Synthetic Migrastatic: A New Class of Anticancer Drug

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Abstract

Cancer remains one of the fatal diseases in the last century. The mortality rate of different types of cancer is mainly related to metastasis, where the traveling cancer cell clusters migrate to other organs and create a micro-metastatic niche. To date, most of the conventional and approved anticancer drugs belong to the cytostatic and cytotoxic categories. Cancer cells' transcriptional and behavioral plasticity made traditional therapy futile in terms of stopping the spread and relapse of the disease. The recent emergence of drug-resistant cancers requires a new class of drug molecules. In this context, the potential of antimetastatic or migration inhibitory drugs is neither evaluated nor validated correctly. This chapter will introduce a new class of synthetic drugs that could be used to inhibit cancer cell migration and discuss their untapped potential as therapeutic agents.

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Migrastatic drugs working against multiple targets could successfully deter the tumor cells from initiating migration and bypassing the therapeutic effects. In the future, these new classes of antimetastatic compounds combined with conventional drugs could establish a new and improved treatment regime.

Keywords

Cancer · Metastasis · Migrastatic · Synthetic compound

Introduction

In the last few decades, due to increasing pollution and changing lifestyles, cancer has become one of the major causes of death. The mass of cancerous cells, a consortium of heterogeneous population, exert their pathophysiological effects in many different ways, which are classified as cancerous hallmarks. One of the most crucial hallmarks of cancer is metastasis happens during the later stages of the tumor development. During this process, tumor cells from the primary source migrate to the neighboring organs to presumably establish secondary tumor sites. Metastasis is assumed to be one of the major reasons for the disease recurrence and cancer-associated mortality (Tan et al. 2015; Alizadeh et al. 2014). This process includes invasion of extracellular matrix by the solitary or cluster of cancer cells, intravasation, extravasation, and colonization of vital organs (Steeg 2006). Numerous studies have proved that cancer cells utilize different migration modes with plasticity during the invasion of ECM and intravasation, which facilitate their advancement in the ECM and the bloodstream. Multiple cellular and stromal components associated with cell migration, such as the cytoskeleton, matrix-degrading enzymes, kinases, and adhesion proteins, make the process of metastasis seamless. During this process, the cells also produce various cellular protrusions, namely, lamellipodia, invadopodium, and dendritic spine-like structures, to enhance migration speed and efficiency. Such arrangements play a crucial role in the remodeling and degradation of the ECM to allow cancerous cells to reach the bloodstream (Yamaguchi et al. 2005).

Metastasis Modality

Conventionally cancer cell migration mode can be divided into two broad classes, namely, collective and individual. Collective migration is defined by the migration of cellular clusters interconnected by adhesion molecules and other communication junctions. These clusters with leading and following edges penetrate the surrounding tissues through blunt cellular force supported by secretory and membrane-bound MMP-mediated degradation of ECM. Once the cell decides to migrate collectively, cell polarization occurs, leading to the formation of pseudopods. The pseudopods activate the integrin receptors and recruitment of scaffold proteins, forming nascent focal adhesions. These focal adhesions further mature and connect with the actin

filaments. Molecules such as MT1-MMP and uPA/uPAR are recruited to execute the local proteolysis to break the ECM molecules and generate space for the cells to move ahead. The group of collectively migrating cells develops dynamic cytoskeletal structures which includes actin stress fibers comprising of actin and myosin light chain. These stress fibers at the leading edge generate the necessary traction force to move the cellular mass forward. These leader cells remain connected to the other trailing cells through cell-cell interactions. The trailing edge forces the cell-to-cell junctions and focal adhesion complexes between, to drag the neighboring cells along the migration track (Friedl et al. 2004).

On the other hand, migration of individual cancer cells through the ECM is mainly classified depending on their dependence on protease such as mesenchymal (protease dependent) and amoeboid (protease independent) migration. These modalities can switch depending on the cellular and environmental cues and the tumor microenvironment (Gayan et al. 2021; Krakhmal et al. 2015). Such plasticity is an intrinsic virtue of cancer cells which allows the development of variable modes of migration, namely, epithelial-mesenchymal transition (EMT), mesenchymal-epithelial transition (MET), ameboidal-mesenchymal transition (AMT), and mesenchymal-ameboidal transition (MAT) during metastasis. EMT occurs at the primary tumor site, where the tumor cells detach from the epithelial layer of the tumor mass to achieve mobility. Whereas MET, (the counter transition) happens when the tumor cells stop at another organ and differentiate to establish a secondary tumor site (Vasiliev and Gelfand 2006). The characteristic features of EMT include the loss of apicobasal polarity, loss of cell adhesion molecules like E-cadherins, and cytoskeletal rearrangement for the formation of stress fibers (Micalizzi et al. 2010). As observed, different key transcription factors including TWIST1, Snail, Slug, and ZEB1/2 are responsible for initiating EMT (Tsai et al. 2012). Through the EMT transitions, tumor cells perform intravasation and spread to different tissues and organs. After reaching the metastatic loci, these migratory cells return to their epithelial phenotype through MET. This phenomenon occurs through the inhibition or decrease of the factors directly involved in the EMT (Nguyen et al. 2009).

Other modalities of single-cell migration like AMT and MAT are also tightly regulated through the interaction of tumor cells with the tissue microenvironment but observed more rarely (Gayan et al. 2021). AMT has the same molecular basis as MAT, and reversal of conditions leads to AMT. The primary process behind MAT transition, as explained by Friedl, includes membrane protrusion, reduction in pericellular proteolysis, the absence of p27 protein, reduced integrin receptors' activity, and increased GTPase Rho activity A (Friedl 2004). The formation of membrane protrusion is influenced by the localized polymerization of submembrane actin filaments. WASP family proteins, LIM-kinase, cofilin, and cortactin are some of the critical proteins upregulated in invasive and metastatic cancer cells. These are responsible for actin cytoskeletal reprogramming towards a migratory phenotype (Sahai 2005; Yamaguchi et al. 2005). These proteins are responsible for the Arp2/3 complex-dependent nucleation for the dendritic/protrusion phenotype developed by cancer cells. Cortactin and cofilin are required to stabilize these branched filaments/protrusions (DesMarais et al. 2004). Minimal expression of cell adhesion molecules such as E-cadherin and α-catenin leads to the increased metastatic potential of the

tumor. Re-localization of β-catenin to the cell nucleus from cytoplasm is positively associated with the mesenchymal phenotype required for single cellular migration (Jiang 2005). The reduced expression of cell adhesion protein directly co-related with the increased function of matrix metalloproteases (MMPs) which is necessary for degrading various extracellular matrix proteins to ensure cell motility during metastasis. Transcription factors including tumor growth factor β (TGFβ) and epithelial growth factor (EGF) induce MMP production to enhance cell motility (Xu et al. 2010). Kinases of the Src family, especially c-Src, play a supportive role in tumor metastasis in colorectal and breast cancers (Summy and Gallick 2003) through mutations, chromosomal translocation, and epigenetic deregulation mediated malfunctioning (Cicenas et al. 2018).

Main Text

Current Therapeutic Regime and Problems

The conventional therapeutic approach towards solid tumors and other types of cancer has been primarily inclined towards cytotoxic drugs paired with surgery and radiation therapy. These cytotoxic drugs differ in their mode of action and majorly include anti-metabolites, alkylating agents, topoisomerase, mitotic inhibitors, antibiotics, and lastly corticosteroids (Huang et al. 2017). Alkylating agents damage the cellular DNA, thereby preventing DNA replication and progression of the cell cycle. These drugs are commonly used to treat different types of aggressive cancers, including sarcomas, carcinoma, and lymphomas. A subcategory of alkylating agents called nitrosoureas includes lomustine and carmustine which can cross the blood-brain barrier (Gate and Kenneth 2011). Anti-metabolites interfere with the nucleic acids and replace their nucleotides to inhibit the replication process. Anthracyclines interfere with DNA synthesis preventing cell reproduction. Topoisomerase inhibitors (plant alkaloids) interfere with enzymes such as Topoisomerases I and II. Mitotic inhibitors inhibit cell division and induce apoptosis. These cytotoxic drugs are part of the decade-old treatment regime for most aggressive cancers despite multiple side effects and the eventual development of resistance.

Cytotoxic drugs could not differentiate between normal and target cells; hence prolonged use of cytotoxic drugs can have toxic side effects on other tissues and organs of the body (Table 1). Most of these cytotoxic drugs are very efficient in the late tumor stages. However, they have many significant deleterious effects, including hair loss, skin rash, anemia, and others. Other minor side effects such as nausea and vomiting are also common occurrences (Nurgali et al. 2018). Further, there is a risk of hypersensitivity reactions against various cytotoxic drugs in the system (Ruggiero et al. 2017).

Along with the patients, many unintended targets such as healthcare workers can be exposed to these agents. For example, studies reported health workers handling cytotoxic drugs with increased risk of leukemia and breast cancer. Unintended exposure to these drugs may also occur during the preparation, administration, and

Table 1 Major classes of anticancer drugs with their target and major side effects

Drug category	Drug name	Target	Cancer	Major side effects
Alkylating agents	Altretamine	DNA	Ovarian cancer	Peripheral neuropathy and nausea
	Bendamustine	DNA	Low-grade non-Hodgkin's lymphomas	Lymphocytopenia, fatigue, and dry mouth
	Busulfan	DNA	Leukemias	Interstitial pulmonary fibrosis, hyperpigmentation, and seizures
	Carboplatin	DNA	Non-small-cell lung cancer	Low blood cell and platelet bone marrow output
	Carmustine	DNA	Glioblastoma	Pulmonary fibrosis
	Chlorambucil	DNA	Lymphocytic leukemia	Bone marrow suppression, anemia, and neurotoxicity
	Cisplatin	DNA	Non-small-cell lung cancer	Nephrotoxic effects, neurotoxicity
	Cyclophosphamide	DNA	Small-cell lung cancer	Neutropenia and organ failure
	Dacarbazine	Nucleic acids	Melanoma	Nausea, vomiting and rarely diarrhea, and flu-like syndrome
	Ifosfamide	Nucleic acids	Small-cell lung cancer	Nephrotoxicity and neurotoxicity
	Lomustine	Nucleic acids	Glioblastoma	Lung fibrosis, drug-induced hepatitis
Antimetabolites	5-fluorouracil	DNA	Rectal cancer	Cardiovascular toxicities, diarrhea, stomatitis, and hand-foot syndrome
	6-mercaptopurine	PRPP aminotransferase	Acute childhood leukemia and chronic myelocytic leukemia	Low blood counts, anemia, nausea, and vomiting
	Azacitidine	DNA methyltransferase	Myelodysplastic syndrome	Hemorrhoids, nausea, vomiting, and diarrhea
	Capecitabine	DNA	Colorectal cancer	Abdominal or stomach pain, numbness or blistering in palms
	Cladribine	DNA	Chronic lymphocytic leukemia	Skin rash, cough, nausea, diarrhea, and headache
	Clofarabine	DNA Ribonucleotide reductase enzyme	Acute myeloid leukemia and myelodysplastic syndromes	Bleeding gums, stomach pain, area rash, and black stools

(continued)

Table 1 (continued)

Drug category	Drug name	Target	Cancer	Major side effects
	Cytarabine	DNA	Acute myeloid leukemia	Hypersensitivity, bone marrow suppression, cerebellar toxicity, respiratory distress
Anthracyclines	Bleomycin	DNA	Cervical cancer	Fever, skin reaction and alopecia
	Doxorubicin	DNA Topoisomerase II	Soft tissue sarcoma	Cough, skin redness, and irregular heartbeat
	Mitomycin-C	DNA	Rectal cancer	Anorexia, nausea, vomiting and temporary hair loss.
Topoisomerase inhibitors	Irinotecan	Topoisomerase I	Colon cancer	Constipation, shortness of breath, insomnia, cough, headache
	Topotecan	Topoisomerase I	Small-cell lung cancer	Myelosuppression, neutropenia, nausea, loss of appetite
	Etoposide	Topoisomerase II	Small-cell lung cancer	Anemia, kidney damage, and alopecia
	Teniposide	Topoisomerase II	Small-cell lung cancer	Myelosuppression
Mitotic inhibitors	Docetaxel	Tubulin	Prostate cancer	Neutropenia, anemia, nausea
	Paclitaxel	Tubulin	Ovarian cancer	Adverse drug reactions, peripheral sensory neuropathy, and hematological toxicity
	Vincristine	Tubulin	Brain stem glioma	Hematological toxicity, constipation, mucositis, and emesis
	Vinblastine	Tubulin	Langerhans cell histiocytosis	Peripheral sensitive neuropathy, alopecia, digestive disorders

transport of the drug along with the disposal of the organic waste. Other sources of environmental contamination include patient excreta and secretions (Alehashem and Baniasadi 2018).

Along with the unwanted side effects and unintended contaminations, developing resistance against those drugs is also becoming a point of concern. The critical factors influencing the resistance are physical barriers, tumor burden, and tumor heterogeneity, TME (tumor microenvironment), TIME (tumor-immune microenvironment), and therapeutic pressures (Vasan et al. 2019). Cancer heterogeneity caused by genomic instability, transposition, translocation, microRNA, and epigenetic factors generates chronic drug resistance and poor prognosis (Mansoori et al. 2017). The tumor's heterogeneous microenvironment and the different cells like the immune cells and stromal cells prevent immune clearance and drug absorption. Immunosuppressive cancer microenvironment consists of different cellular (Treg cells, natural killer cell, and tumor-associated macrophages) and acellular components (cytokines and chemokines) majorly influence the effectiveness of anti-tumor drugs (Sharma et al. 2017). Long-term therapies can also lead to resistance, and it could be an early adaptive response or resistance acquired after prolonged exposure (Mok et al. 2017). The adaptive response happens due to negative feedback-mediated activation of the alternative metabolic pathways or reactivation of the initial ones. Acquired resistance happens with the emergence and accumulation of new mutations of the target followed by the diversion of pathways and changes in phenotypes (Vasan et al. 2019).

Drug resistance is the most significant hurdle in cancer treatment and seems to be an unattainable goal. These disadvantages pose a problem for commonly used cytotoxic drugs and make it necessary to develop a new genre of drugs targeted explicitly towards cancer. Recently, a unique class of molecules referred to as migrastatic is recognized as a potential mode of therapy. Effectivity of cytotoxic or cytostatic drugs is measured quantitatively through tumor shrinkage, which is assumed as the main criteria in the current world of cancer therapeutics. With the emergence of drug resistance cancers, it is proposed that the importance of tumor shrinkage as the main criteria of drug efficacy should be revisited. The hour needs a critical understanding of the holistic effect of the used drug and its intended effectiveness (Fernandes et al. 2019). Deep analysis of the physical properties of the tumor, dependencies and vulnerabilities, and personalized study of the patient is required to solve the current problems.

Migrastatics: A New Class of Drugs

Even though metastasis is the deadliest aspect of a tumor, no antimetastatic drugs are available to date as a treatment modality. The main aim behind developing the migrastatic molecules is to prevent local and global invasion. The term migrastatic has been proposed for molecules that target pathways involved in cell migration and interfere with different modalities of migration, thus inhibiting invasion, extravasation, and colonization (Gandalovicova et al. 2017). They do not directly affect cell viability but impede tumor cell dissemination and further migration.

The dissemination of cancer cells initiated by the destruction of the cell-cell adhesions followed by the conversion of E-cadherin to N-cadherin provoke cell migration and invasion. The cadherin switch induces reorganization of actin filaments and degradation of extracellular matrix through matrix metalloproteinases. Migration of a single cell involves activation of multiple cell and substratum adhesion molecules along with the change of cell-polarity and cytoskeletal arrangement (Yilmaz and Christofori 2010). Migrastatic drugs are proposed to target molecular mechanisms that are common and essential in cancer cell migration and cannot be bypassed. Therefore, the ultimate downstream effectors like actin polymerization and contractility are targeted as prime candidates. Cancer cell migration and invasion culminate in actomyosin contractility and actin polymerization, irrespective of the migration modality (Gandalovicova et al. 2017).

Inhibitors of these processes from natural sources are available, which has been proposed in the past as potential migrastatic agents (Table 2) (Gandalovicova et al. 2017) (Gandalovičová et al. 2020). However, many synthetic compounds developed against such targets can also be classified as migrastatics depending on their function. This chapter will discuss the potential targets for such synthetic migrastatic molecules and focus on few therapeutic agents for future experimental evaluation and validation.

Potential Targets for Migrastatic Compounds

Metastasis is a process that requires different cellular components, including cytoskeletal proteins, focal adhesion proteins, and enzymes, which could have been potential targets for the migrastatic molecules (Fig. 1).

Cytoskeletal Proteins

Cytoskeletal proteins, namely, the microtubules (MTs), microfilaments (MFs), and intermediate filaments (IMFs), are involved in many cellular processes, including migration. Microtubules, the heterodimers of α- and β-tubulins, are consisting of different isotypes. Different isotypes of tubulin and microtubule-associated proteins (MAPs) contribute to cancer progression and chemoresistance. Microfilaments are polymers of actin protein, which exist either as in globular monomers (G-actin) or in the polymeric filamentous form (F-actin). The continuous turnover between these two states controls the migration status. An increment in the ratio of globular-filament actin promotes metastasis in cancerous cells. Actin filaments interact with myosin to form actin stress fibers, which participate in cancer cell migration. Intermediate filaments including different polymers, namely, cytokeratin, vimentin, desmin, glial fibrillary acidic protein, neurofilaments, nuclear lamins, and nestins, are also involved in cell migration. Epithelial to mesenchymal transition (EMT) is promoted by reorganization of intermediate filaments, leading to migration, acquiring a metastatic trait. Another class of cytoskeletal proteins, including cell adhesion molecules (CAM), catenin, and actin-related proteins, also plays a significant role in cytoskeletal re-organization (Ong et al. 2020). Direct inhibitors of the

Table 2 List of natural migrastatic compounds

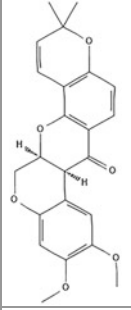
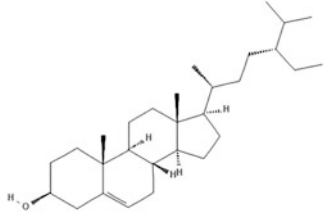
Migrastatic agent	Structure	Source	Target substrate	Mechanism	Activity
Deguelin (Zhao et al. 2015)		*Mundulea sericea* (shrub)	1. Genes expressing, Rac1 Rock 1 2. F actin filaments.	1. Decreases generation of filopodia and lamellipodia through direct disorganization of F-actin filaments. 2. Deguelin also downregulates protein expression of ROCK1 and Rac1 associated with cell migration	>10 μM suppresses migration and invasion
Vincetoxicum arnottianum plant extract (main components β-Silosterol and Lupeol) (Adamus et al. 2021)		*Vincetoxicum arnottianum* (Wight) plant roots	Genes expressing Sphingosine-1-phosphate (S1P) metabolizing enzyme sphingosine-1-phosphate lyase (SGPL1)	Overall plant extract induces overexpression of SGPL1 genes. SGPL1 degrades S1P (bioactive chemoattractant forcing metastatic invasion of RMS cells), leading to reduced migration and colony-forming potential	25 μg/ml reduces 60% migration and 99% invasion

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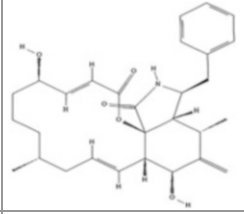
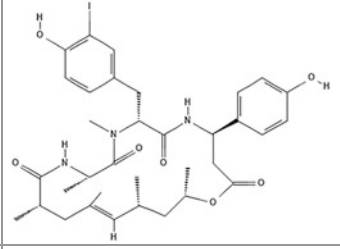
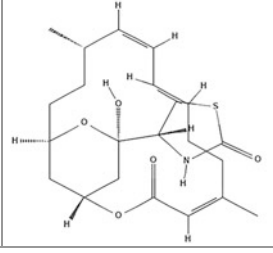
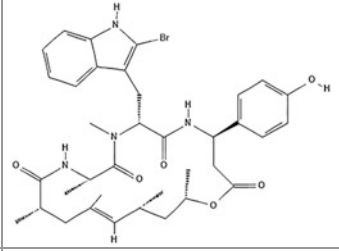
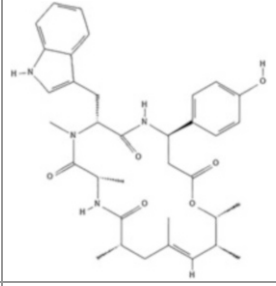
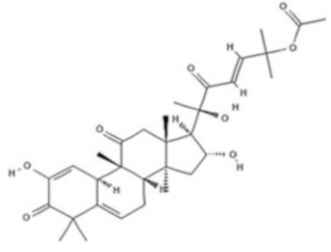
Table 2 (continued)

Migrastatic agent	Structure	Source	Target substrate	Mechanism	Activity
Cytochalasins (Mainly Cytochalasin B and D) (Glenn et al. 2016)		Fungi	Actin filaments	Cytochalasin B disrupts actin cytoskeleton of tumor cells in both tumor and non-tumor cells	1 μg/mL inhibited migration
Geodiamolides (Geodiamolide H) (Freitas et al. 2008)		Marine sponges (Brazilian sponge *Geodia corticostylifera*)	Actin filaments	Geodiamolide H selectively disrupts actin cytoskeleton of tumor cells	120 nM decreases migration and invasion
Latrunculins (Latrunculin A) (Sayed et al. 2008)		Marine sponges/red sea sponge *Negombata magnifica*	G-actin monomers	Latrunculin A complexes with G-actin monomers, binding reversibly to the cytoskeleton actin monomers, disrupting polymerization	500 nM decreases migration, IC50 6.7 μM

Jasplakinolide (Hayot et al., 2006)		Marine sponge	Actin filaments	Jasplakinolide stabilizes actin filaments, preventing filament disassembly. Selectively inhibits cell migration in breast cancer cells MCF-7	IC50: 10^{-9} and $5X10^{-8}$ M
Chondramides (Menhofer et al. 2014)		*Chondromycescrocatus crocatus* (Myxobacterium)	F-actin	Chondramide treatment disrupts the actin cytoskeleton and decreases the ability of cells for contraction preventing migration in MDA-MB-231 cells	200 nM abrogates migration and invasion in vitro. 0.5 mg/kg reduced metastasis in mice
Cucurbitacin E (α-elaterin) (Zhang et al. 2012)		Cucurbitaceae (gourd family)	Arp 3 subunit Actin filaments	Cucurbitacin E impairs Arp2/3-dependent actin polymerization (downregulation of Arp3 subunit) and suppresses Src/MMP involving pathways, preventing cell migration in breast cancer	0.1 μmol/L inhibits migration and invasion

Structures adapted from https://pubchem.ncbi.nlm.nih.gov

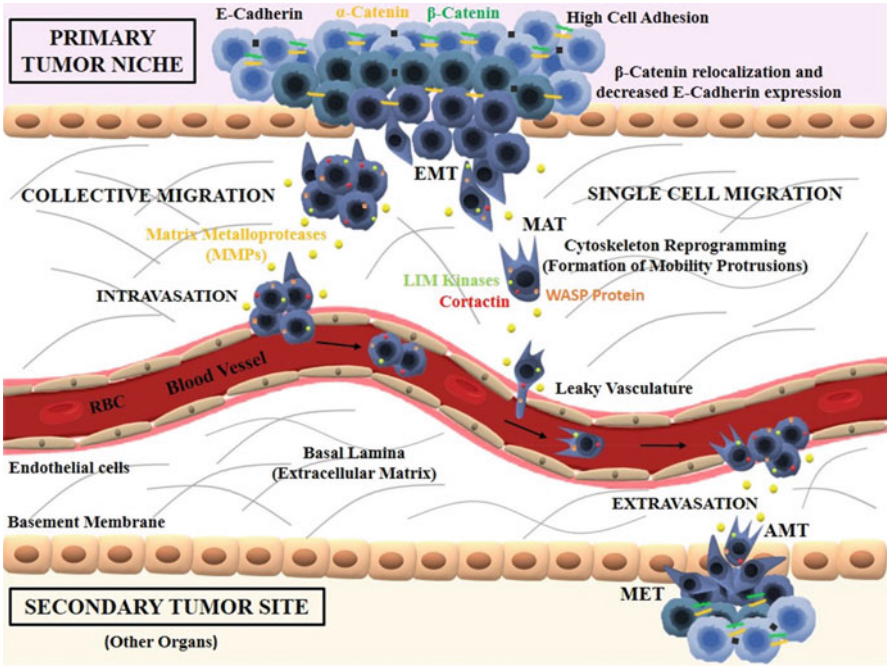


Fig. 1 Components involved in cell migration during metastasis. The figure represents the migration modalities of cancer cells from the primary site to a secondary site during metastasis. In the primary tumor site, the tumor cells are bound closely due to the heightened expression of E-cadherin, N-cadherin, α-catenin, and β-catenin. Gradually, due to the decrease in E-cadherin expression and β-catenin re-localization, the cells tend to undergo EMT for acquiring a migratory phenotype. Both collective and single-cell migration are observed during the tumor metastasis. In single-cell migration, cells undergo MAT and develop migratory protrusion such as lamellopodia and invadopodia for mobility. Tumor cells secrete MMPs to pass through the dense extracellular matrix. Besides, proteins such as WASP, cortactin, and LIM kinases are expressed to maintain mesenchymal phenotype. After reaching the blood vessel, the tumor cells enter the blood vessel (intravasation) and travel to other nearby organs. The cells leak out through extravasation and reach the organ to establish as secondary tumor site. Here the cells return to the non-migratory phenotype via AMT and further MET

polymerization and depolymerization process of cytoskeletal protein can be regarded as potential migrastatics.

Actin-Related Proteins

Seamless turnover of cytoskeletal proteins through polymerization and depolymerization is critical for migration. Several proteins such as Arp2/3, WASP, cofilin, and others participate and maintain the cytoskeleton turnover rate as required. Arp2/3 nucleates the newly formed actin filament and creates a branched network. Members from the WASP family (Wiskott–Aldrich syndrome protein) protein help in the activation of Arp2/3 and actin polymerization (Millard et al. 2004). Cofilin is another essential regulator of actin dynamic, nucleating actin polymerization. It facilitates

the process of cell migration by interacting with both monomeric and filamentous actin. LIM kinases are the upstream regulator of cofilin, which phosphorylate, and inactivate cofilin. Cofilin and LIM kinases have been observed to regulate cancer cell motility (Zebda et al. 2000). Cortactin can serve as another potential migrastatic target as it binds and cross-links with actin filament. It directly initiates the nucleation activity of Arp2/3 and stabilizes the newly formed branched actin filament (Yamaguchi and Condeelis 2007). Tropomyosin binds to the helical groove of the actin filament and stabilizes the filament actin. Tm5 (hTm5NM1), another isoform of tropomyosin, recruits myosin II into actin stress fibers. Another isomer, TmBr3, binds to cofilin and participates in migration (Bryce et al. 2003). Inhibition of these proteins can disturb the cytoskeletal turnover successfully and, hence, function as a potential target.

Focal Adhesion Complex Protein

Protein molecules involved in the formation of physical connection between cell-extracellular matrix or cell-basement membrane are critical regulators of cell migration. First, of such molecules, integrins (different isoforms of a and b types) mediate the cellular contact with the ECM components such as fibronectin. Those nascent structures also recruit other adaptors/scaffold proteins like talin, paxillin, tensin, p130Cas, and α-actinin to stabilize the focal adhesion complex. Stable focal adhesion complexes generate the necessary contractile force and tension through actin stress fibers (Nagano et al. 2012). Small molecule inhibitors or active site-specific antibodies against focal adhesion complex proteins can successfully inhibit their participation in migration and function as potential migrastatics.

Enzymes and Signaling Protein

Along with the scaffold proteins, multiple enzymes, including kinases, phosphatase, and proteases, also play essential role during both collective and single-cell migration. Signaling proteins like tyrosine kinases, Src kinases, and focal adhesion kinase (FAK) play a vital role in the substratum integrin-mediated signaling cascades. They transmit the ECM-derived signal to cellular pathways controlling cell migration through phosphorylation/dephosphorylation of their targets (Nagano et al. 2012). Protease enzymes, an essential component behind cancer cell invasion and multidrug resistance, could be another candidate for migrastatics. Different classes of proteases, including matrix metalloproteases, serine, threonine, cysteine, and aspartate, help to degrade and remodel intracellular and extracellular matrix (ECM) proteins. The secretion of cysteine proteases accomplishes podosome-mediated degradation of extracellular matrix and invasion. Serine proteases like matriptase are actively involved in the process of angiogenesis and degradation of extracellular matrix in some epithelial cancer. Cathepsin–D (Cath-D), an aspartic endo-protease, stimulating proliferation, angiogenesis, and metastasis, is categorized as a prognostic marker of breast cancer. Procathepsin D promotes the pro-invasive and pro-metastatic properties in both tumor and stromal cells (Rakash 2012). Matrix metalloproteinases (MMP) help to degrade the cell-matrix adhesions, thereby enabling cancer cells to migrate and invade (Martin et al. 2013). MMPs are also

involved in the preliminary steps of tumor evolution, which include proliferation of cancer cells and angiogenesis. MMP induction also helps in invasive growth at the secondary site (Rakash 2012). Successful inhibition of these enzymes can minimize the migration potential of cancer cells; hence they can be regarded as potential targets for migrastatics.

Migration-Specific Small GTPase

During migration, cytoskeletal proteins primarily interact with the motor proteins (specifically myosin) to generate cell surface contractions. Among different classes of the myosin superfamily, non-muscle myosin II is known to play a critical role in cellular adhesion and migration (Vicente-Manzanares et al. 2009). The formation of the actomyosin couple depends on Ca + 2 efflux and the Rho family of small GTPase. Ca + 2-dependent functionalization of myosin light chain kinase (MLCK) leads to phosphorylation of myosin light chain (MLC) and formation of actomyosin complex (Chi et al. 2014). Small GTPase Rho A can also phosphorylate Rho-associated protein kinase (ROCK), which further phosphorylates MLC2. The phosphorylated MLC2 promotes actomyosin interaction followed by myosin ATPase activation (Pandya et al. 2017). ROCK can also activate LIM kinases leading to the inhibition of cofilin activity and blocking of actin depolymerization. Myotonic dystrophy kinase-related Cdc42-binding kinase (MRCK), another effector of actomyosin interaction, can regulate pathways involved in cancer cell migration along with ROCK (Kale et al. 2015). Another membrane glycoprotein, gp38 (podoplanin or Aggrus,) controls actomyosin contractility in lymphoid fibroblasts and influences the migration (Quintanilla et al. 2019). Podoplanin also influences the cytoskeletal contractility, thus promoting invasive amoeboid morphology in melanoma cells (de Winde et al. 2020). These small GTPases play a critical role in migrational plasticity of cancerous cells and can be asserted as potential target for migrastatic agents.

Potential Migrastatic Compounds

Various known chemicals and pharmacologically active compounds are available, which can function specifically against the cell migration pathways and hence could be classified as migrastatics. Several molecules of natural origin are classified as migrastatics (Table 2) in previous studies (Gandalovicova et al. 2017; Gandalovičová et al. 2020). However, synthetic and semi-synthetic inhibitors with similar purposes have not been studied or classified in detail. Therefore, this chapter focuses on synthetic and semi-synthetic compounds and ascertains their role migrastatic (Fig. 2).

Myosin Inhibitor

Blebbistatin, a 1-phenyl-2-pyrrolidinone derivative, inhibits non-muscle myosin II activity, which is required for force generation and contractility during cell migration. It binds with the myosin-ADP-Pi complex and inhibits the release of the

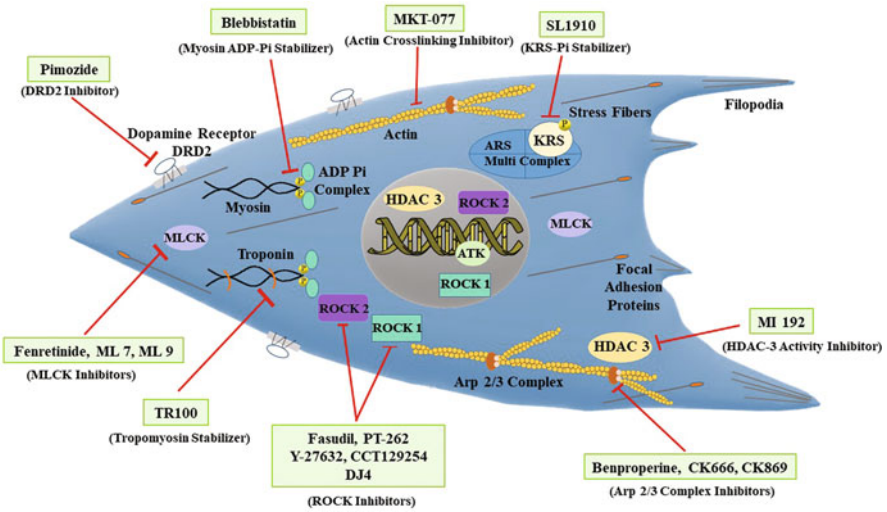


Fig. 2 Synthetic migrastatic compounds and their targets in migrating tumor cells. The diagram shows a migrating tumor cell with various molecules present in its cytoplasm and nucleus that are responsible for maintaining a migratory phenotype and associated gene expression. The presence of stress fibers and motility protrusions like filopodia is the hallmark of a migrating cancer cell. Here, 16 synthetic migrastatic compounds have been highlighted along with their specific molecular target in the cancer cell for inhibiting cell migration (as shown using red arrows). These compounds are divided into three categories based on their target. The first category of compounds acts on cytoskeletal elements such as actin and myosin. This category includes TR100 and MKT-077 and Blebbistatin. The second category of migrastatic compounds acts on molecules involved in the Rho/Rac signaling pathway such as Rho Kinase, ROCK1, and ROCK2 that get activated during tumor cell migration. This category involves, Fasudil, PT-262, DJ4, Y-27632, and CCT129254. The third category acts on molecules other than those in the previous two categories. The action is on molecules such as dopamine receptors, HDAC 3, MLCK, Arp 2/3 complex, and KRS subunit of ARS multi complex. The compounds in this category are pimozide, MI 192, fenretinide, ML7, ML9, SL1910, CK666, CK869, and benproperine. The action that each compound performs on the target has been mentioned in the bracket below each compound

phosphate group. Thus, blebbistatin stabilizes myosin II in an actin-devoid state and inhibits actomyosin crosslinking (Kovács et al. 2004). Recent reports show that it inhibits pancreatic adenocarcinoma (Duxbury et al. 2004) and E6 glioma cell (Ivkovic et al. 2012) invasion. In few studies, blebbistatin (5 μmol/L) impedes cell division and leads to G0/G1 arrest in mesenchymal stromal cells, which needs to be studied in depth (Sharma et al. 2014) to avoid un-intended cell death.

Arp2/3 Inhibitor

Actin-related protein (Arp2/3) complex interacts with existing actin filament and nucleates the development of branched filament. Small molecules (such as CK-666 and CK-869) bind to Arp2/3 and inhibit it (Nolen et al. 2009). CK-666 interact with both Arp2 and Arp3 and block their involvement in the activated filament conformation. CK-666 inhibits the migration of glioma cells (U251, LN229, and SNB19)

(Liu et al. 2013). In prostate cancer cells (DU145), CK-666 did not affect the actin cytoskeletal structure and the mechanical properties of the cells but impaired their motility (Efremov et al. 2015). C-869 binds to the hydrophobic core of Arp3, destabilizing the active site (Hetrick et al. 2013). However, inactivation of Arp2/3 is not enough to influence the cell motility in all types of migratory cells, as CK-666 could not inhibit the migration of A2780 ovarian carcinoma cell (Paul et al. 2015). Another small molecule, Pimozide, belonging to the diphenylbutylpiperidine group of drugs, targets dopamine receptor D2 (DRD2) to reduce cell migration and the dissemination of xenograft tumors in the mice (Jandaghi et al. 2016). Pimozide also interacts with ARPC2 and inhibits actin polymerization, leading to the disappearance of lamellipodia and inhibited migration. It resulted in detectable cytotoxicity and could be categorized as valuable a migrastatic (Choi et al. 2019).

Similarly, benproperine (Benp), an FDA-approved antitussive drug, can block tumor cell dissemination in pancreatic and colorectal cancers through ARPC2 binding. In addition, in liver metastasis model, Benp significantly inhibited the metastasis of colon cancer to the liver (Yoon et al. 2019). Thus, these molecules can suppress tumor growth and dissemination into the major organs like the liver, kidney, and colon, as observed in an orthotopic mouse model.

Tropomycin Inhibitor

Development of anti-tropomycin compound targets different isoforms of tropomyosin and effective against melanoma, neural crest-derived tumor cell lines, and neuroblastoma cells. At a sublethal dose of 3 mmol/L, TR-100 impacted the migration of cancer cells in the 2D and 3D conditions (Stehn et al. 2013). In addition, this lead compound shows minimal effect on cardiac cells, which is a matter of concern for anti-actin drugs.

Inhibitors of Rho-Kinase (ROCK)

Fasudil (1-(5-isoquinolinesulfonyl)-homopiperazine) is the first developed inhibitor of Rho-kinase, (Yamaguchi et al. 2006) and inhibits the progression of tumor in the syngeneic peritoneal dissemination model, lung metastasis model, and the breast cancer orthotopic model. The prodrug Fasudil gets converted to 1-(hydroxy-5-isoquinoline sulfonyl-homopiperazine) (fasudil-OH) after the cellular entry and interacts with the phosphate loop of Rho-kinase. The prodrug showed more potency in inhibiting the migration of MDA-MB-231 and HT1080 cells (Ying et al. 2006). It also successfully inhibited the migration of urothelial cancer cells (5637 and UM-UC-3) (Abe et al. 2014) and breast cancer cell (MDA MB 231) (Guerra et al. 2017). Another ROCK kinase inhibitor Y-27632, a pyridine derivative, inhibits actomyosin contraction (Uehata et al. 1997) and disrupts tumor cell motility and chemotaxis in human prostate cancer cell lines (Somlyo et al. 2000). Y27632 treatment also reduced in vitro and in vivo breast cancer migration to bone (Liu et al. 2009). However, in a contradictory report, ROCK inhibition is observed to promote migration of breast cancer cells (MCF-7) in both 2D and 3D environments (Yang and Kim 2014). Y27632 blocked the migration of human tongue squamous cell carcinoma cells (Tca8113 and CAL-27) (Wang et al. 2016). Similarly, another

ROCK kinase inhibitor, PT-262 (7-chloro-6-piperidin-1-yl-quinoline-5,8-dione), a derivative of 5,8-quinolinediones, induces cytoskeletal remodeling. It inhibits ROCK-mediated phosphorylation of the MLC and formation of stress fibers, thus inhibiting migration of lung carcinoma cells. In A549 lung carcinoma cells, PT-262 is found to be more effective than Y27632 or H-1152 (Tsai et al. 2011). Another inhibitor of ROCK RKI-1447 binds to the ATP site of ROCK 1 and selectively inhibits the phosphorylation of ROCK substrates such as MLC-2 and MYPT-1. It is seen to inhibit tumor growth and initiates tumor regression in ErbB2-driven breast cancer mouse model. It inhibits migration and mammosphere formation of breast cancer cells (MDA-MB-231 and MDA-MB-468) and lung cancer cell line (H-1299) (Patel et al. 2012). A multikinase inhibitor DJ4 {(5Z)-2–5-(1H-pyrrolo[2,3-b] pyridine-3-ylmethylene)-1,3-thiazol-4(5H)-one} selectively inhibits the Rho-kinases, ROCK1, and ROCK2 in addition to myotonic dystrophy kinase-related Cdc42-binding kinases (MRCKα and MRCKβ). DJ4 significantly blocked the formation of stress fibers and inhibited cell migration in non-small-cell lung cancer (A549, CCL-185; H522, CRL-5810; H23, CRL-5800; H2126, CCL-256; H460, HTB-177), melanoma (A375M, CRL-1619), pancreatic cancer (PANC-1, CRL-1469), breast cancer (MDAMB-231, HTB-26), and glioblastoma (U251) cell lines. Combined inhibition of ROCK and MRCK has a much potent effect in inhibiting metastasis compared to the inhibition of either kinase individually, which may hold DJ4 as a more promising migrastatic drug across a broad spectrum of cancer types (Kale et al. 2015). CCT129254 and AT13148 are another class of AKT inhibitors that also inhibits ROCK 1 and ROCK 2. They impair both amoeboid and mesenchymal modes of invasion in melanoma cells and inhibit cell proliferation (Sadok et al. 2015).

Actin Filament-Related Inhibitor

Inhibition of actin polymerization through synthetic and semi-synthetic molecules emerges as a critical approach for migrastatic. A synthetic actin inhibitor MKT-077 (1-ethyl-2-[[3-ethyl-5-(3-methyl-2(3H)-benzothiazolylidene)-4-oxo-2-thiazolidinylidene] methyl]-pyridinium chloride) shows antitumor activity in cancer cell lines like colon carcinoma (CX-1), breast carcinoma (MCF-7), pancreatic carcinoma (CRL142O) (Koya et al. 1996). It crosslinks with actin leading to the bundling of the actin filament and thus blocking membrane ruffling. In Ras-transformed neoplastic cells, it has the advantage of binding with p45 and p75 but not in normal parental cells (Tikoo et al. 2000). The semi-synthetic derivatives of Latrunculin, C-17 hydroxyl, and thiazolidinone nitrogen, inhibitors of actin polymerization, successfully modulate the binding affinity of G-actin. They exhibit anti-invasive effects in breast carcinoma (MDA MB 231 and MCF-7 cells) (Khanfar et al. 2010).

MLCK Inhibitor

MLCK-mediated phosphorylation of the myosin II influences its activity which leads to contraction, motility, and cytoskeletal remodeling. MLCK inhibitors such as ML-7 and ML-9 inhibit the phosphorylation of myosin regulatory light chain and activation of myosin II which prevents migration of rat prostatic adenocarcinoma (R-3327-AT-1)

(Tohtong et al. 2003) and human glioma cells (U251MG) (Gillespie et al. 1999). ATPR (retinoid 4-amino-2-trifluoromethyl-phenyl ester), a synthetic retinoic acid derivative, downregulates the expression of MLCK and phosphorylation of MLC protein through the p38-MAPK pathway inhibiting the migration of breast cancer cells (MDA MB 231) (Wang et al. 2013). Another synthetic analog of all trans retinoic acid (ATRA) known as 4-HPR or fenretinide hinders migration of human liver cancer cells (HepG2) by inhibiting the activation and expression of MLCK (Zhang et al. 2018). Two synthetic derivatives of curcumin, ST03 (1,2-bis[(3E,5E)-3,5-bis [(2-chlorophenyl)methylene]-4-oxo-1-piperidyl]ethane-1,2-dione) and ST08 ([4-[(E)-[(5E)-1-[2-[(3E,5E)-3,5-bis[(4-hydroxyazonylphenyl)methylene]-4-oxo-1-piperidyl]-2-oxoacetyl]-5-[(4-hydroxyazonylphenyl)methylene]-4-oxo3-piperidylidene]methyl] phenyl] azinic acid), exhibit migrastatic properties by inhibiting migration of the breast (MDA-MB-231) and ovarian cancer cell lines (PA-1) (Koroth et al. 2019).

Protein Enzyme Inhibitor

Synthetic inhibitors of cellular enzymes can also act as migrastatic molecules. For example, an inhibitor of histone deacetylase 3 (HDAC3), MI-192, is involved in tubulin's epigenetic regulation and microtubules' stabilization. It inhibits the migration of adult glioma cell (U251 and KNS42) spheroids embedded in collagen (Harmer et al. 2019). SL-1910 (N, N-dialkylthiazolo [5,4-b] pyridine-2-amine), a novel potent migrastatic drug, directly interacts with KRS (Lysyl-tRNA Synthetase). KRS, a Class II aminoacyl-tRNA synthetase, gets phosphorylated and stabilizes laminin receptor (67LR) in the laminin signaling pathway to stimulate cell migration. SL-1910 inhibits breast cancer cell migration in both in vitro (MDA MB-231) and in vivo 4 T1 xenograft metastasis models without detectable toxicity (Lee et al. 2021).

Probable Problems with Migrastatic Candidates as Anticancer Drugs

Irrespective of the successful preliminary reports, migrastatic compounds may have few drawbacks that need to be addressed before embracing them as a potential anticancer drug. Rigorous evaluation of these compounds needs a detailed analysis of their effect on different aspects of cellular behavior, including cell division, migration, cell-cell interaction, and others. Additionally, a functional model for metastasis is needed to assess their impact on migration pathways. Such a model should indeed recapitulate the cancer cell plasticity and include different modes of migration. Traditional 2D cell cultures that cannot incorporate such vast modalities should be replaced with advanced 3D and microfluidics models. The successful development of human-relevant 3D tumor models and tumor-on-chip is required to fill this gap.

Developing ideal xenograft models to screen migrastatics would be the next technical hurdle. Another problem would be the identification of predictable biomarkers and quantitative measures to analyze the expected effects. Developing advanced imaging tools to study the impact of drugs and monitoring metastasis in the in vivo model will be another matter of concern (Kale et al. 2015).

While choosing a target, all the undesirable effects of inhibiting the target should be kept in mind so that it does not cause harm to the cancer patient. As migrastatic drugs

will be targeting cancer cell migration, the intermittent application will be anticipated. So, the requirement of low cytotoxicity should be a point of concern compared to conventional cytotoxic drugs (Gandalovicova et al. 2017). As migrastatic drugs will be targeting actin polymerization and cellular contractility without any specificity, the non-cancerous cell can also be a bystander target. Cells involved in migration such as stem cells, lymphocytes, macrophages, dendritic cells, fibroblasts, and others could be the unintended target for such molecules. Depending on the nature of the inhibitors (targets involved in the collective or single-cell migration), the "bystander effect" can be assumed and utilized to measure the toxicity score. For example, potential inhibitors of collective migration can inhibit typical wound healing within a cancer patient and delay the fibroblast-mediated scar tissue formation. Deregulation in cell migration may also lead to pathological conditions like inflammation (Pijuan et al. 2019).

Furthermore, such inhibitors may hamper other critical biological processes like gastrulation, organogenesis, neurogenesis, tissue homeostasis, and immune cell trafficking, which must be considered and weighed judiciously against the risk of metastasis.

Future Perspective and Conclusion

Migrastatics are a new class of drugs that primarily targets actin polymerization and contractility, the significant proponents of all kinds of cancer cell migration. The purpose of introducing migrastatic is not to completely replace cytotoxic or cytostatic drugs but rather to use them in synergy with other drugs. The therapeutic stratagem of combinatorial therapy using migrastatics with other traditional anticancer drugs might prove more effective in treating cancer while reducing chemoresistance and side effects.

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References

Abe H, Kamai T, Hayashi K et al (2014) The Rho-kinase inhibitor HA-1077 suppresses proliferation/migration and induces apoptosis of urothelial cancer cells. BMC Cancer 14:412. https://doi.org/10.1186/1471-2407-14-412

Adamus A, Ali I, Vasileiadis V, Al-Hileh L, Lisec J, Frank M, Seitz G, Engel N (2021) Vincetoxicum arnottianum modulates motility features and metastatic marker expression in pediatric rhabdomyosarcoma by stabilizing the actin cytoskeleton. BMC Complement Med Ther 21(1):136. https://doi.org/10.1186/s12906-021-03299-x

Alehashem M, Baniasadi S (2018) Safe handling of anti-neoplastic drugs in the university hospitals: a descriptive survey study among oncology nurses. Int J Cancer Manag 11(2):e6482. https://doi.org/10.5812/ijcm.6482

Alizadeh AM, Shiri S, Farsinejad S (2014) Metastasis review: from bench to bedside. Tumour Biol 35:8483–8523. https://doi.org/10.1007/s13277-014-2421-z

Bryce NS, Schevzov G, Ferguson V et al (2003) Specification of actin filament function and molecular composition by tropomyosin isoforms. Mol Biol Cell 14:1002–1016. https://doi.org/10.1091/mbc.E02-04-0244

Chi Q, Yin T, Gregersen H et al (2014) Rear actomyosin contractility-driven directional cell migration in three-dimensional matrices: a mechanochemical coupling mechanism. J R Soc Interface 11

Choi J, Lee Y, Yoon YJ et al (2019) Pimozide suppresses cancer cell migration and tumor metastasis through binding to ARPC2, a subunit of the Arp2/3 complex. Cancer Sci 110:3788–3801. https://doi.org/10.1111/cas.14205

Cicenas J, Zalyte E, Bairoch A, Gaudet P (2018) Kinases and cancer. Cancers (Basel) 10:63. https://doi.org/10.3390/cancers10030063

de Winde CM, George SL, Arp AB et al (2020) Podoplanin drives dedifferentiation and amoeboid invasion of melanoma. bioRxiv. https://doi.org/10.1101/2020.07.23.218578

DesMarais V, Macaluso F, Condeelis J, Bailly M (2004) Synergistic interaction between the Arp2/3 complex and cofilin drives stimulated lamellipod extension. J Cell Sci 117:3499–3510. https://doi.org/10.1242/jcs.01211

Duxbury MS, Ashley SW, Whang EE (2004) Inhibition of pancreatic adenocarcinoma cellular invasiveness by blebbistatin: a novel myosin II inhibitor. Biochem Biophys Res Commun 313: 992–997. https://doi.org/10.1016/j.bbrc.2003.12.031

Efremov YM, Dokrunova AA, Efremenko AV et al (2015) Distinct impact of targeted actin cytoskeleton reorganization on mechanical properties of normal and malignant cells. Biochim Biophys Acta 1853:3117–3125. https://doi.org/10.1016/j.bbamcr.2015.05.008

Fernandes M, Rosel D, Brábek J (2019) Solid cancer: the new tumour spread endpoint opens novel opportunities. Br J Cancer 121:513–514

Freitas VM, Rangel M, Bisson LF, Jaeger RG, Machado-Santelli GM (2008) The geodiamolide H, derived from Brazilian sponge Geodia corticostylifera, regulates actin cytoskeleton, migration and invasion of breast cancer cells cultured in three-dimensional environment. J Cell Physiol 216(3):583–594. https://doi.org/10.1002/jcp.21432

Friedl P (2004) Prespecification and plasticity: shifting mechanisms of cell migration. Curr Opin Cell Biol 16:14–23. https://doi.org/10.1016/j.ceb.2003.11.001

Friedl P, Hegerfeldt Y, Tusch M (2004) Collective cell migration in morphogenesis and cancer. Int J Dev Biol 48:441–449. https://doi.org/10.1387/ijdb.041821pf

Gandalovicova A, Rosel D, Fernandes M et al (2017) Migrastatics — anti-metastatic and anti-invasion drugs: promises and challenges. Trends in Cancer 3:391–406

Gandalovičová A, Rosel D, Brábek J (2020) Migrastatics – anti-metastatic drugs targeting cancer cell invasion. In: Approaching complex diseases. Springer, Cham, pp 203–211

Gate L, Kenneth DT (2011) Cancer management in man: chemotherapy, biological therapy, hyperthermia and supporting measures. Springer, Dordrecht

Gayan S, Ghuge PS, Chitnis MS, Dey T (2021) Oxidative stress in cancer and its influence on amoeboidal migration. In: Handbook of oxidative stress and cancer. Springer, Singapore. https://doi.org/10.1007/978-981-15-4501-6_79-

Gillespie GY, Soroceanu L, Manning TJ et al (1999) Glioma migration can be blocked by nontoxic inhibitors of myosin II. Cancer Res 59:2076–2082

Glenn H, Messner J, Meldrum D (2016) A simple non-perturbing cell migration assay insensitive to proliferation effects. Sci Rep 6:31694. https://doi.org/10.1038/srep31694

Guerra FS, De Oliveira RG, Fraga CAM et al (2017) ROCK inhibition with Fasudil induces beta-catenin nuclear translocation and inhibits cell migration of MDA-MB 231 human breast cancer cells. Sci Rep 7:1–8. https://doi.org/10.1038/s41598-017-14216-z

Harmer J, Struve N, Brüning-Richardson A (2019) Characterization of the effects of migrastatic inhibitors on 3D tumor spheroid invasion by high-resolution confocal microscopy. J Vis Exp 151:e60273. https://doi.org/10.3791/60273

Hayot C, Debeir O, Van Ham P, Van Damme M, Kiss R, Decaestecker C (2006) Characterization of the activities of actin-affecting drugs on tumor cell migration. Toxicol Appl Pharmacol 211(1): 30–40. https://doi.org/10.1016/j.taap.2005.06.006

Hetrick B, Han MS, Helgeson LA, Nolen BJ (2013) Small molecules CK-666 and CK-869 inhibit actin-related protein 2/3 complex by blocking an activating conformational change. Chem Biol 20:701–712. https://doi.org/10.1016/j.chembiol.2013.03.019

Huang C-Y, Ju D-T, Chang C-F et al (2017) A review on the effects of current chemotherapy drugs and natural agents in treating non–small cell lung cancer. Biomedicine 7:23. https://doi.org/10.1051/bmdcn/2017070423

Ivkovic S, Beadle C, Noticewala S et al (2012) Direct inhibition of myosin II effectively blocks glioma invasion in the presence of multiple motogens. Mol Biol Cell 23:533–542. https://doi.org/10.1091/mbc.E11-01-0039

Jandaghi P, Najafabadi HS, Bauer AS et al (2016) Expression of DRD2 is increased in human pancreatic ductal adenocarcinoma and inhibitors slow tumor growth in mice. Gastroenterology 151:1218–1231. https://doi.org/10.1053/j.gastro.2016.08.040

Jiang WG (2005) E-cadherin and its associated protein catenins, cancer invasion and metastasis. Br J Surg 83:437–446. https://doi.org/10.1002/bjs.1800830404

Kale VP, Hengst JA, Desai DH et al (2015) The regulatory roles of ROCK and MRCK kinases in the plasticity of cancer cell migration. Cancer Lett 361:185–196. https://doi.org/10.1016/j.canlet.2015.03.017

Khanfar MA, Youssef DTA, El Sayed KA (2010) Semisynthetic latrunculin derivatives as inhibitors of metastatic breast cancer: biological evaluations, preliminary structure-activity relationship and molecular modeling studies. ChemMedChem 5:274–285. https://doi.org/10.1002/cmdc.200900430

Koroth J, Nirgude S, Tiwari S et al (2019) Investigation of anti-cancer and migrastatic properties of novel curcumin derivatives on breast and ovarian cancer cell lines. BMC Complement Altern Med 19:273. https://doi.org/10.1186/s12906-019-2685-3

Kovács M, Tóth J, Hetényi C et al (2004) Mechanism of blebbistatin inhibition of myosin II. J Biol Chem 279:35557–35563. https://doi.org/10.1074/jbc.M405319200

Koya K, Li Y, Wang H et al (1996) MKT-077, a novel rhodacyanine dye in clinical trials, exhibits anticarcinoma activity in preclinical studies based on selective mitochondrial accumulation. Cancer Res 56:538–543

Krakhmal NV, Zavyalova MV, Denisov EV et al (2015) Cancer invasion: patterns and mechanisms. Acta Nat 7:17–28. https://doi.org/10.32607/20758251-2015-7-2-17-28

Lee S, Kwon NH, Seo B et al (2021) Discovery of novel potent migrastatic Thiazolo[5,4-b] pyridines targeting Lysyl-tRNA synthetase (KRS) for treatment of Cancer metastasis. Eur J Med Chem 218:113405. https://doi.org/10.1016/j.ejmech.2021.113405

Liu S, Goldstein RH, Scepansky EM, Rosenblatt M (2009) Inhibition of Rho-associated kinase signaling prevents breast cancer metastasis to human bone. Cancer Res 69:8742–8751. https://doi.org/10.1158/0008-5472.CAN-09-1541

Liu Z, Yang X, Chen C et al (2013) Expression of the Arp2/3 complex in human gliomas and its role in the migration and invasion of glioma cells. Oncol Rep 30:2127–2136. https://doi.org/10.3892/or.2013.2669

Mansoori B, Mohammadi A, Davudian S et al (2017) The different mechanisms of cancer drug resistance: a brief review. Adv Pharm Bull 7:339–348. https://doi.org/10.15171/apb.2017.041

Martin TA, Ye L, Sanders AJ et al (2013) Cancer invasion and metastasis: molecular and cellular perspective. In: Metastatic cancer: clinical and biological perspectives

Menhofer MH, Kubisch R, Schreiner L, Zorn M, Foerster F, Mueller R, Raedler JO, Wagner E, Vollmar AM, Zahler S (2014) The actin targeting compound Chondramide inhibits breast cancer metastasis via reduction of cellular contractility. PLoS One 9(11):e112542. https://doi.org/10.1371/journal.pone.0112542

Micalizzi DS, Farabaugh SM, Ford HL (2010) Epithelial-mesenchymal transition in cancer: parallels between normal development and tumor progression. J Mammary Gland Biol Neoplasia 15:117–134. https://doi.org/10.1007/s10911-010-9178-9

Millard TH, Sharp SJ, Machesky LM (2004) Signalling to actin assembly via the WASP (Wiskott-Aldrich syndrome protein)-family proteins and the Arp2/3 complex. Biochem J 380:1–17

Mok TS, Wu Y-L, Ahn M-J et al (2017) Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 376:629–640. https://doi.org/10.1056/NEJMoa1612674

Nagano M, Hoshino D, Koshikawa N et al (2012) Turnover of focal adhesions and cancer cell migration. Int J Cell Biol 2012:1–10. https://doi.org/10.1155/2012/310616

Nguyen DX, Bos PD, Massagué J (2009) Metastasis: from dissemination to organ-specific colonization. Nat Rev Cancer 9:274–284. https://doi.org/10.1038/nrc2622

Nolen BJ, Tomasevic N, Russell A et al (2009) Characterization of two classes of small molecule inhibitors of Arp2/3 complex. Nature 460:1031–1034. https://doi.org/10.1038/nature08231
Nurgali K, Jagoe RT, Abalo R (2018) Editorial: adverse effects of cancer chemotherapy: anything new to improve tolerance and reduce sequelae? Front Pharmacol 9:245. https://doi.org/10.3389/fphar.2018.00245
Ong MS, Deng S, Halim CE et al (2020) Cytoskeletal proteins in cancer and intracellular stress: a therapeutic perspective. Cancers (Basel) 12:238. https://doi.org/10.3390/cancers12010238
Pandya P, Orgaz JL, Sanz-Moreno V (2017) Actomyosin contractility and collective migration: may the force be with you. Curr Opin Cell Biol 48:87–96
Patel RA, Forinash KD, Pireddu R et al (2012) RKI-1447 is a potent inhibitor of the rho-associated ROCK kinases with anti-invasive and antitumor activities in breast cancer. Cancer Res 72:5025–5034. https://doi.org/10.1158/0008-5472.CAN-12-0954
Paul NR, Allen JL, Chapman A et al (2015) α5β1 integrin recycling promotes Arp2/3-independent cancer cell invasion via the formin FHOD3. J Cell Biol 210:1013–1031. https://doi.org/10.1083/jcb.201502040
Pijuan J, Barceló C, Moreno DF et al (2019) In vitro cell migration, invasion, and adhesion assays: from cell imaging to data analysis. Front Cell Dev Biol 7:107. https://doi.org/10.3389/fcell.2019.00107
Quintanilla M, Montero LM, Renart J, Villar EM (2019) Podoplanin in inflammation and cancer. Int J Mol Sci 20:1–38
Rakash S (2012) Role of proteases in cancer: a review. Biotechnol Mol Biol Rev 7:90–101. https://doi.org/10.5897/BMBR11.027
Ruggiero A, Rizzo D, Catalano M et al (2017) Hypersensitivity to carboplatin in children with malignancy. Front Pharmacol 08. https://doi.org/10.3389/fphar.2017.00201
Sadok A, McCarthy A, Caldwell J et al (2015) Rho kinase inhibitors block melanoma cell migration and inhibit metastasis. Cancer Res 75:2272–2284. https://doi.org/10.1158/0008-5472.CAN-14-2156
Sahai E (2005) Mechanisms of cancer cell invasion. Curr Opin Genet Dev 15:87–96. https://doi.org/10.1016/j.gde.2004.12.002
Sayed KA, Khanfar MA, Shallal HM, Muralidharan A, Awate B, Youssef DT, Liu Y, Zhou YD, Nagle DG, Shah G (2008) Latrunculin A and its C-17-O-carbamates inhibit prostate tumor cell invasion and HIF-1 activation in breast tumor cells. J Nat Prod 71(3):396–402. https://doi.org/10.1021/np070587w
Sharma T, Kumari P, Pincha N et al (2014) Inhibition of non-muscle myosin II leads to G0/G1 arrest of Wharton's jelly-derived mesenchymal stromal cells. Cytotherapy 16:640–652. https://doi.org/10.1016/j.jcyt.2013.09.003
Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A (2017) Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell 168:707–723
Somlyo AV, Bradshaw D, Ramos S et al (2000) Rho-kinase inhibitor retards migration and in vivo dissemination of human prostate cancer cells. Biochem Biophys Res Commun 269:652–659. https://doi.org/10.1006/bbrc.2000.2343
Steeg PS (2006) Tumor metastasis: mechanistic insights and clinical challenges. Nat Med 12:895–904. https://doi.org/10.1038/nm1469
Stehn JR, Haass NK, Bonello T et al (2013) A novel class of anticancer compounds targets the actin cytoskeleton in tumor cells. Cancer Res 73:5169–5182. https://doi.org/10.1158/0008-5472.CAN-12-4501
Summy JM, Gallick GE (2003) Src family kinases in tumor progression and metastasis. Cancer Metastasis Rev 22:337–358
Tan AS, Baty JW, Dong LF et al (2015) Mitochondrial genome acquisition restores respiratory function and tumorigenic potential of cancer cells without mitochondrial DNA. Cell Metab 21:81–94. https://doi.org/10.1016/j.cmet.2014.12.003
Tikoo A, Shakri R, Connolly L et al (2000) Treatment of ras-induced cancers by the F-actin-bundling drug MKT-077. Cancer J Sci Am 6:162–168
Tohtong R, Phattarasakul K, Jiraviriyakul A, Sutthiphongchai T (2003) Dependence of metastatic cancer cell invasion on MLCK-catalyzed phosphorylation of myosin regulatory light chain. Prostate Cancer Prostatic Dis 6:212–216. https://doi.org/10.1038/sj.pcan.4500663

Tsai CC, Liu HF, Hsu KC et al (2011) 7-Chloro-6-piperidin-1-yl-quinoline-5,8-dione (PT-262), a novel ROCK inhibitor blocks cytoskeleton function and cell migration. Biochem Pharmacol 81: 856–865. https://doi.org/10.1016/j.bcp.2011.01.009

Tsai JH, Donaher JL, Murphy DA et al (2012) Spatiotemporal regulation of epithelial-mesenchymal transition is essential for squamous cell carcinoma metastasis. Cancer Cell 22:725–736. https://doi.org/10.1016/j.ccr.2012.09.022

Uehata M, Ishizaki T, Satoh H et al (1997) Calcium sensitization of smooth muscle mediated by a Rho-associated protein kinase in hypertension. Nature 389:990–994. https://doi.org/10.1038/40187

Vasan N, Baselga J, Hyman DM (2019) A view on drug resistance in cancer. Nature 575:299–309. https://doi.org/10.1038/s41586-019-1730-1

Vasiliev JM, Gelfand IM (2006) Cellular search migrations in normal development and carcinogenesis. Biochemist 71:821–826. https://doi.org/10.1134/S0006297906080013

Vicente-Manzanares M, Ma X, Adelstein RS, Horwitz AR (2009) Non-muscle myosin II takes centre stage in cell adhesion and migration. Nat Rev Mol Cell Biol 10:778–790

Wang B, Yan Y, Zhou J et al (2013) A novel all-trans retinoid acid derivatives inhibits the migration of breast cancer cell lines MDA-MB-231 via myosin light chain kinase involving p38-MAPK pathway. Biomed Pharmacother 67:357–362. https://doi.org/10.1016/j.biopha.2013.03.016

Wang ZM, Yang DS, Liu J et al (2016) ROCK inhibitor Y-27632 inhibits the growth, migration, and invasion of Tca8113 and CAL-27 cells in tongue squamous cell carcinoma. Tumor Biol 37: 3757–3764. https://doi.org/10.1007/s13277-015-4115-6

Xu Z, Jiang Y, Steed H et al (2010) TGFβ and EGF synergistically induce a more invasive phenotype of epithelial ovarian cancer cells. Biochem Biophys Res Commun 401:376–381. https://doi.org/10.1016/j.bbrc.2010.09.059

Yamaguchi H, Condeelis J (2007) Regulation of the actin cytoskeleton in cancer cell migration and invasion. Biochim Biophys Acta 1773:642–652

Yamaguchi H, Wyckoff J, Condeelis J (2005) Cell migration in tumors. Curr Opin Cell Biol 17: 559–564. https://doi.org/10.1016/j.ceb.2005.08.002

Yamaguchi H, Kasa M, Amano M et al (2006) Molecular mechanism for the regulation of rho-kinase by dimerization and its inhibition by fasudil. Structure 14:589–600. https://doi.org/10.1016/j.str.2005.11.024

Yang S, Kim H-M (2014) ROCK inhibition activates MCF-7 cells. PLoS One 9:e88489. https://doi.org/10.1371/journal.pone.0088489

Yilmaz M, Christofori G (2010) Mechanisms of motility in metastasizing cells. Mol Cancer Res 8: 629–642

Ying H, Biroc SL, Li W-W et al (2006) The Rho kinase inhibitor fasudil inhibits tumor progression in human and rat tumor models. Mol Cancer Ther 5:2158–2164. https://doi.org/10.1158/1535-7163.MCT-05-0440

Yoon YJ, Han Y-M, Choi J et al (2019) Benproperine, an ARPC2 inhibitor, suppresses cancer cell migration and tumor metastasis. Biochem Pharmacol 163:46–59. https://doi.org/10.1016/j.bcp.2019.01.017

Zebda N, Bernard O, Bailly M et al (2000) Phosphorylation of ADF/cofilin abolishes EGF-induced actin nucleation at the leading edge and subsequent lamellipod extension. J Cell Biol 151:1119–1127. https://doi.org/10.1083/jcb.151.5.1119

Zhang T, Li J, Dong Y, Zhai D, Lai L, Dai F, Deng H, Chen Y, Liu M, Yi Z (2012) Cucurbitacin E inhibits breast tumor metastasis by suppressing cell migration and invasion. Breast Cancer Res Treat 135(2):445–458. https://doi.org/10.1007/s10549-012-2175-5

Zhang L, Huang D, Shao D et al (2018) Fenretinide inhibits the proliferation and migration of human liver cancer HepG2 cells by downregulating the activation of myosin light chain kinase through the p38-MAPK signaling pathway. Oncol Rep 40:518–526. https://doi.org/10.3892/or.2018.6436

Zhao H, Jiao Y, Zhang Z (2015) Deguelin inhibits the migration and invasion of lung cancer A549 and H460 cells via regulating actin cytoskeleton rearrangement. Int J Clin Exp Pathol 8(12): 15582–15590