription 3.

epithelial–mesenchymal states that preserve phenotypic plasticity while supporting multiple adaptive functions [82].

Lineage tracing studies and single-cell analyses have revealed a spectrum of hybrid epithelial–mesenchymal states that combine features of both identities [50,76,82]. Consistent with this view, invasive carcinomas frequently retain epithelial organization while invading collectively and integrating multiple adaptive functions [83]. For instance, keratin 14-positive/p63-positive leader cells coordinate collective migration, ECM remodeling, and invasion [83], whereas cohesive clusters of circulating tumor cells couple dissemination with enhanced survival and metastatic

colonization [84]. Likewise, E-cadherin-mediated adhesion actively promotes metastatic fitness, demonstrating that epithelial traits can contribute to tumor progression beyond their traditional role in tissue cohesion [85].

Viewed through the lens of invasive growth, epithelial plasticity is, therefore, no longer interpreted as an autonomous program but as an adaptive module within a broader, coordinated biological response. Rather than asking whether tumor cells undergo EMT, this framework shifts the focus toward how plasticity is integrated with survival, tissue adaptation, proliferation, and metastatic outgrowth to sustain tumor progression.

Metastasis: from dissemination to a morphogenetic program

Despite the enormous number of tumor cells released into the circulation, metastatic colonization remains remarkably inefficient [86,87]. This inefficiency reflects the fact that dissemination alone is insufficient for metastatic success. Tumor cells must also survive environmental stress, adapt to unfamiliar tissue environments, and ultimately reinitiate proliferation to generate metastatic outgrowth. Failure of any one of these adaptive functions prevents successful colonization.

Even among tumor cells that successfully establish residence within distant tissues, many fail to generate overt metastases [88,89]. Successful metastatic outgrowth instead depends on the ability of disseminated tumor cells to establish productive interactions with their new tissue environment. Consistent with this view, Shibue and Weinberg demonstrated that β1-integrin–focal adhesion kinase (FAK) signaling—a canonical downstream effector of invasive growth pathways [7,52]—promotes the proliferation of disseminated cancer cells within the lung, linking ECM sensing to micrometastatic expansion [90].

Beyond supporting proliferation, invasive-growth signaling can also sustain stem-like properties. In patient-derived metastatic colorectal cancer cultures, microRNA-483-3p-mediated suppression of N-myc downstream-regulated gene 1 (NDRG1) activated Erb-B2 receptor tyrosine kinase 3 (ERBB3)-protein kinase B (AKT) signaling, increasing invasiveness, proliferation, and stem-cell frequency; ERBB3 blockade counteracted invasive growth [91]. Similarly, an activating mutation in plexin-B2, a guidance receptor implicated in invasive growth, supported self-renewal, proliferation, and invasiveness in stem-like cells derived from cancers of unknown primary—metastatic cancers with no identifiable primary tumor—through epidermal growth factor receptor (EGFR)-dependent signaling [92]. These findings support the coordinated deployment of stem-like properties, proliferation, and invasiveness in cells derived from metastatic cancers.

Metastatic outgrowth also involves tissue reorganization. Recent work demonstrated that breast cancer macrometastases activate a three-dimensional trabecular morphogenetic program that reuses developmental branching logic to sustain metastatic growth [93]. In this view, a metastasis is not simply a growing mass, but an organized morphogenetic structure that actively reconstructs tissue architecture. Together, these observations suggest that metastatic cells are selected by their ability to coordinate plasticity, environmental adaptation, survival, tissue colonization, and morphogenesis, illustrating how apparently distinct concepts become more coherent when interpreted as manifestations of invasive growth (Figure 4).

However, a fundamental question remains unresolved. If invasive growth is a physiological program that normally supports development, tissue repair, and regeneration, what goes wrong in cancer? Under physiological conditions, invasive growth is tightly regulated in space and time and resolves once tissue architecture has been restored. In cancer, persistent **environmental adversity** may prevent resolution, stabilizing invasive growth as a chronic adaptive state. The central question is

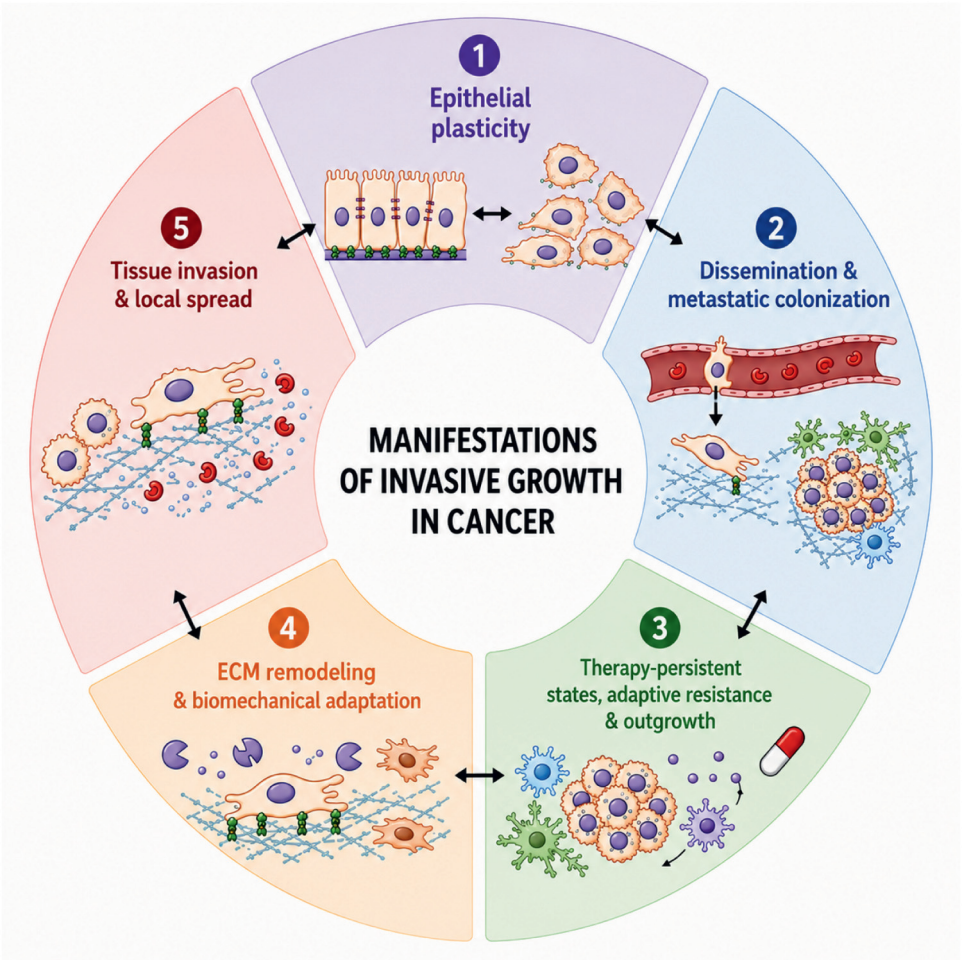


Figure 4. Invasive growth as a unifying framework for cancer progression. Processes traditionally viewed as distinct features of tumor progression—including epithelial plasticity, metastatic dissemination, therapy persistence, extracellular matrix remodeling, and tissue invasion—can be interpreted as interconnected manifestations of invasive growth. Within this framework, these adaptive states may reinforce one another within hostile tumor ecosystems, potentially supporting tumor progression through their coordinated deployment. This figure was created using BioRender (http://biorender.com/). ECM: extracellular matrix.

therefore not how invasive growth is initiated, but why a program that is normally transient becomes chronically stabilized during tumor progression. Addressing this question may be key to understanding how physiological adaptive responses become chronically entrenched, transforming mechanisms of tissue repair into self-sustaining drivers of cancer progression.

Chronic environmental adversity and stabilization of invasive growth

Invasive growth is normally transient

If invasive growth provides such an effective solution to tissue injury and environmental adversity, why is it not constitutively active? The answer cannot simply lie in the presence of its signaling machinery. HGF, integrin ligands, and receptors such as MET, RON, plexins, and integrins are broadly expressed across tissues [52,59,94,95]. However, healthy tissues do not continuously undergo invasive growth. Instead, this program appears to be conditionally deployed in response to environmental contexts that require tissue adaptation, repair, or regeneration.

Environmental constraints engage invasive growth

Despite their apparent diversity, the physiological contexts that engage in invasive growth share a common feature: environmental adversity. Tissue injury, hypoxia, nutrient limitation, inflammation, and mechanical perturbation all challenge tissue integrity and homeostasis, creating conditions that require coordinated adaptation rather than isolated cellular responses. Invasive growth emerges as an **adaptive program** that enables tissues to preserve their integrity and restore function despite environmental adversity [7,11,96,97].

The link between environmental adversity and invasive growth is not merely conceptual but is embedded within the molecular architecture of cellular stress-response pathways. For example, MET expression and signaling can be induced by hypoxia, ionizing radiation, tissue injury, and wound-healing programs [96–100]. Consistent with this adaptive role, MET has recently been identified as a direct translational target of the **integrated stress response (ISR)**, an evolutionarily conserved pathway activated by diverse forms of environmental stress [97,101,102]. Notably, MET is only rarely selected as a tumor-initiating driver, but is recurrently engaged during tumor progression and therapy resistance, consistent with its role as a stress-responsive coordinator of adaptive responses [97,103]. In parallel, ECM remodeling and increased matrix stiffness engage integrin–FAK signaling, providing a complementary route through which mechanical stress can reinforce invasive growth [52,104,105]. Together, these observations suggest that these pathways are intrinsically wired to translate environmental adversity into coordinated adaptive programs.

Importantly, this adaptive logic extends far beyond multicellular organisms (Figure 2). From unicellular systems to vertebrate tissues, environmental adversity repeatedly engages coordinated responses that integrate survival, migration, environmental remodeling, and expansion [40–46]. For instance, the ISR, which promotes MET expression and invasive growth in mammalian cells [97], is also required for filamentous and invasive growth in *S. cerevisiae* [44,46,106]. Invasive growth, therefore, emerges as a conserved adaptive strategy that allows biological systems to maintain organized structure and function despite environmental perturbations.

Cancer is characterized by chronic environmental adversity

Cancer differs from physiological tissue repair not in the nature of the environmental challenges it generates but in their persistence. Rather than resolving, tumor ecosystems continuously recreate conditions of hypoxia, inflammation, fibrosis, nutrient limitation, mechanical stress, immune pressure, and therapeutic injury [107–110]. Consequently, the environmental cues that transiently engage invasive growth during tissue repair become enduring features of the tumor microenvironment.

Importantly, environmental adversity should not be viewed narrowly as metabolic stress. It encompasses any persistent condition that threatens tissue homeostasis, including therapeutic injury. Chemotherapy and radiotherapy—designed to eliminate tumor cells—remodel tumor ecosystems through inflammation, fibrosis, and tissue damage, potentially reinforcing the very adaptive programs they seek to suppress [89,97,111–113].

The persistence of these environmental cues may therefore sustain invasive growth beyond its normally transient deployment, leading to chronic stabilization.

Chronic stabilization of invasive growth

In this section, we use ‘chronic stabilization’ to describe the sustained deployment of the coordinated invasive-growth program in which its physiological counterpart would be transient. Such persistence may arise through three not mutually exclusive routes: (i) a normally reversible

response continuously maintained by persistent or recurrent environmental cues; (ii) a stable cellular state maintained after the initiating stimulus is no longer present; or (iii) the selective survival or expansion of tumor cells possessing these properties.

The first route involves continuous environmental reinforcement of invasive growth. Hypoxic, therapy-remodeled, and vascularly compromised niches are enriched in invasive cellular states. Experimental and spatial studies further indicate that tissue necrosis and therapy-induced ecosystem remodeling can promote tumor progression and persistent adaptive states [78,114–116]. Reciprocal tumor–stroma interactions may sustain these conditions through self-reinforcing feedback loops (Figure 5). Tissue injury, fibrosis, and ECM remodeling activate **cancer-associated fibroblasts**, promote growth-factor production, including HGF, and enhance integrin-dependent mechanosignaling [117–123]. In parallel, stress-response pathways sustain invasive-growth effectors such as MET [97,99,100]. Invasive growth may, in turn, perpetuate tissue remodeling and regenerate activating cues. Persistence would thus remain dependent on environmental signals without requiring cell-intrinsic memory.

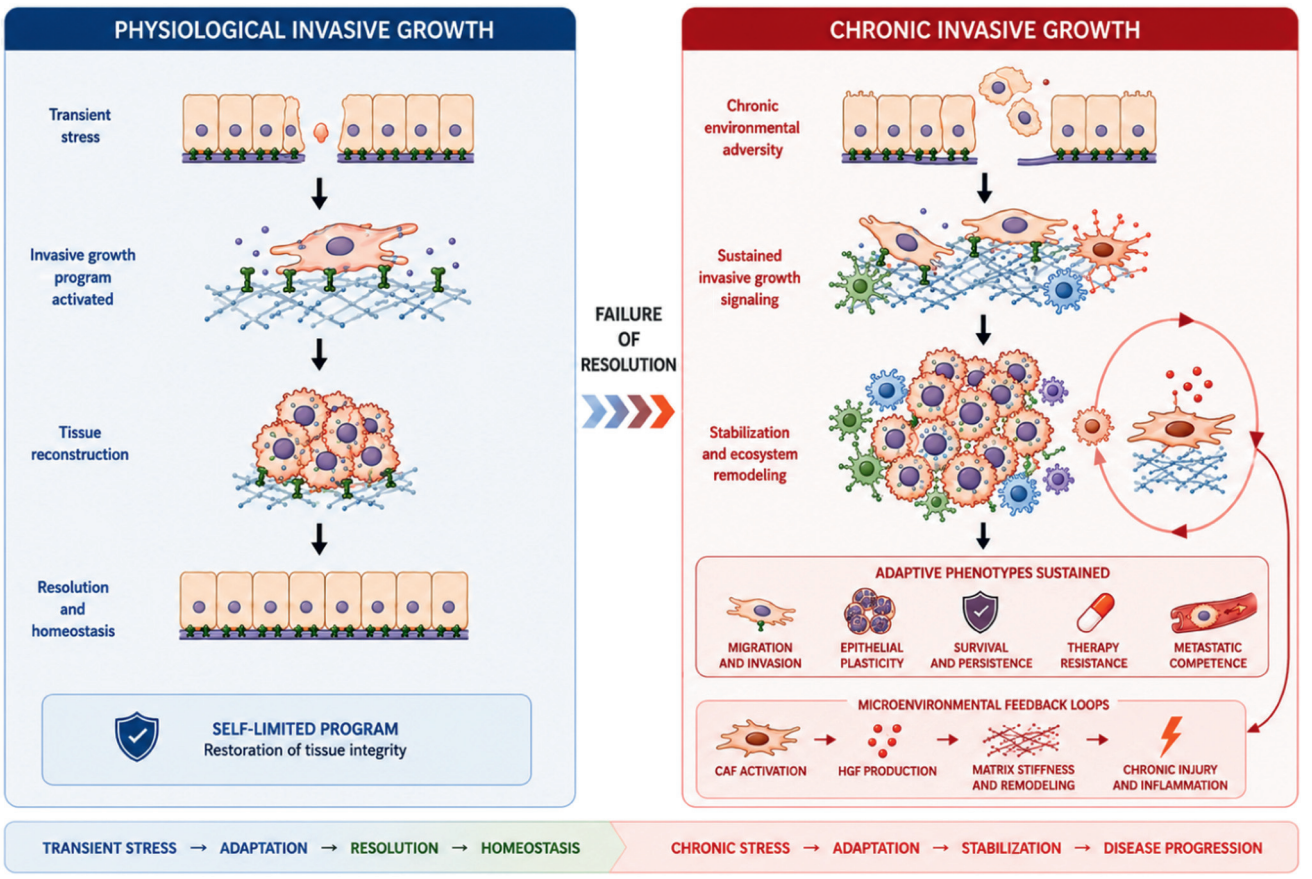


Figure 5. From physiological to chronic invasive growth. Physiological invasive growth is a transient adaptive program engaged during development, tissue repair, and regeneration. Following tissue reconstruction, the program resolves, allowing recovery of homeostasis (left). In cancer, invasive growth may become chronically stabilized through three not mutually exclusive routes: continued environmental reinforcement, maintenance of acquired cellular states after the initiating stimulus has disappeared, and selective survival or expansion of cells possessing these properties. The right panel illustrates environmental reinforcement, whereby reciprocal interactions between tumor cells and their microenvironment may generate self-reinforcing loops that sustain invasive growth. Cellular state maintenance and selection may cooperate with these interactions, favoring the persistence of epithelial plasticity, invasion, survival, therapy resistance, and metastatic competence. This figure was created using BioRender (http://biorender.com/). CAF: cancer-associated fibroblast; HGF: hepatocyte growth factor.

Beyond the persistence of environmental stress itself, adaptive cellular states may become stably maintained even after the initiating stimulus is no longer present. EMT-associated cellular states can persist after transforming growth factor beta (TGF-β) withdrawal, and this persistence has been linked to enhanced metastatic colonization [124]. An example of reversible maintenance is provided by the autocrine TGF-β–zinc finger E-box-binding homeobox (ZEB)–microRNA-200 (miR-200) circuit, which sustains an established mesenchymal state after withdrawal of exogenous TGF-β, while its disruption permits epithelial reversion [125]. Regenerative responses can also leave a latent memory that facilitates subsequent reactivation of functions encompassed by invasive growth. Following experimental colitis, colonic stem cells retained an epigenetic memory associated with an activator protein 1- (AP-1)-regulated program linking tissue repair, cytoskeletal remodeling, cell adhesion, and stem-cell proliferation [126]. Although repair-associated gene expression largely returned to baseline after recovery, subsequent adenomatous polyposis coli (APC) loss enhanced expression of this program and accelerated early tumor growth. AP-1 inhibition reduced this growth advantage without erasing the underlying memory. Persistence after stimulus withdrawal is also observed in drug-tolerant cancer cells, which can retain reduced sensitivity after drug removal [127]. Together, these studies show that both maintained cellular phenotypes and latent changes in responsiveness can outlast the initiating stimulus. However, population-level observations of treatment tolerance alone cannot distinguish acquired changes in drug sensitivity from the selective enrichment of pre-existing drug-tolerant cells.

Such selection provides a third route to persistence. Cells with genetic alterations or pre-existing nongenetic states that favor survival, invasion, or treatment tolerance may become enriched under environmental or therapeutic pressure. In melanoma, rare cells transiently express a resistance-associated transcriptional program before treatment; drug exposure then promotes further reprogramming toward stable resistance, illustrating how selection and state stabilization can cooperate [128]. A genetic example is the selection of pre-existing *MET*-amplified cells during EGFR inhibition, which can be accelerated by HGF [129]. The causal contribution of MET, a key regulator of invasive growth, to resistance is supported by the restoration of sensitivity to EGFR inhibition upon MET blockade [130].

These observations suggest that environmental reinforcement, cellular memory, and selection can act successively or together. We propose that cells sustaining invasive growth through genetic or nongenetic mechanisms may gain a selective advantage under environmental or therapeutic pressure because they can coordinate plasticity, migration, and survival, thereby favoring tumor progression.

Unraveling the mechanisms of chronic invasive growth

The examples discussed earlier do not establish how invasive growth becomes sustained as a coordinated program. Investigating these mechanisms fits with contemporary models of tumors as dynamic, pseudo-organ-like ecosystems shaped by reciprocal interactions among cancer cells, stromal and immune populations, and the ECM and remodeled by therapeutic pressures [94,109–112,117,131–133]. Understanding how these interactions sustain or select adaptive states could reveal new vulnerabilities. The therapeutic aim would be not to suppress adaptation itself but to disrupt the mechanisms that turn a transient physiological response into a persistently maintained tumor program.

Moreover, understanding why invasive growth persists in cancer requires understanding how its physiological execution ends. Evidence from tissue repair identifies several context-dependent controls, including contact inhibition, attenuation of growth-factor signaling, restoration of cell–cell contacts, Hippo–Yes-associated protein (YAP)-mediated growth restraint, inflammatory resolution, and deactivation or clearance of repair-associated stromal cells [134–138]. These

mechanisms act on different components of the regenerative response, but how they collectively bring invasive growth to an end remains incompletely understood. Crucially, resolution need not reverse the cellular changes or tissue architecture generated by the program: its execution can cease while its products persist. Determining whether these controls are disrupted or overridden in cancer could reveal how invasive-growth behaviors become sustained.

More broadly, cancer may represent the best-characterized manifestation of a general biological principle. Distinct chronic diseases could arise when adaptive programs that normally resolve after tissue repair become chronically stabilized under persistent environmental adversity. Consistent with this possibility, recent spatial and single-cell studies identify hybrid cell states associated with aberrant repair in chronic disorders such as idiopathic pulmonary fibrosis [139,140]. This interpretation shifts the focus from disease-specific mechanisms to the shared principles governing the failure of adaptive program resolution.

Concluding remarks and future perspectives

The invasive-growth framework shifts attention from focusing on individual tumor phenotypes to investigating how their coordinated deployment may arise, as well as the conditions that sustain it. A central message emerging from this opinion article is that invasive growth should not be viewed simply as a program activated in cancer. Physiological invasive growth is transient and self-limiting, whereas chronic tumor ecosystems may prevent its resolution, progressively stabilizing an adaptive program that originally evolved to preserve tissue integrity. The fundamental question in cancer progression, therefore, shifts from how invasive growth is activated to why a physiological adaptive program fails to resolve (see Outstanding questions).

This conceptual framework generates experimentally testable predictions and directions for future investigation. First, the most aggressive tumor cell states should not be those maximizing a single phenotype but those exhibiting the greatest functional integration of invasive growth modules. Second, identifying the mechanisms that stabilize invasive growth may reveal novel vulnerabilities, providing a rationale for exploring therapies directed at tumor ecosystems and program resolution alongside approaches targeting cancer cell-intrinsic vulnerabilities [109,141,142]. Finally, if chronic stabilization of adaptive programs represents a general biological principle, malignant and nonmalignant diseases—such as fibrotic and inflammatory disorders—should converge on common mechanisms of unresolved adaptation despite their distinct clinical manifestations.

This framework may also provide a mechanistic explanation for a long-standing clinical observation: tumors arising in chronically injured or fibrotic tissues are often particularly aggressive [143,144]. Rather than acquiring invasive capabilities *de novo*, tumor cells may be positively selected within tissue ecosystems in which invasive growth is already chronically engaged, favoring clones capable of exploiting an established adaptive program before overt malignant progression.

Ultimately, cancer progression may be viewed not as the invention of a new pathological program but as the chronic stabilization of an evolutionarily conserved adaptive program normally engaged during development, tissue repair, and regeneration. This perspective reframes one of the fundamental questions in cancer biology. The central question is no longer how invasive growth is activated but why a physiological program that normally resolves after tissue repair fails to do so in cancer.

Outstanding questions

Can tumor progression be understood as the coordinated deployment of an evolutionarily conserved biological program rather than the accumulation of independent cellular behaviors?

Why does invasive growth, a transient physiological program during development and tissue repair, fail to resolve in cancer?

How do persistent environmental cues, cellular memory, and selection contribute, individually or together, to the chronic stabilization of invasive growth?

Can identifying the mechanisms that sustain invasive growth reveal therapeutic vulnerabilities distinct from those involved in its initial activation?

Could chronic stabilization of adaptive physiological programs represent a general principle underlying diseases beyond cancer, including fibrosis and chronic inflammatory disorders?

Author contributions

D.M.A. and P.M.C. jointly developed the conceptualization of this opinion article. D.M.A. developed the central conceptual framework and wrote the original draft of the manuscript. Both authors contributed to the critical review and editing of the final version. Both authors have read and approved the final manuscript.

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Declaration of interests

The authors declare no competing interests.

Author biographies

Dogus M. Altintas is a molecular biologist at the Laboratoire de Biologie Tissulaire et Ingénierie Thérapeutique (LBTI), CNRS UMR 5305, Université Claude Bernard Lyon 1, France. His research focuses on the role of translational control in cancer adaptation. His work demonstrated that the integrated stress response directly upregulates *MET* oncogene translation, establishing a mechanistic link between the hostile tumor microenvironment and invasive growth. His current research investigates how a normally transient invasive growth program becomes persistently maintained in nonmalignant and malignant diseases.

Paolo M. Comoglio is a scholar at IFOM – The AIRC Institute of Molecular Oncology, Milan, Italy. His pioneering work established hepatocyte growth factor (HGF) as the ligand for the MET receptor and identified the HGF/MET signaling pathway as a central regulator of invasive growth during development, tissue regeneration, and cancer. Over several decades, his laboratory has made fundamental contributions to receptor tyrosine kinase signaling, tumor invasion, metastasis, and the development of MET-targeted therapies, helping establish invasive growth as a coordinated biological program. He is an elected member of EMBO and the Accademia Nazionale dei Lincei and has received numerous international awards for his contributions to cancer biology and signal transduction.

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