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Review

# Educate, not kill: treating cancer without triggering its defenses

Aneta Škarková[1], Mariano Bizzarri[2], Radoslav Janoštiak[3], Jan Mašek[4], Daniel Rosel[1,*], and Jan Brábek[1,*]

**Traditionally, anticancer therapies focus on restraining uncontrolled proliferation. However, these cytotoxic therapies expose cancer cells to direct killing, instigating the process of natural selection favoring survival of resistant cells that become the foundation for tumor progression and therapy failure. Recognizing this phenomenon has prompted the development of alternative therapeutic strategies. Here we propose strategies targeting cancer hallmarks beyond proliferation, aiming at re-educating cancer cells towards a less malignant phenotype. These strategies include controlling cell dormancy, transdifferentiation therapy, normalizing the cancer microenvironment, and using migrastatic therapy. Adaptive resistance to these educative strategies does not confer a direct proliferative advantage to resistant cells, as non-resistant cells are not subject to eradication, thereby delaying or preventing the development of therapy-resistant tumors.**

## Highlights

Cytotoxic therapies expose cancer cells to direct killing, instigating the process of natural selection favoring survival of resistant cells that become the foundation for tumor progression and therapy failure. Recognizing this phenomenon has prompted the development of alternative therapeutic strategies.

Strategies targeting cancer hallmarks beyond proliferation have potential to re-educate cancer cells towards a less malignant phenotype. These strategies include controlling cell dormancy, transdifferentiation therapy, normalizing the cancer microenvironment, and migrastatic therapy.

Adaptive resistance to these educational strategies does not provide resistant cells with a direct proliferative advantage, holding substantial promise in delaying or preventing the development of therapy-resistant tumors.

## Re-educating cancer cells: treatment strategies overcoming resistance and relapse

Cancer is a disease characterized by loss of homeostasis, manifesting through abnormal cell proliferation and migration. Despite years of extensive effort to combat cancer, it represents a worldwide leading cause of death. The main strength of cancer lies in its versatility – as the tumor evolves, it adapts to current conditions using its most dangerous weapon of natural selection. Cancers display large inherent genotype and phenotype plasticity, which enables an adaptive response that confers cancer cells with enhanced survival capabilities and resilience to treatment. Along with natural selection of the fittest, these forces drive cancer populations to constantly evolve when facing selective pressures and stress conditions. Unfortunately, these mechanisms also underlie treatment resistance and disease relapse [1].

Traditionally, conventional therapies have primarily focused on restraining uncontrolled proliferation, and less on additional oncogenic traits such as phenotypic plasticity or invasion. Nevertheless, **cytotoxic therapies** (see Glossary) expose cancer cells to direct killing, instigating the process of natural selection that favors the survival of cells inherently resistant or acquiring resistance. This fosters the emergence of therapy-resistant subpopulations within the tumor, surpassing the original cancer cell population and ultimately leading to therapy resistance and tumor recurrence [2–4]. Recognizing this phenomenon has prompted the development of alternative therapeutic strategies directed towards cancer hallmarks beyond mere proliferation [5,6]. Gaining control over these traits by manipulating the behavior of cancer cells represents a possible strategy to mitigate negative outcomes.

Importantly, by targeting the behavior of cancer cells and forcing them to adopt a less-malignant state instead of inflicting lethal damage, we bypass the strongest weapon of cancer – natural selection that produces resistant and highly adaptable clones – thereby mitigating the risk of therapeutic failure due to the emergence of treatment-resistant cells. In this review, we summarize four strategies focusing on re-educating cancer cells into a less malignant phenotype: controlling **cell dormancy**, **transdifferentiation therapy**, **cancer microenvironment** normalization, and the

[1]Department of Cell Biology, BIOCEV, Faculty of Science, Charles University, Vestec, Czech Republic
[2]System Biology Group Laboratory, Sapienza University, Rome, Italy
[3]First Faculty of Medicine, BIOCEV, Charles University, Vestec, Czech Republic
[4]Department of Cell Biology, Faculty of Science, Charles University, Prague, Czech Republic

*Correspondence:
rosel@natur.cuni.cz (D. Rosel) and
brabek@natur.cuni.cz (J. Brábek).

migrastatic strategy, and include examples of successful treatments using available drugs (Figure 1, Key figure). The implementation of these educative cancer treatment strategies to a greater extent coupled with the establishment of appropriate efficacy criteria holds the potential to revolutionize cancer treatment and bring tremendous benefit to the patients.

## Strategy 1: controlling cell dormancy

The phenomenon of dormancy or **quiescence**, characterized by a temporary and reversible growth arrest, is an adaptive strategy employed across species to confront unfavorable and challenging conditions to ensure survival.

The ability of cancer cells to survive by becoming dormant facilitates metastasis, disease recurrence, the emergence of therapy resistance, immune evasion, and **cancer stem cell (CSC)** maintenance [7–9]. Dormancy is generally understood on the scale of the tumor mass, where a balance between cell death and proliferation results in the overall stability of the tumor size, and at the cellular level, where cells, be it individual or in the form of disseminated micrometastases, are arrested in the G0 phase of the cell cycle. While entry into the G0 phase used to be regarded as a mere absence of proliferative signaling, it is now clear that G0 entry is an active and programmable response that can be initiated by a variety of stimuli [10]. The integration of these signals determines whether cells proliferate, enter a quiescent state, or awaken from dormancy. The duration and nature of proquiescent signaling correlates with quiescence depth which is then associated with metabolic and epigenetic reprogramming [11–13].

Quiescent cells can serve as reservoirs of genetic and epigenetic variability that become advantageous conditions suddenly change, such as cytotoxic therapy. For example, a slow cycling, **persister phenotype** of a subset of cancer cells was identified and enriched in residual disease after therapy. Initially, these cells are characterized by high epigenetic plasticity and cell cycle arrest and low mutational burden [14]. However, these cells have buffering systems (proteome stability, folding, and degradation) with greater activity [15], which could allow them to accumulate phenotypic diversity. Recently, a polyploid phenotype of dormant cells was identified [16] – a common strategy for evolution facilitation shared throughout the metazoan kingdom [17]. The whole genome is multiplied and provides spare copies of crucial genes that can be modified leading to higher variability with the potential emergence of selective advantage.

Since the ability of cancer cells to initiate the quiescent program is one of the key resistance mechanisms, controlling the dormancy of cells might be a valuable therapeutic approach (Figure 2). In general, this approach involves three strategies – lock-in, lock-out, and direct killing strategies. The lock-in strategy targets residual dormant cells or micrometastases, where the treatment would keep the cells arrested by inhibiting reawakening pathways. For example, CDK4/6 inhibitors such as palbociclib could be used for such purposes as they block the transition through the G1 phase [18]. The obvious disadvantage is that it is not a curative approach, and the therapy would need to be administered throughout the affected individual's life, which is only possible once drugs with minimal side effects are available.

However, currently, drugs like palbociclib are associated with a high burden of severe side effects [19]. The lock-in approach could also stimulate a transition to a permanent cell cycle arrest state – the senescent phenotype, to be targeted by **senolytics** thereafter. Nevertheless, this transition is not well understood, and recent reports show that even senescent cancer cells can be reactivated and enter the cell cycle [20] or play an indirect role in promoting invasive behavior by secreting promigratory cytokines [21].

## Glossary

**Amoeboid invasion mode:** a cancer cell invasion mode characterized by a rounded cell shape, blebbing, or pseudopodal protrusions, as well as by weak or absent cell–matrix adhesions.
**Apoptosis:** process of programmed cell death. It is used during development to eliminate unwanted cells and, in adults, to rid the body of cells that have been damaged beyond repair.
**Cancer microenvironment, also known as the tumor microenvironment (TME):** a complex ecosystem surrounding a tumor composed of cancer cells, stromal tissue (including blood vessels, immune cells, fibroblasts, and signaling molecules) and the ECM.
**Cancer stem cells (CSCs):** a small subpopulation of cells within tumors with capabilities of self-renewal, differentiation, and tumorigenicity when transplanted into an animal host.
**Cell dormancy:** status of reversible cell growth arrest, also known as quiescence.
**Cytotoxic therapy:** treatment approaches that can kill cancer cells or slow their growth.
**Epithelial–to-mesenchymal transition (EMT):** a multistep activation and differentiation process by which epithelial cells achieve mesenchymal phenotypes, activate migration, and delay cell-cycle progression.
**Exosomes:** membrane-bound extracellular vesicles that are produced in the endosomal compartment of most eukaryotic cells. They are mediators of near and long-distance intercellular communication in health and disease and affect various aspects of cell biology.
**Mesenchymal invasion mode:** a cancer cell invasion mode characterized by fibroblast-like morphology, focalized interactions with the ECM, and protease-dependent ECM degradation.
**Mesenchymal to epithelial transition (MET):** a reversible biological process that involves the transition from motile, multipolar, or spindle-shaped mesenchymal cells to polarized epithelial cells.
**Migrastatic therapy:** treatment approaches aiming to prevent metastasis by inhibiting cancer cell migration and invasiveness.
**Persister phenotype:** the ability to evade drug treatment without the need for new genetic alterations.

## Key figure

Overview of strategies for cancer treatment avoiding Darwinian selection of resistant clones

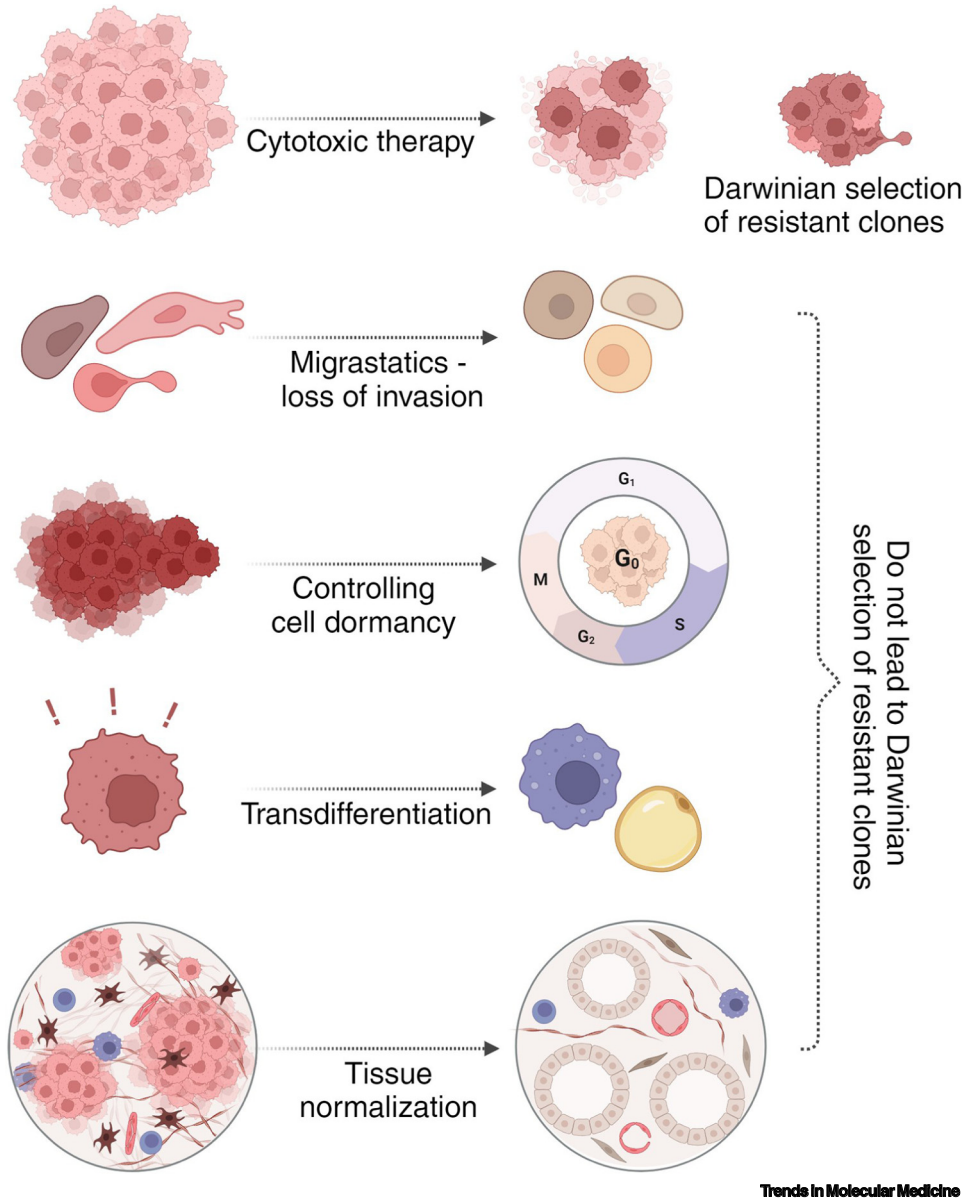


Figure 1. Cytotoxic therapy (first row) impedes cellular proliferation, thus prompting a Darwinian process that favors the survival of drug-resistant clones (dark red), as they gain a selective advantage over their non-resistant counterparts. By contrast, strategies focused on inhibiting invasion, controlling dormancy, promoting trans-differentiation, or tissue normalization approaches (lower rows) do not directly influence fitness for survival. Thus, resistant clones do not gain a competitive advantage in terms of proliferation. Consequently, under such regimens, the prevalence and dominance of drug-resistant sub-clones is curtailed. This prevents the emergence of drug-resistant tumors with high proliferative capacity. Created with BioRender.com.

**Quiescence:** status of reversible cell growth arrest, also known as cellular dormancy.
**Senolytics:** a class of drugs that selectively clear senescent cells.
**Transdifferentiation therapy:** treatment approaches based on differentiation of cancer cells into other cell types.
**Yamanaka factors (OCT4, SOX2, KLF4, and MYC – OSKM):** a group of protein transcription factors that play a vital role in the creation of induced pluripotent stem cells – cells that can differentiate into any cell in the body.

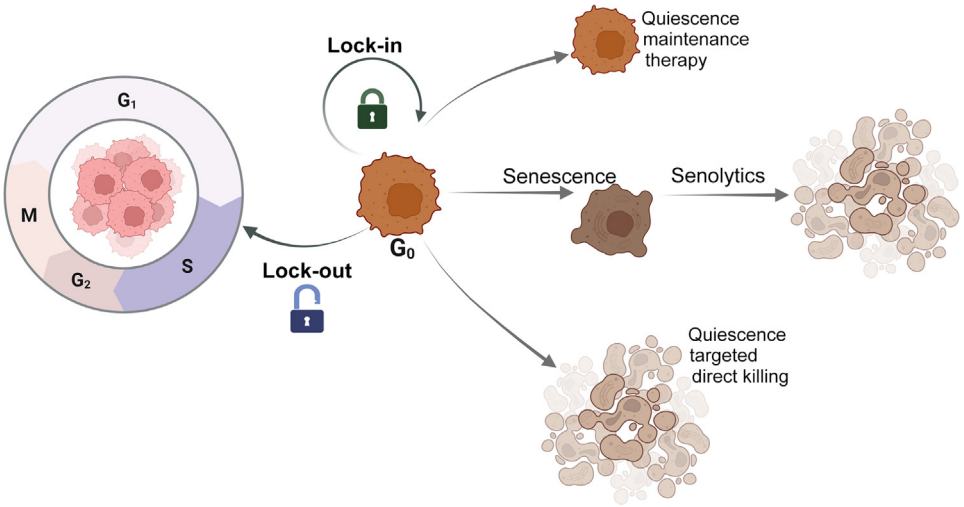


Figure 2. Cell-cycle-altering drugs: there are several options to take advantage of cell cycle manipulation. One option is to inhibit quiescence-promoting signaling (the lock-out strategy), which keeps cancer cells in the proliferative stage, making them more vulnerable to standard therapeutics (left). By contrast, quiescence-promoting compounds (the lock-in strategy) keep the cells in the quiescent stage. This strategy offers three sub-approaches: (i) cells can be maintained in the quiescent stage through long-term quiescence maintenance therapy (top right); (ii) additional compounds can be used to deepen the quiescence level and move the cells to senescence, which could then be targeted by senolytics (middle right); and (iii) quiescent cells could be directly targeted using additional compounds specific to key quiescence-regulating pathways (bottom right). Created with BioRender.com.

The lock-out strategy exploits pathways that facilitate the entry into quiescence and/or pathways that maintain the quiescent state. In the first scenario, such therapy could target the decision point of whether cells treated with conventional anticancer therapy enter dormancy or undergo **apoptosis** and facilitate execution of the apoptotic program, rather than entering quiescence. In the second scenario, impairing dormancy maintenance would lead to a reawakening of the cancer cells and their proliferation, where again cytotoxic and targeted therapy would be effective. The feasibility of this approach was demonstrated by inhibition of DYRK1/2 kinases, which resulted in cell cycle entry of quiescent cells and re-sensitization to anticancer therapy [22,23]. More recently, resensitization of dormant cells to chemotherapy was achieved by inhibiting interactions of dormant cells within the perivascular niche [24]. One major drawback of this approach is the possible emergence of mutations and other adaptive mechanisms (epigenetic and/or protein expression alterations) that would lead to therapy failure. However, unlike cytotoxic treatment, dormancy therapy would not kill non-resistant cells, maintaining competitive suppression within the tumor, during which non-resistant cells limit the outgrowth of resistant clones [25], which is a phenomenon utilized by adaptive therapy [3].

The design of potential clinical trials should consider various scenarios based on the selected approach. Preventing exit from quiescence through inhibition of key cell-cycle-promoting pathways has been successfully tested in mice models [26,27], but comes with a major disadvantage of the necessity to administer such therapy throughout the life of the patient. By contrast, approaches that specifically eliminate the quiescent niche would only be administered during the treatment period. Such specific eradication of dormant cancer cells can be achieved via targeting key quiescence mechanisms (e.g., autophagy and oxidative phosphorylation). Inhibition of autophagy could serve as proof-of-concept evidence where treatment of breast cancer cells with autophagy inhibitors eradicated quiescent cells *in vitro* as well as *in vivo* [28]. Similarly, targeting oxidative phosphorylation has proven effective in a murine cancer model [29]. Combinatory approaches

for the elimination of dormant cancer cells are also currently being investigated in clinical trials (NCT03400254[i], NCT04841148[ii]).

Complete elimination of cancer cells is obstructed by their resilience and adaptability. However, gaining control over both actively dividing and dormant cancer cells holds promise in transforming malignant cancer into a manageable, chronic condition.

## Strategy 2: transdifferentiation therapy

For over half a century, the field of developmental biology has consistently offered a valuable resource for potential therapeutic approaches by uncovering how cell fate evolves in the context of cancer growth and metastasis [30,31]. Overall, the view is that by using the signaling pathways that normally act during embryonic development, cancer cells create new abnormal structures – tumors [32]. For example, during metastasis, cells lose their original differentiation and initiate migratory programs, such as the **epithelial-to-mesenchymal transition (EMT)**, which is reminiscent of processes seen during embryonic development or wound healing [33,34].

Tumors consist of a heterogeneous population of cells that vary in their extent of differentiation. Among these cells, a subset exhibits the characteristics of CSCs. These CSCs can originate from true stem cells, which have become cancerous due to the acquisition of procarcinogenic mutations, or they may be derived from descendant progenitor cells, resulting in a diverse pool of CSCs with various somatic mutations [35]. The targeted induction of Wnt/NF-κB-dependent tumorigenesis in intestinal stem (Lgr5$^{+}$) or somatic cells highlighted the feasibility of inductive, bi-directional conversion between the two cell populations [36]**.** Experiments involving the targeted deletion of tumor suppressor genes *Trp53* and *Nf1* in neural crest cells or neural progenitors demonstrated that tumor formation consistently occurred in the descended, differentiated glial cells [37] or oligodendrocyte progenitor cells [38], but not the neural crest cells themselves. These findings, together with previously identified similarities between stem cells and CSCs [39,40], and concomitant discovery of cell reprogramming by **Yamanaka factors (OCT4, SOX2, KLF4, and MYC – OSKM)** [41,42] have fueled the concept of reversing cancer through targeted cell state alteration (Figure 3).

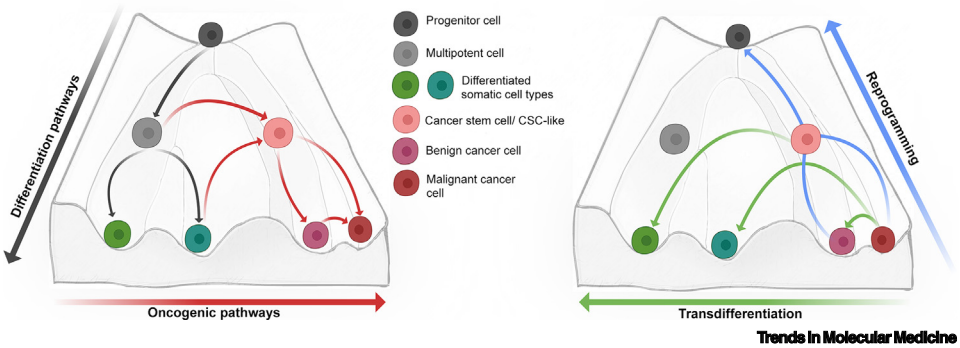


Figure 3. Cancer cell reprogramming and transdifferentiation approaches. Under physiological developmental conditions, pluripotent cells differentiate via transient multipotent cell states into terminally differentiated cell types (left; black arrows). However, under the influence of oncogenic pathways, these cells undergo a transformation, leading to the formation of the cancer population (left; red arrows), which consists of cancer stem cells (CSCs), and benign and/or malignant cancer cells. To mitigate the malignant potential of the cancer cells and manipulate them towards a more controlled and regulated state, reprogramming and transdifferentiation strategies can be employed (right; blue and green arrows, respectively). Created with BioRender.com.

Importantly, although systemic expression of OSKM in somatic cells is pro-oncogenic [43], OSKM factors can rejuvenate the tissue and extend the expected lifespan when expressed in a controlled manner [44]. In cancer cells, reprogramming of the tumor population with Yamanaka factors leads to the loss of diverse cancer cell identity and can reset the population to the CSC state and sensitize them to differentiation stimuli [45,46].

The redirection of cell state through transcription-factor-mediated cancer cell reprogramming or, if available, transdifferentiation using a drug that affects activity of the desired transcription factors has become a promising avenue in current cancer therapy research [45,47]. Intriguingly, this approach also applies to metastatic cancer cells as has been demonstrated in non-solid leukemias. For example, introduction of C/EBPα drives the conversion of lymphoblastic leukemia B cells into macrophage-like cells, impairing their tumorigenicity [48]. A well-known example is the acute promyelocytic leukemia (APL) treatment, in which the terminal differentiation and/or apoptosis of the leukemic promyelocytes into mature granulocytes is routinely achieved by combination of all-*trans* retinoic acid (ATRA) with arsenic trioxide (ATO). This regime turned a devastating condition into a disease curable in ~80% of cases [49].

A similar success of the reprogramming/(trans)differentiation approach was reported for solid tumors and their metastases. Building on the research of proliferator-activated receptor (PPAR)γ role in adipogenesis [50,51], a study revealed that breast cancer cells that have undergone EMT can be terminally differentiated into adipocytes using the PPARγ agonist rosiglitazone combined with the MEK inhibitor trametinib. The conversion of invasive cancer cells into adipocytes repressed primary tumor invasion and metastasis formation in mouse models of breast cancer. The adipocytes derived from transdifferentiated cancer cells were growth-arrested and lost their cellular plasticity [52]. Epigenetic-, metabolic-, and transcription-factor-mediated reprogramming of glioma [53], prostate cancer [54], and hepatocellular carcinoma [55], respectively, indicates the great potential of using the increased cell plasticity inherent to invasive cancer cells for differentiation therapy.

The extensive research that led to the development of transdifferentiation strategies in hematopoietic malignancies identified several challenges that can be expected when seeking transdifferentiation treatment alternatives for solid tumors [56]. Unlike in blood cancer, where transplantation can recover complete ablation of a cell type, systemic loss of stem cells in, for example, the intestine, would result in an undesired outcome for the entire organ. Therefore, a synergistic therapy of a cancer-specific and generic treatment possibly provides a safer solution, as demonstrated with APL treatment [49]. Another challenge is related to surveillance. While blood sampling is more straightforward compared with biopsy, single-cell RNA sequencing offers an elaborate dissection of the cancer cell states, enabling informed decisions about the most suitable therapy, with the possibility of reevaluation in subsequent follow-up [57].

With examples of successful reprogramming treatment in development, it is becoming clear that steering cancer rather than fighting it might bring the long-sought treatment options. However, this approach will require flexibility in targeting CSC differentiation, metabolism, the surrounding cellular microenvironment (discussed in the next section), or their combinations, depending on the cancer type and stage.

## Strategy 3: cancer microenvironment normalization

The possibility of tumor reversion, that is, converting tumors into tissues with normalized, non-malignant properties, has been advocated as a valuable alternative research and therapeutic option (Figure 4) [58].

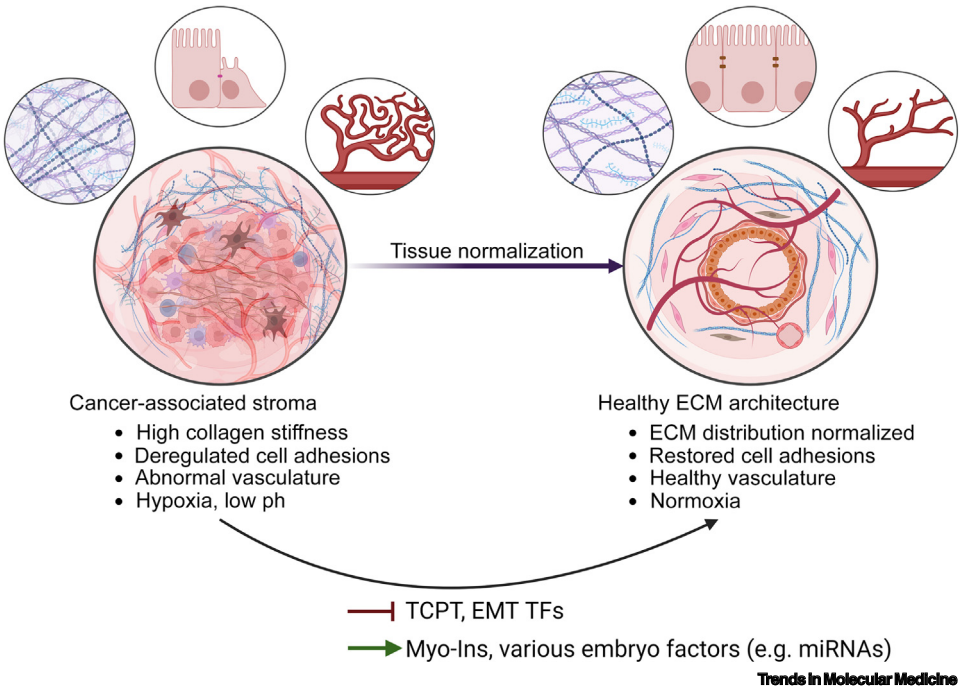


Figure 4. Tissue normalization. The cancer microenvironment exhibits altered features when compared with healthy tissue. Various compounds, including inositol and miRNAs extracted from oocytes/embryos, have proven effective in modifying these characteristics. They achieve this by inhibiting TCTP and EMT factors, impacting cell-to-cell and cell-to-substrate adhesions. As a result, these compounds restore junctional structures of E-cadherin/β-catenin, facilitate cytoskeleton remodeling, and downregulate the expression of PI3K/Akt, as well as the activation of associated biochemical cascades. Collectively, these effects reverse the migratory and invasive, prometastatic properties of cancerous cells and normalize the changes associated with cancer within the stroma. Abbreviations: ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; Myo-Ins, myo-inositol; TCTP, translationally controlled tumor protein; TFs, transcription factors. Created with BioRender.com.

Cancer reversion can be efficiently achieved downstream of cytoskeletal reconfiguration induced by a wide range of molecular and biophysical factors, particularly when these modifications involve complex interactions between cells and their microenvironment. Indeed, the **tumor microenvironment (TME)** plays a pivotal role in both cancer initiation and regression [59]. Cancer progression is associated with changes in the TME, including increased stiffness, reduced nutrient and oxygen supplies, lower pH levels, and intricate cell–cell interactions involving the secretion of various cytokines. Altering these characteristics can shift the TME towards a more normalized state, and as a result, re-educate cancer cells into a less-malignant phenotype [60].

The EMT plays a pivotal role in tumor development, especially metastasis, while the opposite process – the **mesenchymal to epithelial transition (MET)** – is an essential step to trigger reversion of the migratory phenotype acquired during EMT [61]. Evidence shows that MET occurs as an early event during phenotypic reversion [62], and systematic screening has uncovered the key role sustained by specific miRNAs [63] in enacting MET [64]. Key aspects of the reversion process involve the remodeling of the cytoskeleton and the downregulation of specific molecular hubs. These include adhesion structures such as E-cadherin/β-catenin, translationally controlled tumor protein (TCTP), and the downregulation of presenilin and PI3K/Akt, as an example of a few. Over past decades, it has become evident that silencing of TCTP is instrumental in promoting EMT reversion in various types of cancers [65].

Notably, myo-inositol has been demonstrated to promote MET by pleiotropically modulating several intra- and extracellular targets [66] including TCTP, PI3K, and p53, leading to reversal of EMT [67]. Moreover, myo-inositol efficiently rescues normal breast cells committed to an inflammatory phenotype upon the addition of a TGF-β1 stimulus. Specifically, inositol acts by reinforcing connectivity among cells by re-establishing E-cadherin-based cell-to-cell junctions, which are instrumental in the recovery of a tissue-like structure. It also contributes to normalizing the microenvironment by reducing collagen and metalloproteinase release [68], or by inhibiting IP6K1-related pathways that are critical for both cytoskeleton and metabolic reprogramming [69].

Numerous experimental studies demonstrated that cancer cells might be brought under control when exposed to the influence of a particularly influential environment exemplified by eggs and embryonic tissues in their early stages of differentiation [70,71]. For instance, the treatment of cancer cells with fish embryonic extract inhibits EMT and cancer growth while promoting tumor reversion through modulation of TCTP [72,73].

Similarly, **exosomes** derived from human embryonic stem cells display antiproliferative and proapoptotic effects in xenograft models [74]. These exosomes can transfer certain factors (some yet unidentified) into tumor cells, thereby eliciting a substantial alteration in the gene expression pattern with a dose-dependent increase in several genes principally involved in phenotype reversion – namely SOX2, OCT4, and Nanog – that allow the cell population to regain a higher plasticity [74]. Similar results have been obtained using embryonic-derived exosomes in the treatment of melanoma [75]. It is likely that the restoration of a totipotent state allows cells to be redirected toward more benign differentiation [76]. These anticancer effects have garnered validation through *in vivo* studies [77], encompassing research conducted in rats [78] as well as randomized clinical trials, which have demonstrated improved overall survival in advanced liver cancer patients [79] following the administration of fish embryo extracts.

Adjusting the TME composition and structure is sufficient to amend pre-tumoral lesions, as observed in conditions such as Barrett's esophagus. By coating the metaplastic esophageal mucosa with a mucoadhesive hydrogel composed of normal porcine esophageal extracellular matrix (ECM) components, a normal, homeostatic state of the epithelium can be restored [80].

Another strategy for normalizing the TME involves the targeting of lysyl oxidase (LOX). LOX is an enzyme produced by cancer cells responsible for the cross-linking of collagen, which contributes to ECM stiffening [81]. Inhibition of LOX activity by blocking antibodies has demonstrated the capability to hinder tumor stiffening and reduce metastatic potential in pancreatic cancer [82] and improve treatment efficacy in various mouse tumor models [83].

So far, cancer microenvironment normalization treatments have been tested only by a few observational and randomized clinical trials. Embryo extract for inducing tumor dormancy/reversion has been studied in advanced liver cancer patients, refractory to conventional treatments, with a significant increase in the overall survival rate in responding versus not responding patients [79,84]. Several other studies and case reports suggest that even complete regression can be obtained with these treatments [85,86].

Overall, the aforementioned research suggests that tumor reversion, which recovers the functional input/output relationships of normal cells [87], can be achieved by modulation of the microenvironment, and represents a strategy for early intervention in cancer progression.

## Strategy 4: migrastatic drugs

Most metastatic cancers remain incurable with current therapy. Metastatic dissemination directly depends on cancer cell invasion, which is the defining characteristic of malignant cells compared with benign tumor cells. Cancer cells have mastered the invasive process and exhibit a remarkable repertoire of invasion modes, ranging from collective migration of whole strands or sheets of cells to single detached cells. Individual cell invasion can be further categorized into two main subtypes - the proteolytically active, adhesion-dependent **mesenchymal invasion mode**, or the protease-independent, highly dynamic **amoeboid invasion mode** [88–90]. Drugs targeting cancer invasion regardless of specific invasion modes, collectively referred to as migrastatics, serve as a new approach designed to impede tumor invasion rather than tumor proliferation (Figure 5) [91–93].

Migrastatics should ideally target underlying mechanisms of cancer invasion, such as actin polymerization and contractility, to avoid adaptive responses leading to therapy escape. For example, due to contrasting dependency on proteolysis, adhesion to the ECM, and/or specific signaling, pharmacological intervention targeting of these mechanisms so far has proven insufficient in arresting the invasive behavior of cancer cells. Instead, such interventions can trigger escape mechanisms that make use of a phenomenon known as cancer invasion plasticity, which allows cells to adopt alternative invasion modes. For instance, the inhibition of matrix metalloproteinases (MMPs) or integrin function both result in the mesenchymal-amoeboid transition (MAT). Also,

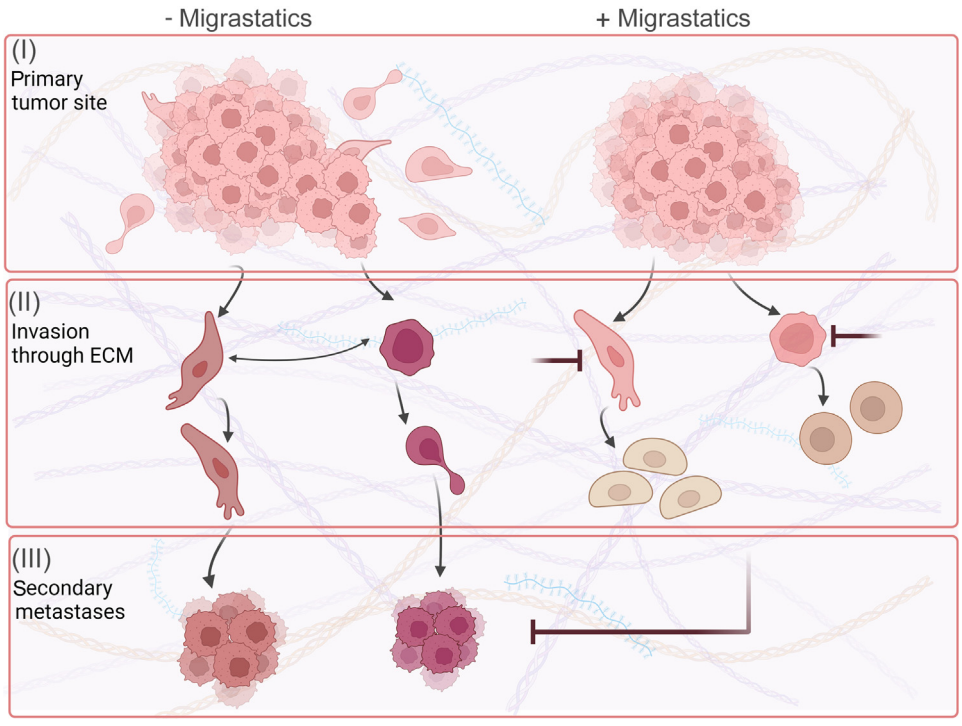


Figure 5. Migrastatic drugs. Cancer cells disseminate from the primary tumor (I, left) and invade through adjacent extracellular matrix (ECM) (II, left), enabling the establishment of metastases at secondary sites (III, left). Cancer cells can adopt various invasion modes, which are mutually interconvertible. Thus, solely targeting specific invasion modes is insufficient to block the progression of metastasis. However, treatment of cancer with migrastatic drugs that target all forms of cancer cell invasion impedes dissemination from the primary tumor (I, right). These drugs also hamper the further invasion of cancer cells that have already disseminated before treatment administration (II, right). As a result, migrastatic drugs diminish the formation of metastatic lesions (III, right). Created with BioRender.com.

### Clinician's corner

The intrinsic plasticity of cancerous cells may be therapeutically exploited to promote phenotypic reprogramming. Randomized clinical trials have already demonstrated improved overall survival in advanced cancer patients following the administration of embryonic extracts.

The redirection of cell state through cell transdifferentiation into another cell type has become a promising avenue in current cancer therapy. A well-known example is the acute promyelocytic leukemia (APL) treatment, in which the terminal differentiation of the leukemic promyelocytes into mature granulocytes is routinely achieved by the combination of all-trans retinoic acid (ATRA) with arsenic trioxide (ATO). This regimen has turned a devastating condition into a disease curable in ~80% of cases. Other similar treatments are in development (e.g., transdifferentiation of invasive breast cancer cells into fat cells).

Metastasis-free survival as a novel primary endpoint for the approval of antimetastatic drugs opens the possibility for the development of a novel class of drugs – migrastatics, that are neither cytotoxic or antiproliferative but are solely directed towards inhibition of cancer cell invasiveness and metastasis. Such drugs have potential to prevent metastasis or interfere with colonization of secondary sites. Some approved drugs have migrastatic properties and their antimetastatic efficacy in humans will be tested in the near future.

Educative cancer treatment strategies have potential to improve the outcomes of cancer treatment when applied synergistically or in combination with standard treatment.

many signal transduction networks show redundancy and crosstalk, which complicates treatment and may be responsible for resistance or recurrence to narrow spectrum-targeted therapy [94]. Hence, to efficiently target the invasive ability of cancer cells and avoid drug evasion mediated by cancer invasion plasticity, all modes of cancer invasion would need to be targeted concurrently.

In contrast to cytotoxic drugs, however, migrastatic drugs do not aim to kill cancer cells. Instead, these drugs impose limitations on their ability to migrate into adjacent regions. Hence, even if certain cancer cells are resistant to migrastatics, these cells would not gain a proliferative advantage compared with the non-resistant cells, remaining limitedly present within the TME.

Despite the absence of migrastatic drugs in current clinical practice, many compounds have demonstrated encouraging results in preclinical studies. For example, a multikinase inhibitor targeting ROCK/PKA/PKB has demonstrated efficacy in impairing both amoeboid and mesenchymal modes of cancer cell invasion [95]. Several experimental frameworks have been established to assess the efficacy of migrastatics, encompassing *in vitro* and *in vivo* models [96], thereby laying the groundwork for their potential translation into clinical practice. The ultimate goal is to develop effective therapeutic strategies that specifically target the invasive behavior of cancer cells, thereby expanding existing antiproliferative treatments to improve patient outcomes (Box 1).

## Concluding remarks and future perspectives

Cancer arises due to deregulation of the intrinsic pro-proliferative and promigratory pathways that operate during normal development or healing. The ability of cancer cells to reawaken these programs underlies cancer cell plasticity and results in the loss of homeostatic balance on both the level of intracellular signaling and microenvironment.

Although conventional cytotoxic therapy undeniably plays a role in reducing the proliferative rate of cancer cells, leading to initial tumor regression, it does select for adaptive responses with proven potential to result in drug resistance. This allows resistant cancer cells to proliferate despite treatment contributing to tumor growth, which, consequently, leads to tumor progression

### Box 1. Challenges in implementation of migrastatics into clinical practice

The aim of migrastatic therapy is not to control cancer growth but to prevent cancer dissemination and limit the formation of secondary metastases. The effect of migrastatic drugs is thus fundamentally different from that of cytostatic therapy (and of the other mentioned strategies), requiring a new approach to administration and evaluation of efficacy. Importantly, metastasis-free survival (MFS) was approved by the Food and Drug Administration (FDA) in 2018 as a novel primary endpoint in clinical trials and has already been utilized to assess the efficacy of treatments for patients with nonmetastatic castration-resistant prostate cancer and soft tissue sarcoma [99]. The approval of MFS as an endpoint enables us to shift the focus of anticancer drug research and development to metastasis, and allows for the use of MFS, rather than tumor shrinkage, as a more representative endpoint for antimetastatic drugs, including migrastatics [100].

To date, migrastatic drugs have not been tested in patients, so the most appropriate approach to their administration can only be estimated based on their presumed mechanisms of action. The level of cancer progression would most probably be the most critical criteria in determining how migrastatics should be used. In cases of early-stage cancer with little or no metastatic burden, a neoadjuvant/adjuvant use of migrastatics before and after surgical removal of the primary tumor could represent their effective use. Here, the aim of migrastatic therapy would be to minimize metastatic development prior to surgery and minimize the risk of any remaining tumor cells initiating a metastatic program; for example, due to changes in their microenvironment caused by surgery. For advanced cancers with existing metastases, a combination of migrastatics and cytostatics, or other systemic approaches, may be warranted. In such cases, migrastatics would reduce the likelihood of secondary metastases and minimize the risk of treatment-induced metastasis. To be effective in later stages of cancer, migrastatic therapy should be administered as a long-term regimen, even after cytostatic treatment is discontinued. This implies a requirement for low toxicity of migrastatics.

In both cases, the administration of migrastatics could benefit patients by prolonging overall survival, by preventing the development of any further metastases, and potentially transforming cancer into a chronic disease, at least temporarily.

### Outstanding questions

Can educative cancer treatment strategies, by avoiding the induction of a direct proliferative advantage to resistant cells, delay or even prevent the development of therapy-resistant tumors?

In solid cancer, does ongoing metastatic activity negate the benefit of tumor shrinkage? Why are regulatory end points of preclinical drug selection still primarily based on tumor shrinkage, and not on their antimetastatic activities?

Can educative cancer treatment strategies yield enhanced outcomes when applied synergistically and/or in combination with standard treatment? Can they transform cancer into a manageable disease?

and therapy failure. Hence, approaches that avoid inducing such responses may offer benefits that current therapy lacks (see Clinician's corner). We have highlighted four possible strategies: **migrastatic therapy**, controlling cell dormancy, transdifferentiation of cancer cells, and cancer reversion through tissue normalization. Opposing cytotoxic treatment, adaptive resistance to the educative approaches listed earlier does not endow resistant cells with a direct proliferative advantage. Even if therapy-resistant cells were to emerge, they would continually encounter opposition within the tumor mass from non-resistant cells, thereby delaying or preventing the development of therapy-resistant tumors. This stands in stark contrast to cytotoxic therapy, where non-resistant cells are eliminated, enabling resistant clones to uncontrollably expand (see Outstanding questions).

Educative strategies may exhibit enhanced outcomes when applied synergistically. For instance, migrastatic therapy targets cancer cell invasion, limiting the migratory ability of cells without affecting proliferation. When combined with strategies to maintain cells in a non-proliferative, dormant phase, it can restrict both invasion and proliferation. Another synergistic approach involves combining migrastatic therapy with tumor ECM normalization, as tumor-cell-induced collagen reorganization accelerates invasion rates [97]. Targeting invasion both internally (through migrastatics) and externally (by modulating ECM) could be a potent strategy for addressing the invasiveness of cancer cells. The proposed strategies may also be administered after conventional therapy to improve the patient's outcome. For example, direct killing of quiescent cells could represent a complementary approach to deplete residual cells that escaped conventional therapy by adopting a dormant state. Also, administration of migrastatics could counteract what is known as therapy-induced metastasis [98].

As cancer originates from endogenous cells and proliferates at the expense of healthy tissue, aggressive therapeutic interventions inevitably inflict collateral damage upon the host organism. An ideal approach would be to reprogram cancer cells into appropriate behavior, obviating the need for eradicating them. In the case of precancerous lesions, phenotypic reversion aimed at normalizing tissue could effectively prevent further disease progression. Persisting cancer cells could be transdifferentiated into benign states. Further inhibition of invasion would curtail metastatic dissemination, and inducing dormancy could reduce the overall activity of the remaining surviving cancer cells. While this conceptualization unavoidably oversimplifies the nature of cancer, we hope that it will serve as a framework for the development of approaches aimed at cancer cell re-education.

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## Declaration of interests

The authors declare no competing interests.

## Resources

[i]https://classic.clinicaltrials.gov/ct2/show/NCT03400254

[ii]https://classic.clinicaltrials.gov/ct2/show/NCT04841148

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