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Drug repurposing for the inhibition of invasiveness and metastasis of cancer cells
Hledání nové role schválených léků v inhibici invazivity a metastazování nádorových buněk

Bachelor's thesis

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Prohlášení

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Kateryna Turchyna

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Abstract

Metastasis is the primary cause of death from cancer. Current lack of medicines for metastasis makes it a topical issue and encourages the global search for molecules that may potentially inhibit invasiveness of cancer cells, and thus prevent metastatic spread. Drug repurposing is a strategy of identifying new uses for approved drugs that are outside the scope of the original medical indication. The aim of this thesis is to summarize knowledge on the repurposing potential of selected groups of drugs with emphasis on molecular mechanisms of their action. In particular, the work is focused on selected antipsychotics, antidepressants, beta-blockers and statins, whose abilities to inhibit cancer invasiveness have been indicated.

Key words:

Drug repurposing, cancer invasiveness, metastasis, cell migration, EMT, antipsychotics, antidepressants, beta-blockers, statins.

Abstrakt

Metastázování je primární příčinou úmrtí na rakovinu. Současný nedostatek účinných léků proti metastázování činí tento problém aktuálním a vede k intenzivnímu hledání molekul, které mohou potenciálně inhibovat invazivitu nádorových buněk, a tak zabránit i šíření metastáz. Repurposing léků je identifikace nových použití schválených léků, které jsou mimo rámec jejich původní lékařské indikace. Cílem této práce je shrnout poznatky o protimetastatickém potenciálu vybraných skupin léčiv s důrazem na molekulární mechanismy jejich působení. Práce je zaměřena zejména na vybraná antipsychotika, antidepresiva, beta-blokátory a statiny, u kterých byly indikovány schopnosti inhibovat invazivitu nádorových buněk.

Klíčová slova:

Hledání nové role schválených léků, nádorová invazivita, metastázování, migrace buněk, EMT, antipsychotika, antidepresiva, beta-blokátory, statiny.

1. Abbreviations list

AKT (PKB) – protein kinase B

AMT – amoeboid-mesenchymal transition

Arp2/3 complex – actin-related protein 2/3 complex

ARPC1-5 – actin-related protein2/3 complex components 1-5

BBs – beta-blockers

β_2 AR – β_2 -adrenoceptor

cAMP – cyclic adenosine monophosphate

ECM – extracellular matrix

EMT – epithelial-to-mesenchymal transition

Epac – exchange protein directly activated by cAMP

ERK – extracellular signal-regulated kinase

FDA – US Food and Drug Administration

FLZ – Fluphenazine

HMGCR – 3-hydroxy-3-methylglutaryl-CoA reductase

MAT – mesenchymal-amoeboid transition

MET – mesenchymal-to-epithelial transition

MMP – matrix metalloproteinase

mTOR – mammalian target of rapamycin

NF- κ B – nuclear factor kappa-light-chain-enhancer of activated B cells

PI3K – phosphoinositide 3-kinase

PFD – penfluridol

PRO – propranolol

SSRIs – selective serotonin reuptake inhibitors

STAT – signal transducer and activator of transcription

TCAs – tricyclic antidepressants

TFP – Trifluoperazine

TGF- β 1 – transforming growth factor beta 1

THD – Thioridazine

TNBC – triple-negative breast cancer

VEGF – vascular endothelial growth factor

VPA – valproic acid

ZEB1 – Zinc Finger E-Box Binding Homeobox 1

2. Introduction

2.1. Cancer and metastasis

Cancer is the second leading cause of human death according to the latest US national vital statistics report (National Center for Health Statistics & Heron, 2021). Death by the reason of cancer is in the first place provoked by metastasis (Sleeman & Steeg, 2010), or spread, of cancer cells from the place of original tumor to another part of the body, forming there a new (metastatic) lesion. The main mechanism within the process of metastasis is, in turn, invasiveness of cancer cells, or their ability to infiltrate surrounding healthy tissue by means of either active squeezing through the pre-existing holes in the extracellular matrix (ECM), or via ECM degradation by proteases.

2.2. Disadvantages of de novo drug discovering

Treatment methods improve with time, but, unfortunately, to date, there is no effective medicine discovered for prevention of metastasizing (*Metastatic Cancer*, 2015), which also contributes to the increasing number of cancer-related mortalities. Furthermore, lack of medicines for the metastasis makes it a much more relevant and topical issue every single day, and so metastasis becomes a significant therapeutic target (Sleeman & Steeg, 2010). Since no cure for metastasis has been found yet, – attempts can be made to inhibit cancer cells dissemination, so that the patient could live for many months or years controlling cancer growth and reducing its symptoms. For that reason, researchers and scientists all over the world are developing drugs, which could slow the metastasis process and therefore prolong patients' lives. There are two main ways of reaching that goal. On the one hand, we may search for new drugs, study new ways of treatment, which had never been applied before. It is the classical path for clinical trials, which includes pre-clinical (or laboratory) studies, the investigational new drug (IND) application, and then Phases 0 – IV of clinical trials themselves (*Types and Phases of Clinical Trials | What Are Clinical Trial Phases?*, n.d.). However, the whole process of defining a new molecule, testing it in non-human subjects to gather efficacy, toxicity and pharmacokinetic information, then studying its effects on human subjects, the safety of using it in treatments, is very complex, financially demanding, and can take years to complete.

2.3. Drug repurposing

On the other hand, there is a possibility of repositioning already approved drugs, which were utilized for treatment of other diseases before, and, for that reason, are validated,

regulated, and proved to be toxicologically safe. So far, there are over 20 000 prescription drug products approved for marketing by the US Food and Drug Administration (FDA) (Commissioner, 2020). And each one of them came through the long development process mentioned above, including their approval for marketing in Phase III Clinical Trials. The whole procedure of new drug development might take 10 to 15 years or more to complete, with the US average of 12 years, which is a tremendous amount of time compared to the fact, that, for example, 82.3% of women diagnosed with lung cancer in the UK, do not survive longer than 5 years after the disease detection (John & Broggio, 2019). In contrast, a repositioned drug approval process starts from two months only with the average of two or three years. In addition to that, development of - new drug is far more expensive than just repurposing of an existing one. For instance, a recent study (Wouters et al., 2020) showed that the price of bringing a single new drug to the market has an average of \$1.3 billion (in 2018 US dollars), while the reposition-route cost is only US\$40-80 million (Papapetropoulos & Szabo, 2018). Reduced time and cost are also related to the possibility of skipping the preclinical tests and phase I and II clinical trials in drug repurposing if these steps have already passed for other indications and safety has been approved (Pushpakom et al., 2019). Due to approved sufficient safety, the risk of failure on repurposing path is lowered (Ko, 2020; Pushpakom et al., 2019). Computational strategies for drug repositioning might also uncover novel targets or pathways for disease treatment, which can be further exploited (Pushpakom et al., 2019). Finally, most of the chemotherapeutic agents that are parts of systemic therapy conventionally applied in cancer treatments have adverse side effects, which could significantly decrease the patients' life quality. Whereas drug repurposing is usually conducted with the products, which were not related to cancer treatments before, and therefore are usually more targeted and cause slighter side effects.

2.4. Barriers of drug repurposing strategies

Taking into consideration all the aspects described above, the advantages of drug repositioning become obvious. However, with a growing interest to drug repurposing strategies, more and more barriers arise on the path. Krishnamurthy et al. from the Yale University School of Medicine in their as yet unpublished review (Krishnamurthy et al., 2021) studied in detail the issues that drug repurposing faces. The researchers concluded that the main problems are related to financial and resource barriers in the first place, as, even though repositioning way saves money and time spent on preclinical and early-stage research of de novo drug development, it still requires phases II and III clinical trials, and may still have the same, if not

higher, failure rate in later stages as any other compound (Krishnamurthy et al., 2021). The second most common barrier are challenges negotiating intellectual property (IP), in particular, when pharmaceutical companies patent many compounds, even if they are later abandoned as failed in some phase of clinical trials, and thus prevent others from developing these compounds without a license (Tartaglia, 2006). And thirdly, there are a lot of obstacles in accessing shelved compounds and their trial data, as they “disappear” once their development is abandoned, leaving trial data and results unpublished (Fetro & Scherman, 2020). Additionally, investments attraction might become much more sophisticated, due to investors’ unwillingness as they see medication’s failure in past (Sadeghi et al., 2021). Another barrier is insufficient staffing focused on out-licensing shelved products, which limits outside companies’ evaluation of shelved drugs (Krishnamurthy et al., 2021). According to the research, the solution may be partly found in such facilitators, as collaborative initiatives, compound libraries and databases, computational based strategies and tools, regulatory modifications, and tax incentives (Krishnamurthy et al., 2021). Partnership between pharmaceutical companies, who have resources and pools of shelved compounds and data, and academic institutions, who possess knowledge and expertise to study them, can be truly beneficial to facilitate the challenging process of drug repositioning. A brief recapitulation on the advantages and challenges of drug repurposing is summarized in Figure 1.

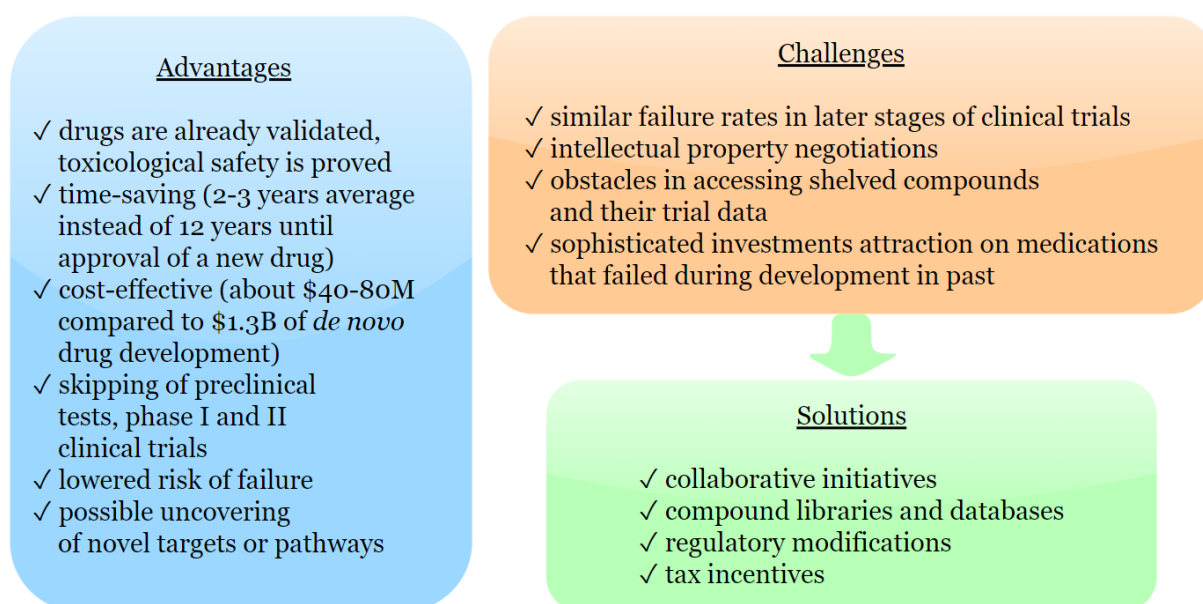


Figure 1. Drug repurposing: advantages, challenges and their solutions.

2.5. Successfully repositioned drugs

Regarding the examples of successfully repositioned drugs, the most frequently discussed repurposing opportunities usually relate to rare and neglected diseases (n=12), Alzheimer's disease (n=10), AIDS (n=2), and central nervous system disorders (n=2) (Krishnamurthy et al., 2021). For instance, *thalidomide*, originally indicated for sedation and morning sickness but later withdrawn for its teratogenic effects, has been launched to the market again after its successful repositioning. The drug was shown to inhibit tumor necrosis factor-alpha (TNF- α) signaling, and was subsequently approved for the treatment of erythema nodosum leprosum (ENL), a life threatening complication of leprosy, and then multiple myeloma (Krishnamurthy et al., 2021). In the US, the FDA approved the drug for acute ENL in 1998, however, "use was limited by very strict guidelines," according to the literature (Tartaglia, 2006). Another well-known example is *sildenafil*, or Viagra. Initially studied for use in hypertension and angina pectoris, it showed lack of efficacy in clinical trials, but induced interesting side effects, which eventually led to its use for erectile dysfunction (Ashburn & Thor, 2004; Boolell et al., 1996). *Daptomycin*, now serving as a last resort medication, could be the next illustration for successful drug repurposing, since it is proven useful in diseases like methicillin-resistant *Staphylococcus aureus* (MRSA) that have become increasingly resistant to front line antibiotics (Tartaglia, 2006). *Saracitinib* was originally developed for multiple oncology indications, but showed limited benefit. Later it has been discovered that the drug rescues memory deficits in transgenic AD mouse models, and thus today it is taken as a potential treatment of Alzheimer's disease (Kaufman et al., 2015). *Azidothymidine* (AZT), originally investigated as a chemotherapy drug, became the first treatment for patients with human immunodeficiency virus (HIV) after its anti-retroviral effect was noted (Fetro & Scherman, 2020; Mullard, 2012). *Tamoxifen* was a failed contraceptive and orphan drug until it has been repurposed and approved for treatment of metastatic breast cancer, and is currently the standard of care for long term adjuvant therapy for estrogen receptor positive breast cancer (Bishop, 2005). *Sunitinib* presents an example of on-target repurposing. It failed in clinical trials for colorectal, breast, prostate, and non-small cell lung cancer, but was successfully repositioned for treatment of gastrointestinal stromal tumor and renal cancers, and after approved for treatment of pancreatic neuroendocrine tumors (Williams, 2013). *Ebselen*, a potential lithium mimetic (Auer et al., 2014), was originally indicated for stroke, but showed a lack of efficacy. Though never marketed, it may have repurposing potential for treatment of bipolar disorder, and is currently under investigation (Fetro & Scherman, 2020).

3. Molecular mechanisms and structures crucial for metastasis

To understand the principles underlying the effect of originally diversely intended drugs on metastasis, it is relevant to firstly describe molecular mechanisms of invasiveness and specialized structures of invasive cancer cells, which these drugs can potentially interfere with. Taking into consideration the broadness of the topic, this work will focus mostly on the main invasiveness mechanisms with emphasis on cancer cell migration and invasion pathways.

3.1. Epithelial-to-mesenchymal and mesenchymal-to-epithelial transitions

For the metastatic process to begin, one of the early steps is local invasion of cells to adjacent tissue. In order to overcome the ECM barriers, tumor cells develop different strategies and may spread either collectively, or individually (reviewed in (Paňková et al., 2010)). The conversion of epithelial cells to motile individually migrating cells with mesenchymal phenotype is a phenomenon known as epithelial-to-mesenchymal transition (EMT) (Hay, 1995). Since it involves the disruption of cell–cell adhesion and cellular polarity, remodeling of the cytoskeleton, and changes in cell–matrix adhesion, this process is associated with an improvement in cells migratory and invasive properties (Roche, 2018). These hallmarks of EMT functionally have been linked to processes of cell motility, local destruction of the basement membrane that aligns the epithelia, and the generation of chemoresistant tumor cells with stem cell abilities that contribute to cancer recurrence after therapy (Nieto et al., 2016). Switch in gene expression from epithelial to mesenchymal phenotype is triggered by complex regulatory networks involving transcriptional control with Snail Family Transcriptional Repressors 1 and 2 (SNAI1 and SNAI2, correspondingly), Zinc Finger E-Box Binding Homeoboxes 1 and 2 (ZEB1 and ZEB2), Twist, and E12/E47 among transcriptional factors, but also non-coding RNAs (miRNAs and long non-coding RNAs), chromatin remodeling and epigenetic modifications, alternative splicing, post-translational regulation, protein stability, and subcellular localization (Craene & Berx, 2013). In addition, EMT is reversible by the mesenchymal-to-epithelial transition (MET), which is thought to be realized by cancer cells when they reach a desirable metastatic niche to develop secondary tumors (Roche, 2018). According to the literature, in various carcinomas (epithelial tumors) EMT contributes to their invasive state, whereas MET is thought to operate once metastatic cells have reached a distant site of secondary growth (Nieto et al., 2016). Based on all of the above, EMT is becoming a target of interest for anti-cancer therapy (Marcucci et al., 2016), and several repurposed drugs are thus aimed at blocking this transition.

3.2. Mesenchymal mode of invasiveness

Single cell migration strategies of tumor cells include two major types: mesenchymal and amoeboid. These two invasiveness modes are mutually interchangeable: suppression or enhancement of the activity of specific molecular pathways that determine either of the modes can cause a switch to the other type of invasiveness – known as mesenchymal-amoeboid transition (MAT) or amoeboid-mesenchymal transition (AMT), respectively (Paňková et al., 2010). In contrast to EMT, a quite rigid process with relatively extensive alternations in gene transcription, MAT/AMT involves rapid changes in a migratory mode that arise as a reply to the current specifics of the environment. Therefore, during the metastatic process when a certain microenvironment requires phenotypical adaptation of the tumor cells, the transitions may play a significant role (Paňková et al., 2010). Relation between EMT, MET, MAT, AMT and basic molecular pathways involved in each of them is summarized in Figure 2.

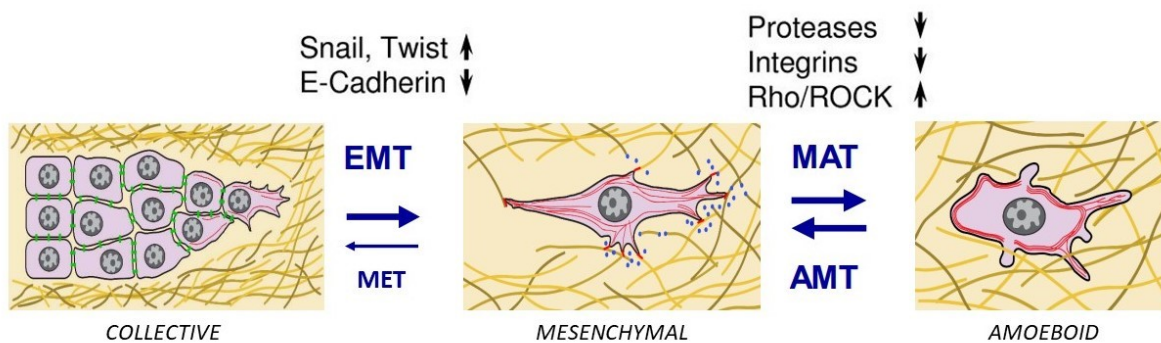


Figure 2. Transitions among cell invasion modes. EMT: epithelial-to-mesenchymal transition; MET: mesenchymal-to-epithelial transition; MAT: mesenchymal-amoeboid transition; AMT: amoeboid-mesenchymal transition. Adapted from (Brábek et al., 2010).

The translocation of the mesenchymally migrating cells begins with the formation of actin-rich filopodia and lamellipodia at the leading edge, a process driven by the small GTPases from the Rho family, primarily by Rac and Cell division control protein 42 homolog (Cdc42) (Nobes & Hall, 1995; Ridley et al., 1992), which mediate actin polymerization by the regulation of WASP/WAVE proteins (i.e., Wiskott-Aldrich syndrome proteins/WASP-family verprolin-homologous proteins) (Miki et al., 1998; Rohatgi et al., 1999). Interaction of neutral WASP (N-WASP) and WAVE2 with Arp2/3 nucleates the polymerization and branching of actin, forming the actin network at the leading edge (Suetsugu et al., 2001). Both cell poles adhere to ECM via focal contacts in the front of lamellipodia using integrins – transmembrane receptors that mechanically link ECM and actin cytoskeleton. The contraction is driven by actin stress fibers

attached to the poles, which generate traction forces between the anterior and posterior cell edges (Sheetz et al., 1998). Contractility of the actin cytoskeleton is maintained largely by Rho signaling (Mierke et al., 2008) as well as Cdc42 signaling (Wilkinson et al., 2005). However, Rho/ROCK (i.e., Rho-associated serine–threonine protein kinase) signaling has been shown to be dispensable for the mesenchymal type of migration of the colon carcinoma and SW962 squamous cell carcinoma cells (Sahai & Marshall, 2003), where activated Cdc42/MRCK (i.e., myotonic dystrophy kinase-related Cdc42-binding kinase) pathway sufficiently compensates the loss of contractility after inhibition of the Rho/ROCK pathway (Wilkinson et al., 2005).

3.3. Invadopodia, integrins and matrix metalloproteinases

Apart from mediating ECM adhesion, integrins clustered on invadopodia recruit proteolytic enzymes, such as matrix metalloproteinases (MMPs) and serine proteases, on the surface of invasive cells, facilitating pericellular ECM remodeling and generating the path for migrating cells (Brooks et al., 1996; Wei et al., 1996). Actin rich invasive protrusions of tumor cells known as invadopodia are active in the secretion of MMPs, which allows them to degrade ECM in order to facilitate invasion and metastasis (Jacob & Prekeris, 2015). Invadopodia formation, a complex cellular event involving substantial reorganization in cytoskeleton dynamics and membrane transport, is divided into three stages: initiation, assembly, and maturation, the final stage of which involves targeted delivery and exocytosis of MMP2, MMP9, and MMP14 (Jacob & Prekeris, 2015). The appearance of these MMPs is thus generally considered to be a mark of functionally mature invadopodia. Matrix metalloproteinases, momentous for both modes of invasion, are a family of zinc endopeptidases targeted to the invadopodia and implicated in ECM remodeling during metastasis of epithelial cancers (Jacob & Prekeris, 2015). They share a catalytic domain with the HEXGH motif responsible for ligating zinc, which is essential for catalytic function (Chambers & Matrisian, 1997). 14 of the 28 known MMPs are involved in tumor development and progression (Köhrmann et al., 2009), and although different MMPs serve specific roles during the different stages of tumor progression, particularly MMP-2 and MMP-9, also known as the gelatinases, have been long recognized as major contributors to the proteolytic degradation of extracellular matrix during tumor invasion (Björklund & Koivunen, 2005; Hofmann et al., 2005; Mook et al., 2004).

3.4. Amoeboid migration strategy

On the other hand, amoeboid-like invasiveness is characterized by cycles of expansion and contraction of the cell body mediated by the cortically localized actin and myosin (Yumura

et al., 1984). Rho/ROCK signaling pathway promotes a rounded bleb-associated mode of amoeboid motility because of the tension maintained by cortical actomyosin (Keller & Eggli, 1998), independently of pericellular proteolysis (Sahai & Marshall, 2003). Enhanced cortical actomyosin contractility of such cells enables them to squeeze through gaps in the ECM fibers and adapt their bodies to the pre-existing spaces (Friedl et al., 2001; Mandeville et al., 1997; Wolf et al., 2003), or to generate sufficient force to deform collagen fibers and push through the ECM (Provenzano et al., 2008; Rösel et al., 2008; Wyckoff et al., 2006) – in metastatic cells, myosin light chain (MLC) organization is altered on account of phosphorylation regulated by ROCK, which allows the cells to elevate force generation and thus increase invasion (Wyckoff et al., 2006). The low-adhesion attachment to the substrate enables cells with amoeboid mode of invasion to translocate at velocities 4 to 50 times higher than those of the mesenchymal type of invasiveness (Friedl et al., 1994, 1998; Sahai & Marshall, 2003).

3.5. Resume

To summarize, there are two mutually interchangeable modes of single cell migration – mesenchymal and amoeboid, which allow tumor cells to change their phenotype depending on the current specifics of the environment. To date, not much studies have been conducted on the issue, and the treatments affecting the MAT and AMT in 3D environment were reported only in specific cell lines, which calls into question the universality of the discovered mechanisms. However, the general conclusion can be made that the mesenchymal invasiveness operates through invadopodia and is protease-dependent, which allows tumor cells to migrate using proteolytic enzymes to degrade ECM on their path; in contrast to amoeboid-like invasiveness, which relies on Rho/ROCK signaling pathway and actomyosin contractility, and is thus protease-independent since such cells translocate via squeezing through ECM gaps or deforming of ECM fibers using force generation for invasion into the surrounding tissue.

Understanding of the basic mechanisms and molecules necessary for the migration and invasion of tumor cells is important for the development of a cancer treatment that would efficiently suppress tumor cell invasiveness, and thus metastasis.

4. Selected groups of drugs

Considering the vast amount of drugs with high repurposing potential, their full enumeration and description would go far beyond the scope of this bachelor's thesis. For that reason, this work will focus only on few selected groups, which are relatively well described and have a wide implementation in daily treatments. Drugs from the selected groups also frequently share common action mechanisms, which may enlighten new potential target pathways and contribute to novel metastasis treatment or/and prevention strategies.

4.1. Antipsychotics

Antipsychotics, or psychiatric drugs (PDs), are widely used to treat rich variety of mental disorders and substance abuse. Recently some anti-neoplastic properties of PDs have been reported, such as autophagy induction, which reduces migration and invasion of cancer cells (Vucicevic et al., 2018). Several classes of antipsychotics show considerable potential in the inhibition of cancer cell invasiveness.

For instance, *phenothiazines* (Thioridazine, Fluphenazine and Trifluoperazine) are able to limit metastatic progression of triple-negative breast cancer (TNBC) cells via reduction of cell invasion owing to reduced PI3K/AKT/mTOR (i.e., phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin, see Figure 3 for mechanism) and ERK (i.e., extracellular signal-regulated kinase) signaling (Goyette et al., 2019). In particular, anti-metastatic properties of 10-20 μM **Thioridazine (THD)**, an antagonist of the dopamine receptor D2, have been emphasized (Avendaño-Félix et al., 2020; Goyette et al., 2019; Zhang et al., 2017a). 10-50 μM THD has shown simultaneous upregulation of apoptosis genes, such as caspase-3 and Bax, and downregulation of anti-apoptosis gene Bcl-2, as well as a decrease in colorectal cancer stem cells (CSCs) mitochondrial membrane potential, leading to apoptosis induction via mitochondrial pathway, and reduced invasion (Zhang et al., 2017a). **Trifluoperazine (TFP)** has been reported as an anti-metastasis agent due to its interference with cancer cell migratory and invasion abilities (Pulkoski-Gross et al., 2015). Mechanistically, treatment with 10 μM TFP results in decreased phosphorylated AKT (Ser⁴⁷³ and Thr³⁰⁸) and β -catenin (Ser⁵⁵²). Lack of phosphorylation of Ser⁵⁵² of β -catenin prevents β -catenin nuclear relocation, resulting in decreased expression of vascular endothelial growth factor (VEGF), likely mediated through dopamine receptor D2 (Goyette et al., 2019; Pulkoski-Gross et al., 2015). The ability of 10-20 μM **Fluphenazine (FLZ)**, a dopamine receptor antagonist, to suppress metastasis by inhibition of migration and invasion was also demonstrated (Goyette et

al., 2019; Xu et al., 2019). Direct anti-cancer target of FLZ, however, remains elusive. Possible mechanistic pathway includes ROS stimulation, which decreases mitochondrial potential and damages DNA, leading to cell cycle arrest, DNA fragmentation, and finally to cell death by apoptosis (an increase of Bax and caspase 3, nuclei fragmentation) (Otręba & Kośmider, 2021; Środa-Pomianek et al., 2019). More accurate experiments are needed to show the precise molecular pathway of the analyzed drugs (Otręba & Kośmider, 2021).

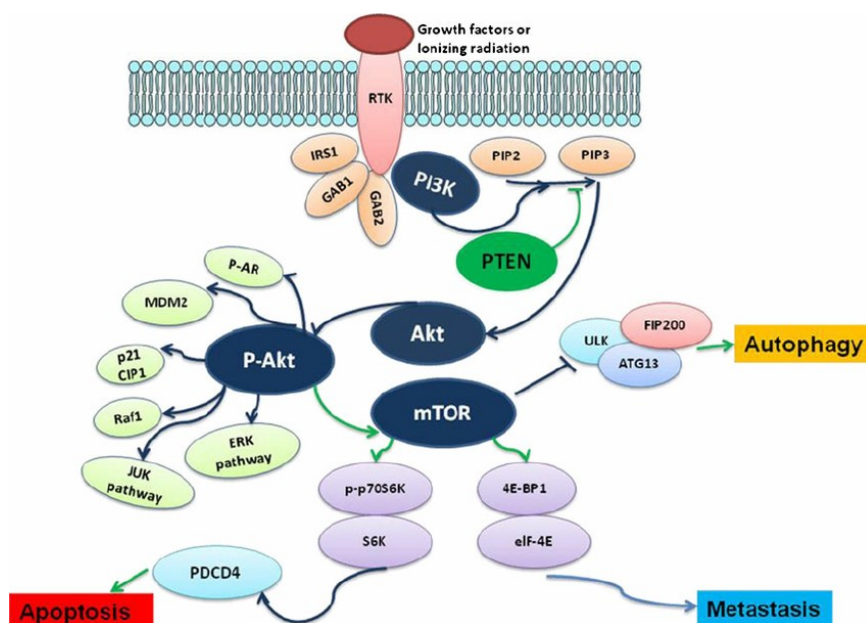


Figure 3. PI3K/Akt/mTOR signaling pathway in the regulation of cancer metastasis, apoptosis and autophagy (Chang et al., 2014).

Anti-epileptic **valproic acid (VPA)** has also been showed to attenuate cancer cell invasion and migration. This classic histone deacetylase (HDAC) inhibitor at 1 mM is capable to reverse Epithelial Mesenchymal Transition (EMT) induced by irradiation on ESCC cells (Kanamoto et al., 2016).

An oral antipsychotic agent, **penfluridol (PFD)**, used for schizophrenia treatment (Soares & Lima, 2006) has been found to reduce cancer cell migration and invasion through downregulation of Integrin $\alpha 6$ and uPAR (i.e., urokinase plasminogen activator surface receptor) levels and suppression of the expression of epithelial-to-mesenchymal transition (EMT) factors, vimentin and Zeb1 (via inhibiting GLI Family Zinc Finger 1 (GLI1) expression), at 2 μ M concentration (Kim et al., 2019). Penfluridol's anti-metastasis activity has been confirmed in an orthotopic human bladder cancer xenograft model at PFD concentrations equivalent to 130 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{week}^{-1}$ (Horst et al., 2020).

Fluspirilene, one of classic antipsychotic drugs that inhibits dopamine D2 receptor and sedates the positive symptoms of schizophrenia, has been demonstrated to suppress invasion of glioma cells in a dose-dependent manner (at 1.5 and 3 μ M) as well as in the model mice (Dong et al., 2017). The effects were associated with the inactivation of the signal transducer and activator of transcription 3 (STAT3) (Dong et al., 2017).

Another antipsychotic, **pimozide**, primarily approved by the FDA for the treatment of Tourette syndrome (Shapiro et al., 1987; Sultana & McMonagle, 2000), acts by blocking the postsynaptic dopamine receptor D2 in central nervous system (CNS), apart from its action as a calcium channel blocker (Dees et al., 2020; Quezada & Coffman, 2018). Studies report that 10 μ M pimozide shows considerable anti-cancer activity including suppression of cell migration in prostate cancer cell lines (Zhou et al., 2016), as well as of cell invasion in TNBC through inhibition of phosphorylated signal transducer and activator of transcription 3 (STAT3) (Dees et al., 2020). Phosphorylation on tyrosine, particularly Tyr705, makes it possible for STAT3 to be translocated into the cell nucleus, where it acts as a transcription factor for matrix metalloproteinase-9 (MMP-9) and vimentin genes, whose products are important for cancer cell migration and invasion. Therefore, lower protein expression of these downstream STAT3 targets, leads to the observed decrease in metastatic progression (Dees et al., 2020).

Another possible pimozide action mechanism is related to cellular cytoskeleton functions. Invasive cell migration requires the formation of various cytoskeletal structures, the actin assembly for which is regulated by specialized actin nucleation factors (Nürnberg et al., 2011). One of them, Actin-related protein 2/3 complex (Arp2/3), consisting of Arp2, Arp3, and Arp2/3 components 1-5 (ARPC1-5) (Gross, 2013; Machesky et al., 1999), is a key regulator of actin nucleation and branching for actin cytoskeletal reorganization (Rohatgi et al., 1999). Particularly ARPC2 is a subunit required for maintaining the structural integrity of the entire Arp2/3 complex, and its expression typically associates with metastasis and poor prognosis of patients with melanoma (Hanniford et al., 2015) or gastric tumors (Zhang et al., 2017b). Recently, a group of researchers have identified pimozide as a migrastatic and thus anti-metastatic drug due to its activity as an ARPC2 inhibitor via direct binding to ARPC2. A dissociation of interaction between ARPC2 and vinculin suppresses focal adhesion, and thus blocks migration (Choi et al., 2019). Besides, pimozide suppresses migration through inhibition of Wnt/ β -catenin signaling pathway (Ren et al., 2018).

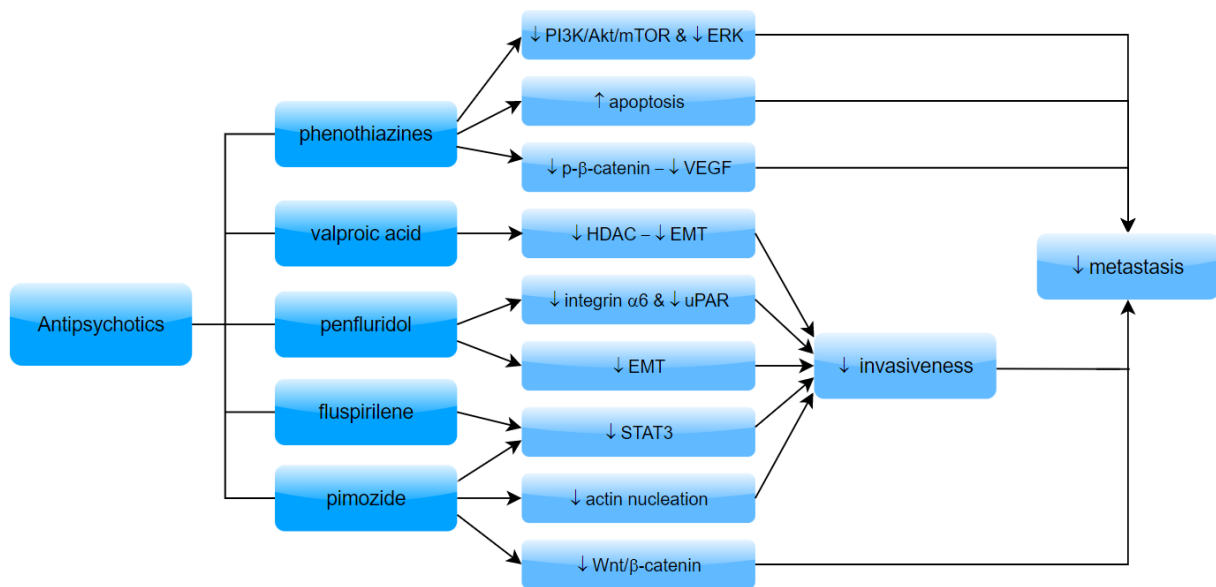


Figure 4. Molecular and cellular mechanisms of the metastasis inhibition by selected antipsychotics.

Collectively, these results suggest that antipsychotics display significant anti-metastatic activity and could be potentially repurposed for the metastasis treatment. In particular, pimozide is an important potential metastasis inhibitor, to date known to function via two different mechanisms. One of them, similar to that of niclosamide, aims at the suppression of phosphorylated STAT3, including a decrease in activity of matrix metalloproteinases; while the other impairs actin polymerization and cytoskeleton reassembly required for formation of invadopodia through the direct binding to ARPC2, a subunit of Arp2/3 complex (see Figure 4).

4.2. Antidepressants

Antidepressants are medications that can help relieve symptoms of depression, social anxiety disorder, anxiety disorders, seasonal affective disorder, and dysthymia, or mild chronic depression, as well as other conditions. They aim to correct chemical imbalances of neurotransmitters in the brain that are believed to be responsible for changes in mood and behavior. There are many types of antidepressants, so the focus will be made on those which have been shown to exhibit some anti-metastatic activity.

Regarding *tricyclic antidepressants (TCAs)*, **imipramine**'s anti-invasive and anti-metastatic activities have been recently demonstrated (Albuquerque-González et al., 2020). Fascin1 is a key protein in actin bundling that plays a crucial role in protease-dependent invasion and is overexpressed in different cancer types with poor prognosis (Conesa-Zamora et al., 2013; Esnakula et al., 2014; Rodríguez-Pinilla et al., 2006; Wang et al., 2016). 10-20 μ M imipramine acts as a fascin1 inhibitor, affecting actin cytoskeleton and lamellipodia formation,

thus reducing migration and invasion of colorectal cancer cells in vitro (Albuquerque-González et al., 2020). In addition, Munson et al. reported the impact of imipramine on glioblastoma (GBM) cells' invasion via inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated reactive oxygen species (ROS) generation and alternating expression of actin regulatory elements (Munson et al., 2012). Other mechanisms involved in cellular migration and invasion in glioma are Cl^- and K^+ secretions through ion channels localized to lipid raft domains on invadopodia, since the voltage-dependent potassium (K_v) channels are known as the main members of potassium channels usually expressed in tumors but not in the normal cells outside the CNS (Abadi et al., 2022). Imipramine can attach to the intracellular $\text{K}_v10.1$ pocket, which subsequently stops both the channel's function and cellular migration (Lefranc et al., 2012). Besides, 10 μM imipramine and 10 μM **amitriptyline**, as glycolysis inhibitors, reduce tumor invasiveness through suppressing lactate accumulation, since lactate decreases pH in tumor microenvironment, which leads to enhanced tumor invasion and inhibition of T-cell motility (Bielecka-Wajdman et al., 2018; Haas et al., 2015). Thus, disturbing glycolysis and decreased lactate concentration can be effective strategies for improving the functionality of immune cells in the tumor and reducing tumor invasiveness (Abadi et al., 2022). It is also relevant to mention that the therapeutic levels of plasma TCAs used in the treatment of depression are estimated to range between 0.3 and 1 μM (Budziszewska et al., 2004; Glotzbach & Preskorn, 1982). Both amitriptyline and imipramine also decrease the expression of p56/NF- κB (i.e., p56/nuclear factor kappa-light-chain-enhancer of activated B cells), which in turn represses the activation of genes that promote cell migration (Troib & Azab, 2015).

As to *selective serotonin reuptake inhibitors (SSRIs)*, **fluvoxamine** is considered as an effective drug to suppress actin polymerization with $\text{IC}_{50} \sim 30 \mu\text{M}$ (Hayashi et al., 2016). Initially administered for depression, anxiety disorders, and obsessive-compulsive disease (OCD), it has been later demonstrated to suppress cell migration via preventing serum-induced lamellipodia formation independently of its anti-proliferation potency. 40 μM fluvoxamine could also manifest its anti-invasive activity by inhibiting focal adhesion kinase (FAK) and AKT/mTOR signaling pathways, which eventually disrupts actin polymerization with no significant toxicity for normal cells (Hayashi et al., 2016). Interestingly, a clinical dose of fluvoxamine administered for the treatment of depression (Bolo et al., 2000) is 100–300 mg/day, which is thus sufficient to prevent invasion of GBM cells (Hayashi et al., 2016).

Escitalopram is another SSRI mainly used for treating major depressive disorders (MDDs) and anxiety disorders. 0.1–0.4 mM escitalopram has been indicated to reduce the invasiveness of U87MG cells (Chen et al., 2018). In particular, it has been shown to significantly induce mitochondria-dependent apoptotic signaling cascades (Chen et al., 2018; Yuan et al., 2018) and autophagy in different cancer cell lines (Chen et al., 2018).

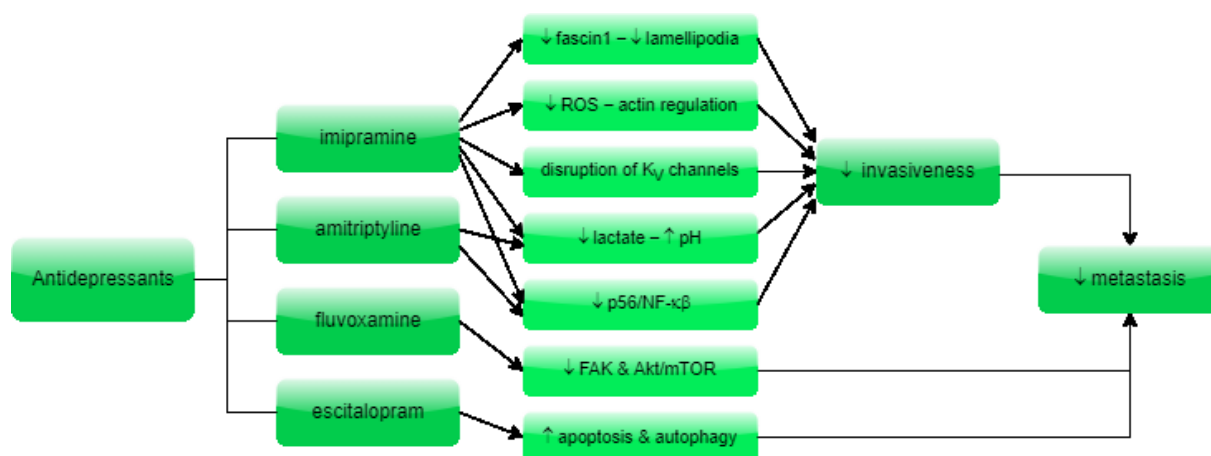


Figure 5. Molecular and cellular mechanisms of the metastasis inhibition by selected antidepressants.

To summarize, across the rich variety of existing approved antidepressants, some of them are high-potential metastasis inhibitors. Hereby, imipramine and amitriptyline, both examples of TCAs, demonstrate significant anti-invasive and anti-metastatic activities by either preventing lamellipodia formation, inhibiting potassium channels, suppressing lactate accumulation, or decreasing the expression of p56/NF- κ B. SSRIs, particularly fluvoxamine, which suppresses cell migration and invasion via affecting actin polymerization, and escitalopram, should also be considered as potential inhibitors of cancer cell invasion and metastasis (see Figure 5).

4.3. Beta-blockers

Beta-blockers (BBs) are a class of medications predominantly used in the treatment of cardiovascular diseases. They act as competitive antagonists of adrenergic beta receptor sites for the endogenous catecholamines, such as epinephrine (adrenaline) and norepinephrine (noradrenaline), that mediate the sympathetic nervous system response to acute stress (Frishman et al., 2005). A distinction is made between non-selective BBs, which block activation of all types of β -adrenergic receptors, and the ones selective for one of the three known types of beta receptors, designated β_1 , β_2 and β_3 receptors (Frishman et al., 2005).

Propranolol (PRO) is a nonselective beta-blocker displaying both β_1 and β_2 antagonism. It was approved for medical use in 1964 and currently is one of most commonly prescribed BBs in the US (*The Top 300 of 2019*, 2021, p. 300). PRO has been repeatedly reported to act as an anti-metastatic agent in different types of cancer via multiple mechanisms. Data from a number of in vivo models has shown that 10 μM PRO (a daily dose of 1 $\mu\text{mol}/100$ g bodyweight) may reduce the rate of metastasis in breast and other cancers via direct effects on beta-adrenergic signaling (Glasner et al., 2010; Palm et al., 2006; Sloan et al., 2010; Strell et al., 2012).

Lamkin et al. found that chronic stress enhanced tumor growth and dissemination of acute lymphoblastic leukemia (ALL) and that the effect could be inhibited by PRO (in equimolar concentrations to norepinephrine) (Lamkin et al., 2012). Masur et al. demonstrated that while norepinephrine caused a dose dependent (at 1, 10, and 100 μM) increase in the number of migrating colon carcinoma cells, treatment with PRO abolished this increase (Masur et al., 2001). 30 mM PRO has also been shown to inhibit the expression of the tissue remodeling factor matrix metalloproteinase-2 (MMP-2) and the pro-angiogenic VEGF in human leukemia cell lines (Hajighasemi & Hajighasemi, 2009). In nasopharyngeal carcinoma cell lines Yang et al. confirmed that 10 μM norepinephrine upregulates levels of metalloproteinases (specifically MMP-2 and MMP-9) and VEGF and increases cell invasiveness, while treatment with 1 μM PRO inhibits all of these effects (Yang et al., 2006). Inhibition of MMP-9 secretion by PRO has also been found in human brain microvascular endothelial cells with an IC_{50} of ~ 8.1 μM (Annabi et al., 2009).

There are several molecular mechanisms of propranolol's action. Firstly, it was proved to reduce cancer invasiveness via inhibition of the norepinephrine-induced upregulation of MMP-2 and MMP-9 (Barbieri et al., 2015; Guo et al., 2009; Kim-Fuchs et al., 2014; Liao et al., 2010; Moretti et al., 2013; Sood et al., 2006; Yang et al., 2006). Decrease in activity of MMPs could result in decrease in metastasizing, as they mediate degradation of the extra-cellular matrix and other pro-metastatic processes (Conlon & Murray, 2019; Shay et al., 2015).

Additionally, BBs interfere with cyclic adenosine monophosphate (cAMP) and Ca^{2+} signaling decreasing tumor cell invasion (Pon et al., 2016). Activation of the β_2 -adrenoceptor ($\beta_2\text{AR}$), a predominantly $\text{G}\alpha_s$ -coupled receptor, in response to endogenous and $\beta_2\text{AR}$ -selective agonists has been found to increase cAMP production (Madden et al., 2011; Vandewalle et al., 1990) due to $\text{G}\alpha_s$ activation of adenylyl cyclase (AC) (Pon et al., 2016). Apart from this, $\beta_2\text{AR}$

activation increases intracellular Ca^{2+} by 2 pathways: directly via $\text{G}\beta\gamma$ subunits and indirectly via cAMP effectors – protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac), which further increase intracellular Ca^{2+} levels, and elevated Ca^{2+} leads to further stimulation of AC and additional increase in cAMP to amplify the signal (Pon et al., 2016). As can be seen from Figure 6, together these effects basically form a highly amplified positive feedforward loop between the cAMP increase and Ca^{2+} mobilization activated by an initial G-coupled $\beta_2\text{AR}$ (Pon et al., 2016). Since PKA promotes tumor cell invasion via phosphorylation, and thus activation, of Src, a tyrosine protein kinase involved in the regulation of cell survival, motility, and invasion (Beristain et al., 2015; Liu et al., 2015), as well as Epac is important for cancer cell migration and invasion either due to supporting formation of invadopodia (Harper et al., 2010) or also regulation of Src kinase activity (Shi et al., 2010), these two cAMP effectors have been linked to increased tumor cell invasion (Pon et al., 2016). In highly metastatic variant of human breast adenocarcinoma cells (MDA-MB-231HM), activation of this positive feedforward loop independently mediates increased cell invasion and highly efficient inhibition of phosphorylated ERK (Pon et al., 2016), which may reduce cell proliferation and/or tumor growth (Bruzzzone et al., 2014; Carie & Sebt, 2007; Pérez Piñero et al., 2012).

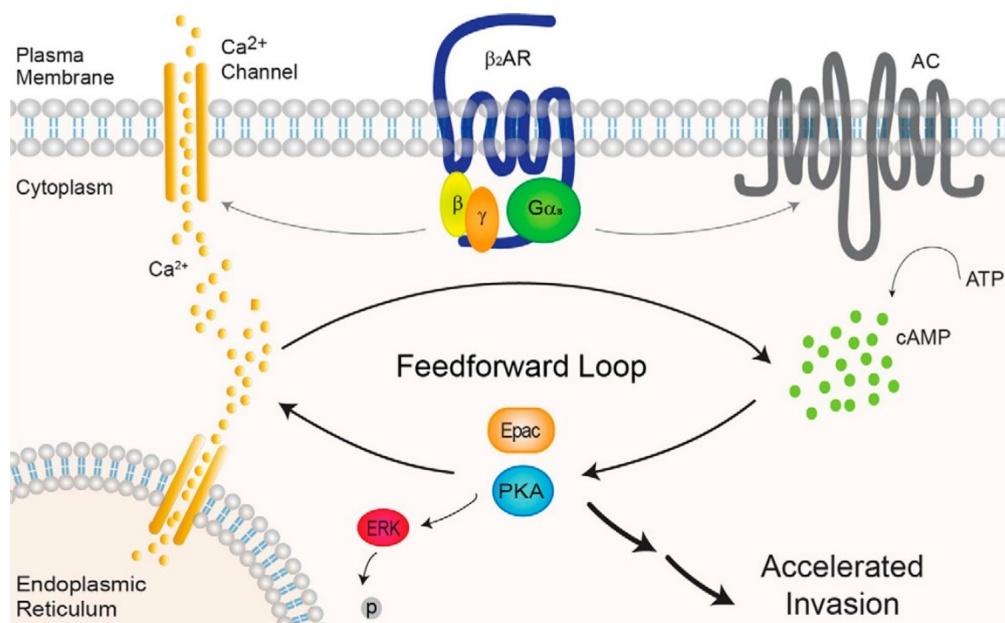


Figure 6. Positive cAMP/ Ca^{2+} loop leads to increased invasion of tumor cells (Pon et al., 2016).

Increased catecholamine signaling (via treatment with 10 μM norepinephrine) was shown to induce EMT mediated by transforming growth factor beta 1 (TGF- β 1) (Shan et al., 2014; Smith & Bhowmick, 2016). 10 μM PRO inhibits the increase in TGF- β 1 and partially decreases the migration and invasiveness of norepinephrine-treated cells (Zhang et al., 2016).

0.05 μM BBs also inhibit the rate of invadopodia formation induced by β_2 adrenergic signaling (Creed et al., 2015).

25 μM PRO could reduce the level of migration by increasing cell-cell adhesion via Rap1B (a small guanosine triphosphatase (GTPase) stabilizing contacts between cells), which is normally activated by adrenergic signaling (Linden, 2013; Ntantie et al., 2013; Wilson et al., 2015). PRO also reverses the catecholamine signaling-promoted creation of a ‘metastatic niche’, on which the process of metastasis depends, probably via the downregulation of receptor activator of nuclear factor kappa-B ligand (RANKL) (Barcellos-Hoff et al., 2013; Campbell et al., 2012; Psaila & Lyden, 2009).

Combination of 5 μM propranolol and 5 mM metformin, both of which are high-potential anti-metastatic repositioned drugs, has been observed to decrease migration and invasion in triple negative breast cancer models, with no symptoms of toxicity (Rico et al., 2016). It has been also shown that a combination of β -adrenergic blockade (via daily treatment with 20 mg propranolol) with cyclooxygenase-2 (COX-2) inhibition provides a safe and effective strategy for inhibiting multiple cellular and molecular pathways related to metastasis and disease recurrence in early-stage breast cancer (Shaashua et al., 2017).

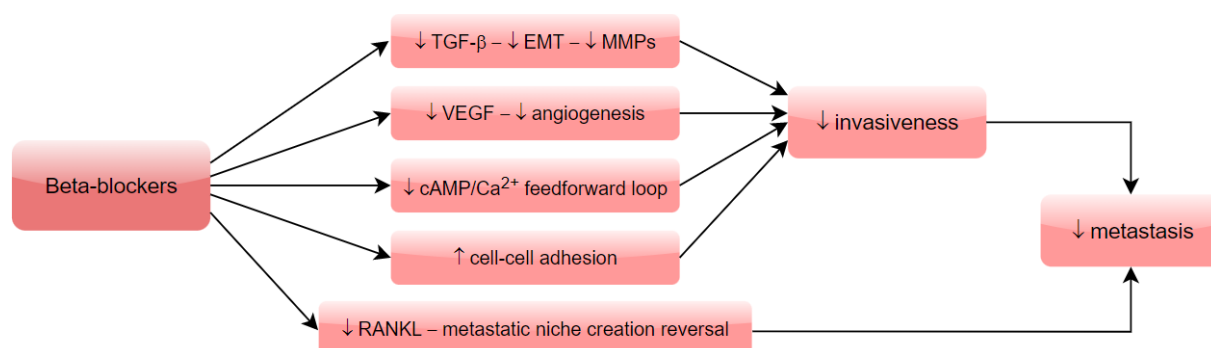


Figure 7. Molecular and cellular mechanisms of the metastasis inhibition by beta-blockers.

To summarize, addition of propranolol, and beta-blockers in general, to standard cancer care is a promising strategy to reduce the rate of metastatic spread (see Figure 7). As the sympathetic nervous system has been identified as a novel neural regulator of cancer metastasis, new strategies for anti-metastatic therapies that target beta-adrenergic induction of pro-metastatic gene expression are of considerable value.

4.4. Statins

Statins, competitive inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), prevent the synthesis of cholesterol and its precursors and, thus, are widely used for the treatment of hypercholesterolemia. High plasma low density lipoprotein (LDL)-cholesterol is a risk factor of cardiovascular diseases and, therefore, cholesterol-lowering drugs are used to prevent them (Shitara & Sugiyama, 2006; Yeganeh et al., 2014). It has been shown by many studies that statins have potent cholesterol-lowering effects and reduce the risk of cardiovascular diseases in everyday medical practice (Bertolini et al., 1997; Sacks et al., 1996; Scandinavian Simvastatin Survival Study Group, 1994; Shepherd et al., 1995; The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998).

Today, many evidences indicate the anti-tumor activity of statins (Pavan et al., 2015), which may be related to the promotion of apoptosis, inhibition of cell growth, cell proliferation and prevention of metastasis (Hindler et al., 2006). Statins-induced prevention of metastasis could be in part caused by their anti-angiogenic effects, particularly, the down-regulation of VEGF, inhibition of cell adhesion to the extracellular matrix and inhibition of endothelial cell proliferation (Dulak & Józkwicz, 2005). As cholesterol is important in blood vessel formation, its downregulation by statins leads to repression of cancer cell angiogenesis, and thus metastasis. Statins could also interfere with EMT, a process causing the loose of cell adhesiveness, dissolution of ECM, and thereby promotion of metastasis (Chen et al., 2017). In their study of prostate cancer cell line, Deezagi & Safari observed that 50 μ M **rosuvastatin** (one of drugs from the statin family) induced a change in the gene expression via a decrease of Vimentin and ZEB-1 expression and an increase of E-cadherin expression – the alteration typical for switching the pattern of gene expression from EMT to MET (Deezagi & Safari, 2020).

Apart from impeding cholesterol synthesis, inhibition of HMGCR by statins blocks the synthesis of isoprenoid intermediates such as farnesylpyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) (Goldstein & Brown, 1990), both of which serve as important lipid attachments for the posttranslational modification of a variety of proteins, including those of the Rho GTPase family (Aelst & D'Souza-Schorey, 1997). These small GTP-binding proteins, which control cytoskeleton remodeling via regulating actin polymerization, depolymerization and the activity of actin-associated myosins (Ridley, 2001), play key roles in coordinating cellular responses required for cell migration (Riganti et al., 2008). Isoprenylation is critical for

their proper function and intracellular trafficking (Hall, 1998) – RhoA/B/C, for example, must be isoprenylated in order to interact with their effectors (Riganti et al., 2008). In other words, by inhibiting HMG-CoA reductase, statins impede the synthesis of isoprenoid intermediates thereby preventing isoprenylation of small GTPases, leading to the inhibition of these signaling molecules, consequently hindering cell migration (Rikitake & Liao, 2005).

Another statin, known as **lovastatin**, has been proved to downregulate genes involved in stemness and invasiveness of mammary tumors. In particular, it inhibited sex-determining region Y (SRY)-box transcription factor 2 (SOX2) promoter transactivation, and reduced the efficiency of mammosphere (mammary epithelial stem cell aggregates) formation and the percentage of ALDH⁺ cells (i.e., with high aldehyde dehydrogenase activity, which is known as a cancer stem cell marker (Zou et al., 2012)) (Vásquez-Boehm et al., 2019). The authors suppose that targeting of cancer stem cells (CSCs) by lovastatin was mediated by the inhibition of HMGCR (Vásquez-Boehm et al., 2019).

In addition, Vainio et al. in their work on E-26 transformation-specific (ETS)-related gene (ERG) positive prostate cancers reported that treatment with 10 μ M statins potentiates anti-migratory effects of phospholipase A2 group VII (PLA2G7) silencing (Vainio et al., 2011). The researchers identified PLA2G7 as a biomarker and a potential anti-metastasis drug target, because it promotes prostate cancer cell migration and invasion. Thus, combining PLA2G7 inhibition with the use of statins could be a promising approach in prostate cancer management (Vainio et al., 2011).

However, there is a growing evidence that statins can cause significant, reversible neurocognitive or psychiatric side effects (Evans & Golomb, 2009; Galatti et al., 2006; Golomb et al., 2004; King et al., 2003; Tatley & Savage, 2007; Wagstaff et al., 2003). Kraft et al. in their investigation (Kraft et al., 2013) showed that all four of four statin compounds tested caused a unique, reversible neurotoxic morphological effect characterized by intraneurite nodules containing aggregations of organelles [‘beads-on-a-string’ (BOS)]. Statin-induced neurotoxicity is enhanced by deficiency of fascin, the actin-bundling protein, whose activity drives filopodia formation, cell-shape changes and cell migration (Kraft et al., 2013). Therefore, fascin-pathway enhancers may attenuate the side effects of statins. In contrast, small-molecule inhibitors of fascin block tumor metastasis in animal models. The researchers also screened a library of known drugs, many of which are FDA-approved, and identified 34 fascin-pathway blockers with potential anti-metastasis activity (Kraft et al., 2013). In other words, fascin

regulation is a double-edged sword, which can reduce neurotoxicity of statins when fascin is upregulated, but impair metastasis when downregulated.

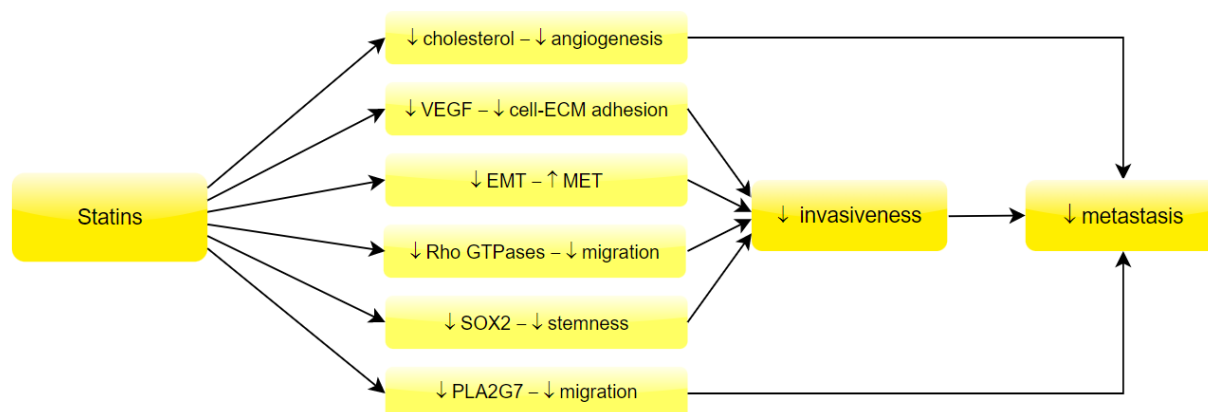


Figure 8. Molecular and cellular mechanisms of the metastasis inhibition by statins.

In conclusion, statins have a high potential to inhibit cancer cell invasiveness and metastasis due to their effects on preventing EMT, inhibition of HMGCoA reductase (see Figure 8), but may lead to neurotoxicity, especially when the fascin regulation is increased.

5. Clinical studies

In order to obtain a more complete picture of the issue, it was relevant to examine whether there are any cancer-related clinical trials of the studied medications. As shown in Table 1, there are some ongoing or completed clinical studies of cancer on these drugs, but currently only few of them are focused in particular on interactions with cancer invasiveness or metastasis. The selected substances are broadly used in present days for treating widespread illnesses due to their original indications, such as diverse psychotic disorders, depressions or cardiovascular diseases; and at the same time, according to the research, they have certain anti-metastatic properties. This poses a great possibility for combining anti-cancer therapy with treatments of currently quite common diseases, and provides us with a clear understanding that more studies must be made in future to determine precise anti-metastatic efficacies of these drugs.

Table 1. A total panel of the described repurposed drugs, their original applications, reported target molecules or pathways, and cancer-targeted clinical trials. ↓ = drug-caused downregulation (inhibition), ↑ = drug-caused upregulation. The last column contains ClinicalTrials.gov identifiers of ongoing or recently completed clinical studies of each particular drug, which are related either particularly to metastasis (normal black font), or to cancer in general (in gray font).

Group of drugs	Repurposed drug	Original application	Cancer invasiveness and metastasis-related targets/pathways reported to be affected by a drug	Clinical trials of cancer
Anti-psychotics	Thioridazine	D2 antagonist	↓ Caspase-3 and Bax, ↑ Bcl-2, ↓ mitochondrial membrane potential (all leading to apoptosis)	NCT02096289 (Aslostovar et al., 2018)
	Trifluoperazine	Schizophrenia, anxiety, and other psychotic disorders treatment	↓ phosphorylation of AKT and β-catenin (Ser ⁵⁵²) leading to less nuclear relocation, ↓ VEGF (likely via D2)	-
	Fluphenazine	Chronic psychoses, such as schizophrenia	Direct anti-cancer target remains elusive, but possibly ↑ ROS leads to cell cycle arrest, DNA damage and apoptosis	NCT00821301, NCT00335647
	Valproic acid	Anti-epileptic	HDAC inhibitor (↓ histone deacetylation), reverses EMT	NCT01106872, NCT02624128 (Caponigro et al., 2016)
	Penfluridol	Schizophrenia treatment	↓ Integrin α6 and uPAR, ↓ EMT factors (vimentin and Zeb1) via ↓ GLI1	-
	Fluspirilene	D2 inhibitor, schizophrenia treatment	Inactivation of STAT3 (↓ invasion)	-
	Pimozide	Tourette syndrome treatment	↓ p-STAT3 (↓ TFs for MMP-9 & vimentin leading to ↓ migration), ↓ ARPC2 (↓ actin nucleation), and ↓ Wnt/β-catenin signalling	-
Tricyclic anti-depressants	Imipramine	Treatment of depression, anxiety and panic disorder	Fascin1 inhibitor (affects actin cytoskeleton and lamellipodia formation), ↓ ROS generation, disturbing K _v channels' function, ↓ lactate (↓ invasion, ↑ T-cell motility), ↓ p56/NF-κβ (↓ migration)	NCT04863950, NCT03122444
	Amitriptyline	Major depressive disorder and pain syndromes treatment	↓ lactate (↓ pH leading to ↓ invasion and ↑ T-cell motility), ↓ p56/NF-κβ (↓ migration)	-
Selective serotonin reuptake inhibitors	Fluvoxamine	Depression, anxiety disorders, and OCD	Inhibition of FAK and AKT/mTOR signaling (all disrupts actin polymerization and prevents lamellipodia formation)	-
	Escitalopram	MDDs and anxiety disorders treatment	Induction of mitochondria-dependent apoptotic signaling cascades and autophagy	-
Beta-blockers	Propranolol	Cardiovascular diseases treatment	↓ MMP-2, ↓ MMP-9, ↓ VEGF, ↓ TGF-β1 (↓ EMT), ↑ cell-cell adhesion via Rap1B, ↓ RANKL (reverses "metastatic niche" creation)	NCT04005365, NCT01847001, NCT04493489, NCT03838029 (Shaashua et al., 2017), NCT03919461, NCT04288700, NCT03245554, NCT00502684, NCT01988831, NCT03323710, NCT03523650
Statins	Rosuvastatin	Hyper-cholesterolemia treatment	Changes in gene expression typical for switching from EMT to MET, e.g., ↓ Vimentin, ↓ ZEB-1, ↑ E-cadherin, ↓ Rho GTPases	NCT01011478, NCT00966472 (Goss et al., 2016), NCT04491643
	Lovastatin		↓ genes involved in stemness and invasiveness, e.g., SOX2, ↓ Rho GTPases	NCT02862470

6. Conclusion

To date, metastatic disease remains the primary cause of cancer-related mortality and therefore the search for anti-metastatic agents is of considerable value (Coghlin & Murray, 2010). Considering that discovery of new drugs for cancer treatment is an expensive and time-consuming process and the percentage of drugs reaching the clinic is quite low, drug repositioning appears to be a beneficial approach. Basically it refers to the identification and development of new uses for existing drugs and represents an alternative drug development strategy, which requires much less time and money, but faces new obstacles on its way as well. Challenges negotiating intellectual property, shelving the compounds that failed at some phase of clinical trials sophisticate the process considerably, but may be facilitated by collaborative initiatives, shared libraries and databases etc., which can truly benefit the process of drug repositioning.

The research conducted in this work elucidates the drug candidates with high potential for repurposing. Antipsychotics, such as phenothiazines (THD, TFP, FLZ), VPA, PFD, and pimozide, proved to have a high therapeutic value of inhibiting metastasis via various mechanisms described above. Tricyclic antidepressants (in particular imipramine and amitriptyline), as well as SSRIs (such as fluvoxamine and escitalopram), demonstrate significant anti-invasive activities primarily by affecting actin cytoskeleton and lamellipodia formation, but some of them may also function through inhibiting potassium channels, suppressing lactate accumulation, or decreasing the expression of p53/NF- κ B. Beta-blockers, or competitive antagonists of adrenergic beta receptors, are one of the most promising classes of compounds, since the correlation between sympathetic nervous system, stress and cancer metastasis regulation has been identified. Propranolol, one of BBs, acts via different mechanisms including inhibition of the catecholamine-induced upregulation of MMP-2 and MMP-9, interfering with cAMP and Ca^{2+} signaling, impairment of EMT mediated by TGF- β 1, and increasing cell-cell adhesion via Rap1B. Statins, particularly rosuvastatin and lovastatin, are also high-potential cancer cell invasiveness inhibitors as they are able to prevent EMT and reduce levels of HMGCoA reductase, thus inhibiting Rho GTPases and affecting cell migration.

All in all, this work provides a clear conclusion that drug repurposing deserves special attention, as it can definitely simplify the search for anti-metastatic drugs, perhaps even become the solution for some of those who suffer from early stages of cancer, when inhibition of cancer cell invasiveness is crucial for patient's survival. For now, a lot of published studies

demonstrate the great potential of repositioning strategies, although many of the compounds proved their efficacy only in specific types of cancer. Therefore, the issue requires further research, but is certainly worth exploring.

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