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Review article

Cancer metastases: Tailoring the targets

Manasi S. Pote [1], Deepshikha Singh [1], Aparna M. A [1], Jully Suchita [1], Rajesh N. Gacche [*]

Department of Biotechnology, Savitribai Phule Pune University, Pune, Maharashtra, India

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ABSTRACT

Metastasis is an intricate and formidable pathophysiological process encompassing the dissemination of cancer cells from the primary tumour body to distant organs. It stands as a profound and devastating phenomenon that constitutes the primary driver of cancer-related mortality. Despite great strides of advancements in cancer research and treatment, tailored anti-metastasis therapies are either lacking or have shown limited success, necessitating a deeper understanding of the intrinsic elements driving cancer invasiveness. This comprehensive review presents a contemporary elucidation of pivotal facets within the realm of cancer metastasis, commencing with the intricate processes of homing and invasion. The process of angiogenesis, which supports tumour growth and metastasis, is addressed, along with the pre-metastatic niche, wherein the primary tumour prepares for a favorable microenvironment at distant sites for subsequent metastatic colonization. The landscape of metastasis-related genetic and epigenetic mechanisms, involvement of metastasis genes and metastasis suppressor genes, and microRNAs (miRNA) are also discussed. Furthermore, immune modulators' impact on metastasis and their potential as therapeutic targets are addressed. The interplay between cancer cells and the immune system, including immune evasion mechanisms employed by metastatic cells, is discussed, highlighting the importance of targeting immune modulation in arresting metastatic progression. Finally, this review presents promising treatment opportunities derived from the insights gained into the mechanisms of metastasis. Identifying novel therapeutic targets and developing innovative strategies to disrupt the metastatic cascade holds excellent potential for improving patient outcomes and ultimately reducing cancer-related mortality.

1. Cancer metastasis: colonial intentions of cancer cells

Metastasis orchestrates the systemic dissemination of new tumours in a distant organ within the human body. This sophisticated and multistep phenomenon unfolds through an eloquent choreography of cancer cell homing and invasion, deftly navigating the complexities of survival within the vascular milieu, poised attachment to distant host tissue or organ, ultimately culminating in the formidable stage of colonization. Throughout each juncture of this intricate progression, cancer cells must elude the cognizant and vigilant onslaught of the immune surveillance apparatus, skillfully evading recognition and eluding the lethal intentions of immune cells. The highly diverse repertoire of intra-tumoural immune cells [1] and their transient, elusive and inscrutable paracrine signalling is one of the hindrances in deciphering the metastatic potential of cancer cells in concert with the tumour microenvironment (TME)

* Corresponding author.
E-mail addresses: rngacche@unipune.ac.in, rngacche47@gmail.com (R.N. Gacche).
[1] Contributed equally.

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Abbreviations

Tumour microenvironment (TME)
Cancer stem cells (CSCs)
Epithelial-to-mesenchymal transition (EMT)
Circulating Tumour Cells (CTCs)
Matrix Metalloproteinase (MMPs)
Metastatic suppressor gene (MSGs)
Extracellular matrix (ECM)
Mono-carboxylate transporter 1 (MCT1)
C-X-C motif chemokine 12 (CXCL12)
C-X-C chemokine receptor type 4 (CXCR4)
Insulin-like growth factors type 1 receptor (IGF-IR)
Receptor activator of nuclear factor-kappa B ligand (Anti-RANKL)
B cell lymphoma-2 (Bcl-2)
Bcl-2-associated death promoter (Bad)
Bcl-2-associated X protein (Bax)
Bcl-2-interacting domain (Bid)
Bcl-2-interacting mediator of cell death (Bim)
Tumour necrosis factor (TNF)-related-apoptosis-inducing ligand (TRAIL)
Death-inducing signaling complex (DISC)
Enhancer of zeste homolog2 (EZH2)
Adherent-to-Suspension Transition
(AST)
High-endothelial venules (HEVs)
Peripheral node addressin (PNAd)
Secreted Protein, Acidic and Rich in Cysteine (SPARC peptides)
Human epidermal growth factor receptor type 2 (Her2)
Pre-metastatic niche (PMN)
Bone marrow-derived dendritic cells (BMDCs)
Liver cancer stem cells (LCSCs)
Hepatocellular carcinoma (HCC)
Highly upregulated in metastatic TNBC (HUMT)
HOX transcript antisense RNA (HOTAIR)
X inactivate-specific transcript (XIST)
methyltransferase-like 14 (METTL14)
Gallbladder cancer (GBC)
Pancreatic neuroendocrine tumours (PNETs)
carboxyl-terminal domain (CTD)
Nanoparticles (NPs)
T cell receptor (TCR)
Cytotoxic T lymphocytes (CTLs)
Natural Killer Cells (NK cells)
Chimeric antigen receptor T cells (CAR-T cells)
Tumour-associated macrophages (TAM)
Photodynamic diagnostic (PDD)
Single-cell sequencing (SCS)

[2]. Despite the efforts towards understanding this pathophysiological process, there is limited success in targeting and arresting this lethal process. Cancer metastasis has been ranked as a primary culprit of death in the majority of cancer patients and low survival rates in patients who are diagnosed in the metastatic stage [3]. The advent of sensitive detection and diagnostic methods has refuted the earlier notion that tumours must attain a specific size to penetrate regional vessels before releasing cells into circulation. It is now known that tumours shed cancer cells into the blood or lymph stream from the earliest stages of growth [4].

The pursuit of tailoring and formulating targeted anti-metastatic agents requires an understanding of the metastatic cascade, necessitating a profound comprehension of the intricate interplay between genetic instability, gene expression patterns, and the mosaic of tumour heterogeneity, as these enigmatic processes intricately intertwine with the inscrutable mysteries underpinning invasion and metastasis [5]. Cancer has been studied as an evolving ecosystem, with the past two decades of research in mainstream cancer biology revealing several molecular switches and mechanisms of cancer progression. Despite these advancements, a major obstacle in designing the anti-metastatic therapeutic regime is the array of factors involved in the orchestration of metastasis and the

limited understanding towards the complex molecular mechanisms involving several factors [3].

This review offers a comprehensive update and engages the scientific community in a nuanced discourse, delving into the intricacies behind the limited efficacy of anti-metastasis treatments. It illuminates emerging treatment prospects, providing a refined understanding of intrinsic determinants of invasiveness, ranging from the intricacies of homing and invasion to the pivotal facets of anchorage independence. The review also explores the dynamic interplay within tumour-host interactions, meticulously addressing the targeting of molecules such as addressins, chemokine receptors, and vascular peptide motifs. Finally, it highlights critical aspects of angiogenesis, the role of exosomes in the pre-metastatic niche, and the genetic and epigenetic underpinnings that govern the intricate regulation of metastatic processes (Fig. 1).

2. Poor success in anti-metastasis treatment endeavors: clinical success remains an intricate and complex puzzle

The current cancer landscape involves over 200 distinct cancer types, replete with nuanced subtypes, heterogeneous intricacies, and a kaleidoscope of pathophysiological characters [6]. Therefore, a personalized treatment guided by an individual's genetic profile is a rational approach for preventing, diagnosing, and treating the disease. A comprehensive survey undertaken in the year 2022 in the USA unraveled a staggering anticipated influx of approximately 1,918,030 novel incidences of cancer, along with a somber projection of over 609,360 mortalities. A 32 % decline in cancer cases can be attributed to improved early detection and treatment [7]. However, 1500 mortalities are still observed due to failure in managing and preventing cancer metastasis. Approximately 90 % of cancer patients succumb to death due to metastasis; one of the reasons is due to the poor prognosis of the disease [8]. To successfully treat metastasis, it is vital to inhibit the fundamental processes related to metastasis and develop specific strategies (clinical and preclinical) which do not rely on primary tumour responses.

The formidable impediments and inherent limitations encountered in the meticulous formulation of anticancer agents, meticulously tailored for the explicit purpose of stymying the rampant outgrowth of cancer metastasis, are multifaceted and stem from an intricate interplay of various discernible and inscrutable factors. A confluence of pharmacological intricacies, the labyrinthine complexity inherent in the pathology, and the complex pathogenicity of diseases underscores the underwhelming successes witnessed

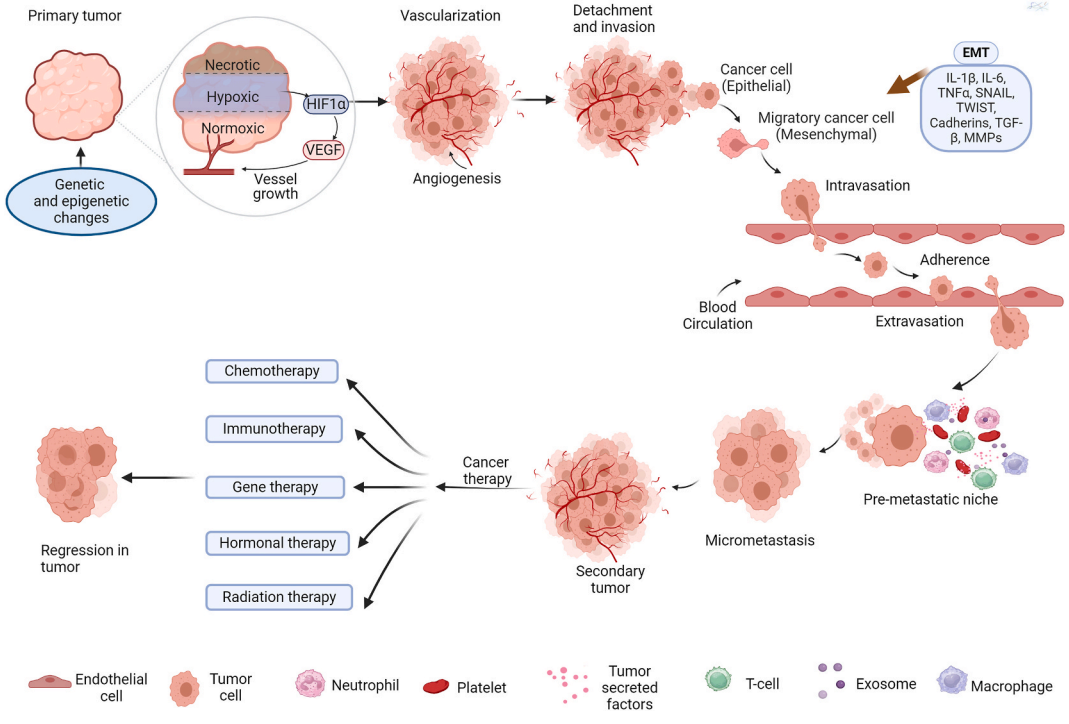

Fig. 1. Overview of cancer metastasis and therapy: The figure illustrates the progression of cancer metastasis from a primary tumor to secondary tumours and the various therapeutic strategies employed to combat cancer. Initially, genetic, and epigenetic changes lead to the formation of a primary tumor, characterized by regions of normoxia, hypoxia, and necrosis. Hypoxic conditions induce HIF1α, promoting VEGF-driven angiogenesis to supply the tumor with nutrients and oxygen. Cancer cells undergo epithelial-mesenchymal transition (EMT), facilitated by various signaling molecules, enabling them to detach, invade surrounding tissues, and enter the bloodstream. These circulating tumor cells then adhere to distant endothelial cells, exit the bloodstream, and form micrometastases. A pre-metastatic niche is established with the help of tumor-secreted factors, exosomes, and immune cells, preparing distant sites for colonization. Metastatic colonization occurs once a pre-metastatic niche has been established. Cells that successfully adapt to their microenvironment and resume proliferation successfully form secondary tumours. Micrometastases grow into secondary tumours, supported by angiogenesis. Various cancer therapies, including chemotherapy, immunotherapy, gene therapy, hormonal therapy, and radiation therapy, are depicted as methods to induce tumor regression and improve patient outcomes.

in antimetastatic treatments. Conspicuously absent from the repertoire of standard anti-cancer drugs, which encompasses immunotherapies, is a deliberate acknowledgment of the pharmaceutical potential to proactively thwart the insidious specter of metastasis. The potential targets for anti-metastatic drug development and discovery of preclinical targets have been elucidated. Still, it remains to be validated by preclinical models, owing to the complex pathogenicity of metastasis diseases in cancer patients. The pharmaceutical sector, confronted with setbacks in late-stage clinical development, has regrettably relegated the pursuit of anti-metastasis drugs, reflecting a prevailing trend. Notably, a preponderance of FDA-approved drugs, initially substantiated as potent anti-tumour agents through rigorous preclinical validation, embark on their clinical odyssey by enlisting cancer patients in advanced metastatic stages. Many anticancer drugs have not been initially tested in pre-clinical metastatic models. The therapeutic agents that target tumour growth might also target metastasis. In adjuvant trials, patients with aggressive disease phenotypes without knowledge of distant metastases are treated to arrest metastatic colonization, recurrence, and overall survival as endpoints of trial outcome. Another challenge is selecting clinical testing candidate anti-metastasis drugs with limited or no effect on the outcomes of conventional preclinical trials [6]. Numerous problems prevent the development of anti-metastatic drugs. Pharmaceutical companies need more access to effective, high-throughput technology for screening their compound library for potential anti-metastatic medications. Anti-metastatic drug development needs to be improved by several issues, such as pharmaceutical companies' limited access to high-throughput technologies for screening their compound libraries for prospective anti-metastatic therapies. Although animal models are widely used in several laboratories, many pharmaceutical corporations still need to create standardized practices. To achieve advancements in the mainstream of anti-metastatic drug development, a paradigm shift in clinical trial architectures may be effective, wherein the pivotal endpoint should be recalibrated to prioritize metastasis-free survival as the quintessential metric. For the development of anti-metastasis drugs, the primary endpoint must be adjusted to set metastasis-free survival [9].

Metastasis is a multi-factorial and multi-step pathway involving multiple cascades of reaction, wherein several inscrutable potential target molecules are yet to be identified. Nevertheless, a conspicuous lacuna exists in preclinical model studies designed to dissect the molecular intricacies of metastatic signalling, further imposing the challenges in developing anti-metastatic agents. Most of the potential metastasis-specific targets act as suppressors. Time and knowledge should be spent activating the suppressors instead of inhibiting the overactive effectors. The complexity of the disease plays a crucial role. It is challenging to design agents targeted for clinical trials. Anti-metastasis treatment or metastasis inhibitors not necessarily synonymous with chemotherapy or cytotoxicity; hence, the endpoint may often not be designed to prevent metastasis. It is very axiomatic that a profound opportunity exists to tackle these challenges, necessitating the innovation and optimization of high-throughput methodologies to accelerate the development of anti-metastatic modalities.

Matrix metalloproteinase (MMPs) inhibitors have been developed as a promising antimetastatic approach. Despite identifying over 50 MMPs to date, numerous clinical trials assessing their potential have regrettably yielded disappointing results, with efficacy remaining elusive against metastatic spread. There are multiple reasons involved in the paucity, one of which is the failure to comprehend the complex nature of metastasis. Within the realm of anti-metastasis therapeutics, an alternative exploration avenue entails strategically utilizing metastasis suppressor genes (MSGs) as a promising approach. The poor success rate in the case of MSGs is due to the difficulty in overcoming the restoration of the suppressed gene product [10].

Moreover, the knowledge regarding regulating organ-specific metastasis and dormancy is yet to be understood completely. Clinical trials frequently fail to examine the direct effects of cancer on metastasis. Because assessing the genesis and growth of metastases is inherently a long-term endeavour, it is sometimes too expensive to include metastasis as an end-point parameter in clinical trials [11].

3. Intrinsic elements of invasiveness

3.1. Homing and invasion

The metastatic cascade comprises six steps: mobilization, invasion, intravasation, transit within the vasculature and arrest, extravasation, and colonization [10]. Strong interactions with the basement membrane are frequently observed in primary malignancies of epithelial origin. The EMT is a process that includes the separation of the tumour from the basement membrane. Cancer cells can undergo metabolic changes during the EMT process to develop a mesenchymal phenotype [12]. Cancer cells are consequently given an improved potential for migration, making them highly invasive, resistant to apoptosis, and able to break down the extracellular matrix (ECM) components. Different mesenchymal markers such as smooth muscle actin, fibroblast-specific protein-1, vimentin, and desmin are expressed during the EMT. The epithelial markers, including the E-cadherin, N-cadherin, and membrane-bound-catenin, are lost by the cancer cells undergoing the EMT process [13]. One of the stages of invasion is the destruction of the ECM and its components by enzymes such as MMPs. This allows the cancer cell to escape the tumour site and cross the tumour boundaries [14].

A series of molecules are implicated in the homing and invasion process of metastasis; for example, metastatic cancer cells deal with oxidative stress through the mono-carboxylate transporter 1 (MCT1). MCT1, which aids in the circulation of lactate and is a crucial energy source for metastasizing cells, is highly present in metastatic cells. By inhibiting MCT1, metastatic cells can lower their ability to spread by decreasing lactate uptake. Metastasis suppressors impede the growth and proliferation of cancer cells. For instance, A-Kinase anchor protein 8 is a splicing regulatory factor that suppresses EMT and breast cancer metastasis [15]. For metastatic bone cancer and osteolytic bone disease, chemokines are an attractive target [16]. C-X-C motif chemokine 12 (CXCL12) is produced by bone marrow stromal cells and osteoblasts, which mediates the homing of cancer cells to bone. An in vitro study demonstrated that the invasion of cancer cells and transendothelial migration was enhanced by the expression of the CXCL12 receptor, C-X-C chemokine receptor type 4 (CXCR4), and an anti-CXCR4 antibody inhibited this. Bone metastasis is also suppressed by inhibiting Akt and NF-kappa B pathways,

which are activated through insulin-like growth factors type 1 receptor (IGF-IR). Anti-RANKL (receptor activator of nuclear factor-kappa B ligand) antibody denosumab and bisphosphonates are used widely and successfully to treat bone metastasis. Inhibitors of COX-2 suppress bone metastasis and reduce the number of osteoclasts [17].

CREKA is a tumour-homing pentapeptide that targets the fibrin-fibronectin complex in tumour stroma. When CREKA is linked with an antiplatelet drug – Ticagrelor, it showed in vivo anti-metastasis activity and can be an efficient therapeutic option for targeting tumour metastasis [18]. 1H7 which targets N-cadherin EC1-3 and 2A9,which targets N-cadherin EC4, these two are monoclonal antibodies which have shown reduced tumour growth and inhibited localized muscle invasion and distant lymph node metastasis in a subcutaneous xenograft prostate cancer mouse model [19]. FUT4 is a terminal α1, 3-fucosyltransferase, which promotes lung cancer progression. It aberrantly fucosylated many components of vesicle transport proteins. FUT4 is a prognostic indicator in lung adenocarcinoma patients. Knockdown of FUT4 in mouse xenograft models has significantly reduced lung metastasis [20].

Antibodies and other cell-penetrating peptides have attracted much interest in creating targeted delivery systems for payloads that might be used as non-invasive carriers in vivo. Tumour-homing peptides are oligopeptides, often with 30 or fewer amino acids, that are efficiently and selectively absorbed into tumour cells, indicating their potential use in developing novel non-invasive tumour imaging systems for diagnostic and therapeutic applications. The practical and precise incorporation of tumour-homing peptides into tumour cells raises the possibility of their utility as non-invasive tumour imaging systems for diagnostic and therapeutic purposes. The benefit of tumour-homing peptides is their rapid incorporation into target cells/tissues, biological safety, as they do not exhibit significant cytotoxicity against non-neoplastic cells, lack of significant antigenicity, which otherwise might elicit unfavorable immune responses leading to inflammation, Tumour-homing peptides are versatile because of their small size and simplicity of design. Owing to these advantages, tumour-homing peptides are widely explored in imaging diagnostics (e.g., with dye-conjugated probes for direct visualization of invasive/metastatic tumour lesions in vivo) and therapeutics (e.g., using peptide-drug conjugates for tumour targeting) in the field of tumour diagnosis and therapy. The research on tumour-homing peptides is in the preliminary stage, and more molecular studies are required to demonstrate their practical utility in clinics. However, this field has significant potential as a next-generation bio-tool in designing precision treatment modalities for cancer patients [21].

3.2. Anchorage independence

The tumour microenvironment provides crucial homeostatic cues not only to healthy cells, but also to malignant cells. Therefore, misplaced cells must be removed to protect the organism from negative effects. It is observed that interactions with the extracellular matrix and counter receptors on surrounding cells and adhesion receptors control cell survival. They can detect mechanical forces and other biochemical factors that arise from the surroundings and then convert the stimuli to intracellular signals. Untransformed non-hematopoietic cells experience a programmed cell death (apoptosis) called anoikis because of losing contact with their substratum. The intrinsic and extrinsic apoptotic mechanisms can both mediate anoikis. The Bcl-2 (B cell lymphoma-2) protein family's pro-apoptotic members, such as Bad (Bcl-2-associated death promoter), Bax (Bcl-2-associated X protein), Bid (Bcl-2-interacting domain), and Bim (Bcl-2-interacting mediator of cell death), permeabilize the outer mitochondrial membrane in the intrinsic pathway. These proteins work in synergy to create pores in the mitochondrial membrane that allow the release of pro-apoptotic substances into the cytosol, including cytochrome *c* and SMAC/DIABLO (second mitochondria-derived activator of caspases/direct inhibitor of apoptosis binding protein with low pI), which activates caspase enzymes [22,23]. The stimulation of death receptors, including those belonging to the TNF superfamily like Apo1/Fas and TRAIL [tumour necrosis factor (TNF)-related-apoptosis-inducing ligand] receptor, initiates the extrinsic apoptosis pathway. As a result, a death-inducing signaling complex (DISC) is formed, which then activates caspase-8. Apoptosis can be brought on by Caspase-8 activation alone, but it can also activate Bid, which initiates the intrinsic pathway [22]. Caspases are sequentially activated by both apoptotic pathways, leading to DNA degradation and cell death [24]. Anoikis signaling converges on established programmed cell death pathways, but different mechanisms than apoptosis trigger it. In the absence of pro-survival signals being processed, anoikis, the default route, is activated upon loss of contact. Transformed cells can remain in circulation for long and stimulate anti-anoikis systems. This method could be more effective. Many cells are regularly released into the bloodstream by malignant tumours [25,26].

Phoyunnanin E, a compound isolated from *Dendrobium venustum*, could inhibit vimentin and the associated EMT transcription factors snail and slug and reverse the E-cadherin to N-cadherin switch. Thus, these properties of suppression of the EMT and inhibition of the anoikis resistance can be employed for the anti-metastatic treatment in cancer therapy [27]. The moscatilin, a compound isolated from *Dendrobium brymerianum*, is found to downregulate the caveolin 1, leading to a reduction in the anti-apoptotic MCl 1 protein, which leads inhibition of the EMT and thus overcome the anoikis resistance and shows the effects of the anti-migration, anti-cancer which make it essential agent for the cancer therapy [28]. Imperatorin, the furanocoumarin isolated from the root of *Angelica dahurica*, downregulates the expression of the Bcl2 family protein and thus can be used to enhance the anoikis. The loss of the integrin enhances the apoptosis pathway, mainly the p53-based mitochondrial apoptosis pathways, but the cancer cells attenuate this p53-based apoptosis and thus develop anoikis resistance. The Imperatorin was found to activate the p53 pathway and thus induce the anoikis and these anti-metastatic properties can be used as anti-cancer therapy [29]. The Enhancer of zeste homolog2 (EZH2), the catalytic subunit of Polycomb repressive complex 2, is known to silence the anti-metastatic genes (e.g., E-cadherin and tissue inhibitors of metalloproteinases) and thus favoring cell invasion and anchorage-independent growth. The EZH2 inhibitors such as the 3-dezaneplanocin-A and many others under study, can be used as the anti-metastatic therapy [30]. Different cell types in the human body can be divided into adherent and suspension cell types based on cell shape and anchorage dependence. Developing a theory that represents the transformation of adherent cells into suspension cells has not yet been possible. Recent studies showed that the mechanism underlying the Adherent-to-Suspension Transition (AST) plays a significant role in the anchorage dependency in the circulating tumour

cells. By precisely blocking AST factors, and CTC formation, metastasis may be prevented without impacting the growth of the underlying tumour. To combat the spread of solid tumour cells, AST thus offers a fresh theoretical foundation for understanding cancer metastasis and identifies AST components as potential therapeutic targets [31].

4. Tumour-host interactions

4.1. Targeting molecules

The advancement of molecularly targeted therapeutics for cancer hinges upon the discernment of optimal targets that wield pivotal influence in orchestrating the intricate landscape of cancer progression. At the crux of this pursuit lies the dynamic phenomenon of genetic profile alterations, wherein mutations or modifications in proteins and receptors unfold, propelling the sustenance and unrestrained proliferation of malignant cells, which is a fundamental etiological underpinning in the genesis of cancer. The creation of molecularly targeted therapies can employ these genetic abnormalities that distinguish cancer cells from healthy ones as molecular targets [32]. The contact between the tumour and the host is crucial for cancer proliferation and metastasis. The tumour-host interaction influences tumour mass, metastasis, host tissue penetration, host immune response evasion, and tumour medication resistance. The interactions are mediated by a vast chain of chemokines, cytokines, and growth factors, pivotal in promoting tumour progression. The formation of secondary tumours in organs distinct from the primary organs is due to various paraneoplastic syndromes, which are often caused by the manifestation of aberrant hormonal production by the tumours. Recent data suggests that tumours actively use multiple methods to disrupt host organs at distant anatomic locations and that these perturbations constitute a driving force in tumour growth [33]. Manipulation of these host response elements has become a significant focus of emerging anticancer treatments since the host response to the tumour microenvironment can either assist or prevent tumour invasion and spread [34]. Addressins, chemokine receptors, and peptide motifs are the elements that can be used to target molecules against tumour metastasis.

4.2. Addressins

Addressin is a less widely used term for a collection of adhesion molecules involved in lymphocyte homing commonly present in high-endothelial venules (HEVs) where lymphocytes exit the circulation and enter the lymph node. Addressins bind to lymphocyte homing receptors. Mucosal addressin cell adhesion molecule is a molecule that is referred to as addressins, which mediate inflammatory responses in the gut. Antibodies MECA-367 and MECA-89 recognize the 60-kDa glycoprotein mucosal addressin. Peripheral node addressin (PNAd) is a sulfated and fucosylated glycoprotein that recognizes HEV, which is important for lymphocyte recruitment into lymphoid organs in non-mucosal tissue sites. They have high HEV expression and poor brain and pancreas expression levels. PNAd has been found as a biomarker for improved disease prognosis in recent cancer investigations in mice and humans. In mouse models, blocking PNAd or its ligand, L-selectin, can abolish protective antitumour immunity [35].

4.3. Chemokine receptors

Chemokine receptors are a large superfamily of G protein-coupled receptors that perform various functions like controlling immune cell behavior, chemotaxis promotion, cell adhesion, and mediator release. Based on the chemokine/ligand interaction motif to which they bind, the chemokine receptor superfamily is split into four classes (CC, CXC, CX3C, or XC) [36]. So far, eighteen chemokine receptors have been cloned, including six CXC receptors, ten CC receptors, one CX3C receptor, and one X receptor [37]. One of the distinct features of this receptor family is the ability of chemokine receptors to bind to more than one chemokine within the subclass [36]. Chemokines and their receptors promote tumour growth by facilitating angiogenesis and EMT. On the surface of cancer cells, the expression of specific chemokine receptors promotes metastasis and organ-specific metastasis [38]. Several chemokines and their receptors are involved in this process. The migration of tumour cells into lymph nodes is facilitated by CCR7 where two of its ligands are produced, CCL19 and CCL21. During metastatic spreading, the adhesion and survival of melanoma cells are mediated by the CCR10/CCl27 axis. Through the MAPK/ERK pathway, CCL28 promotes breast cancer growth and metastasis. Prostate cancer bone metastasis is aided by the chemokine receptor CXCR5 and its ligand CXCL13. The CXCL12/CXCR4 axis, on the other hand, is the primary participant in this process. CXCR4 expression confers cancer cells' capacity to move and metasize into tissues secreting high quantities of CXCL12 [39]. Chemokine and chemokine receptors can be used as therapeutic targets in hampering the progression of tumours and metastasis, thereby aiding in improving the survival rate of cancer patients. The altered expression of chemokines in case of malignancies leads to aberrant chemokine receptor signaling. Recent studies suggest that metastatic cancer cells co-opt chemokine pathways to spread to other sites [38].

4.4. Vascular peptide motifs

The discovery of peptide-based medications that can inhibit angiogenesis to prevent the growth and spread of tumours would be beneficial, as this process plays a significant part in the development of tumours [40]. By utilizing the phage display library, Travassos et al. designed a new melanoma-homing peptide known as peptide C which was conjugated with anti-angiogenic peptide sequence [41]. When systemically injected into mice, the resulting peptide was shown to limit the tumour growth significantly; "proangiogenic" structures were reportedly reduced by 40 % [41]. Additionally, this newly developed peptide sequence binds the human sonic

hedgehog protein, which can be found in the microenvironments of several tumours, including melanoma [42]. Using anti-angiogenic peptides as a treatment for a variety of high-risk tumours can be a practical therapeutic approach. The promising work on tumour-homing peptides known as SPARC peptides (Secreted Protein, Acidic and Rich in Cysteine) that prevent angiogenesis in neuroblastoma tumours is provided by Cohn et al. is another example of homing peptide mediated prevention of angiogenesis [43]. SPARC can interfere with several growth factors, including VEGF, PDGF, and bFGF, and reduce their capacity to promote angiogenesis, although the fact that its precise inhibition mechanism is not entirely understood [44]. The same team then created several peptides that mimicked conserved SPARC domains and discovered that one of them, called FSEC, not only potently reduced angiogenesis but also slowed the growth kinetics of neuroblastoma in a preclinical model [43].

4.5. *Angiogenesis*

Angiogenesis, an intricate biological process, comprises the generation of blood vessels through the sprouting of endothelial cells from pre-existing vascular networks. Protease synthesis, endothelial cell migration and proliferation, vascular tube creation, anastomosis of newly formed tubes, synthesis of a new basement membrane, incorporation of pericytes, and smooth muscle cell integration all lead to angiogenesis. The oxygen and nutrients that tumour tissue needs to grow or locally metastasize will be supplied via blood vessels [45,46]. The metabolism of endothelial cells, which can use oxygen to create sprouts in vitro or a vascular network in vivo, is correlated with the presence and abundance of oxygen. Endothelial cells play a major role in the development of cancers because they release a variety of proteins, including EGF, estrogen, basic and acidic FGF, IL-8, prostaglandin E1 and E2, TNFα, and VEGF, which can stimulate endothelial cell growth and motility when the production of anti-angiogenic factors is inhibited [47]. Blocking angiogenesis and thus blocking tumour nourishment is one of the ways to cease tumour growth Fig. 2.

In recent studies, the role of microRNAs in angiogenesis has been elaborated. For example, miR-30e-5p acts as a metastasis suppressor. It can subdue angiogenesis and metastasis by directly targeting the AEG-1 oncogene in squamous cell carcinoma of the head and neck [48]. Another miRNA, MiR-126-3p, suppresses tumour metastasis and angiogenesis of hepatocellular carcinoma by silencing LRP6 and PIK3R2 [49]. Conversely, other microRNAs such as exosomal miR-619-5p, promote angiogenesis and metastasis in non-small cell lung cancer cells by suppressing the expression of RCAN1.4 [50]. Thus, such microRNAs can act as diagnostic indicators and treatment targets to annihilate metastatic cancer. It has also been found that the expression of various circular RNA promotes metastasis via enhancing invasiveness and angiogenesis. For example, circ3823, circRNA-100338, and circ-001971 elevate metastasis in hepatocellular carcinoma [51–53].

Various cytostatic molecules such as Sodium phenylacetate, has been shown to prevent metastasis in breast cancer by modifying the synthesis of growth factors in mouse models and carbomethyl benzylamide dextran prevents tumour growth and tumour angiogenesis by binding to angiogenic growth factors [54]. The use of nanoparticle-based therapy is being widely scrutinized for the inhibition of angiogenesis in tumours such as 89Zr–Pt@TiO2-SPHINX, is used to target prostate cancer and as a PET imaging agent and anti-angiogenic radio sensitizer [55]. Meticulous gene editing of VEGFR2 using CRISPR–Cas9 systems has shown the potential to treat angiogenesis-associated diseases and prevent mechanisms that contribute to resistance mechanisms [56].

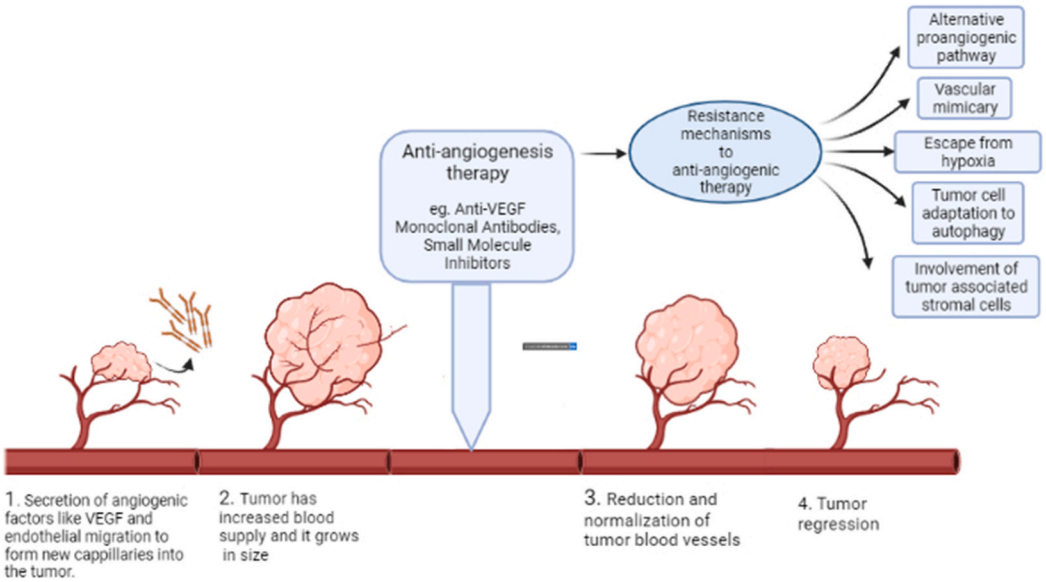

Fig. 2. Anti-angiogenesis therapy and resistance mechanisms. Angiogenesis is stimulated due to anoxic conditions and by the secretion of angiogenic factors such as VEGF. It provides new vessels which provide nutrition to the growing tumor. Angiogenesis can be inhibited by the use of anti-VEGF factors, monoclonal antibodies, small molecule inhibitors etc. Anti-angiogenesis therapy helps in depletion of vessels to the tumor thereby leading to the regression of the tumor. There are various resistance mechanisms also which inhibit the action of antiangiogenic drugs.

There have been instances of resistance to anti-angiogenic drugs by various mechanisms; one recently found novel resistance mechanism is the downregulation of macrophage migration inhibitory factor in Bevacizumab-resistant patients [57]. A combination of antiangiogenic drugs with different modes of action may assist in blocking common pathways of tumour angiogenesis [58]. However, long-term inhibition of angiogenesis reduces the uptake of co-administered chemotherapeutic agents [59] necessitating new drug targets for anti-angiogenic to prohibit angiogenesis effectively.

4.6. *Exosomes and the pre-metastatic niche*

Exosomes, being extracellular vesicles ubiquitously secreted by eukaryotic cells, are intricately engaged in intercellular communication. The diverse repertoire of exosomal constituents, comprising proteins, DNA, mRNA, microRNA, long non-coding RNA, circular RNA, etc., emerges as a reservoir with significant potential as prognostic markers for tumour patients. Their regulatory influence extends to crucial aspects of cancer development, including tumour growth, metastasis, and angiogenesis, thereby spotlighting their importance as valuable indicators in the oncological landscape. Exosomal miR-451a, miR-21, and miR-4257 were shown to be unusually highly expressed in non-small cell lung cancer patients and were closely linked to tumour growth, recurrence, and a poor prognosis [60]. Designing therapeutic efficacy through exosomes entails the targeted elimination of cancer-specific exosomes propelling tumour progression, coupled with the strategic manipulation of cancer-derived exosomes to prime immune cells, a nuanced approach poised to unlock the full therapeutic potential against cancer. Different types of exosomes such as tumour cell-derived exosomes, dendritic-derived exosomes, and ascitic-derived exosomes, are recognized to stimulate the immune system by activating the dendritic cells, i.e., the primary step of the immune system and thus identifying and killing the cancerous cells. A deeper understanding of exosome-mediated molecular underpinnings offers an opportunity to explore the potential exosomes in cancer immunotherapy [61]. The exosomes can be hooked with specific nanoparticles and used effectively as cargo in drug-targeting systems. Such approved nano drug delivery systems approved by the US Food and Drug Administration are available for cancer treatment, including Doxil®-(doxorubicin encapsulated in liposomes) and Abraxane® (paclitaxel attached to nanoparticles). Exosomes, with their potential as cancer vaccines, are currently being invested under clinical trials, marking a pivotal step in exploring their efficacy against cancerous cells [62]. The exosomes with Human epidermal growth factor receptor type 2 (Her2) oncoprotein inhibit the activity of the therapeutic antibody Herceptin®. So, to overcome this extracorporeal hemofiltration of the exosomes can be carried from the entire circulatory system using affinity plasmapheresis platform known as Aethlon ADAPT™- adaptive dialysis-like affinity platform technology to overcome the drug interaction by minimizing the load of the glycosylated surfaces as cancer exosomes [62]. The different Rab proteins are identified to produce the exosomes in tumour cells and normal cells. The knockdown of the Rab27a in the melanoma cells showed decreased exosome production, reducing tumour growth and metastasis [63]. Thus, this approach can give us a new therapeutic opportunity for metastasis treatment Fig. 3.

The development of pre-metastatic niche (PMN) is a multi-step process that involves vascular leakage induced by secretory factors and extracellular vesicles, extracellular matrix remodeling, and immunosuppression [15]. Therapies are targeted against the establishment of a pre-metastatic niche, which could stop metastasis. For example, breast cancer cells release ATP, activating the P2Y purinoceptor 2 and the HIF1-LOX axis. These events lead to the induction of collagen crosslinking and the recruitment of CD11b +

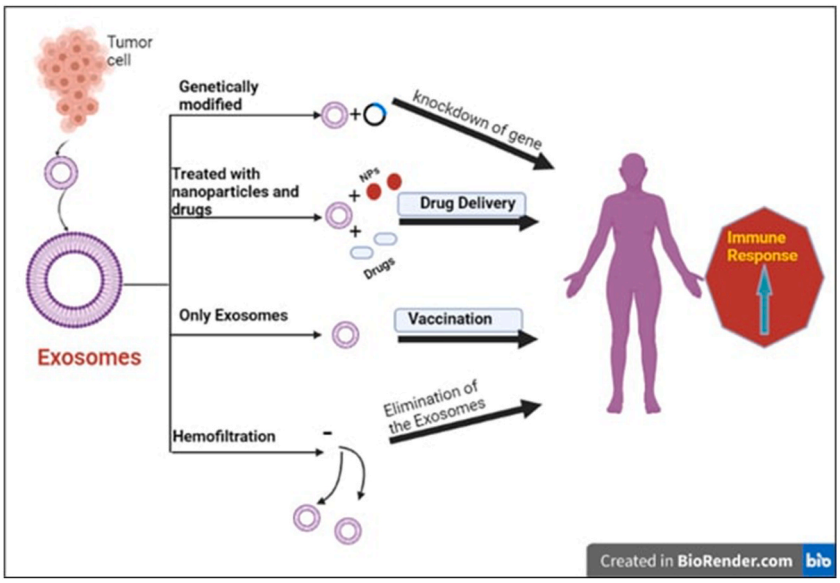

Fig. 3. Exosome-mediated therapeutic approaches. Exosomes represent a dynamic and customizable therapeutic platform. Exosomes can be explored in an impressive range of therapeutic applications by incorporating genetic modifications, nanoparticle/drug loading, targeted vaccination strategies, and innovative elimination techniques.

bone marrow-derived dendritic cells (BMDCs). Inhibiting P2RY2 signaling has proven to be an effective strategy for preventing the formation of pre-metastatic niches in preclinical breast cancer models. Downstream targeting of LOX by treating with beta-amino-propionitrile, LOX-specific RNA interference or function-blocking antibodies have shown to prevent PMN formation in preclinical breast cancer models. Myeloid cell recruitment to liver and lung PMNs was blocked by CXCR4 inhibitor AMD3465, thus preventing metastasis progression in immunocompetent mouse models of breast cancer. Another strategy is to express protein tyrosine phosphatase receptor type O in mouse breast cancer cells, which acts as a multi-target negative regulator of VEGFA, PDGF, and FGF receptor 1, stopping PMN from forming in breast cancer models, and preventing lung metastasis [64].

Many targets can inhibit the formation of PMN, such as by suppressing or inhibiting the BMDCs recruitment, disrupting the local matrix, blocking the production of PMN-promoting molecular components, and re-activation of anti-tumour response, and these target approaches may be used to prevent cancer metastasis in future [65]. G-CSF is a type of tumour derived suppressor factor, by targeting G-CSF the tumour metastasis is suppressed, partially by preventing PMN formation. In primary tumour and myeloid cells, targeting STAT3 impairs the recruitment of BMDCs into the PMN to inhibit metastasis [66]. A series of new therapeutic approaches are emerging that consider the molecular phenotype of metastatic tumours and the environment of the metastatic niche [67].

5. Genetic and epigenetic control of metastasis

The intricate interplay of genetic and epigenetic cross-talks and mechanisms finely tunes the orchestration of metastasis. At the genetic level, mutations in key oncogenes and tumour suppressor genes drive the acquisition of invasive traits, facilitating the escape of cancer cells from their original site. Simultaneously, epigenetic alterations, such as DNA methylation and histone modifications, exert dynamic control over gene expression patterns, steering cells toward a metastatic phenotype. This dual regulation at the genetic and epigenetic levels underscores the remarkable adaptability of cancer cells, enabling them to navigate the challenging journey of metastasis [68]. Deciphering the molecular intricacies of these regulatory networks holds profound implications for developing targeted therapies that may disrupt the metastatic cascade, offering new hope in the relentless pursuit of conquering cancer.

5.1. Metastasis genes and metastasis suppressor genes

Metastasis genes are categorized based on their participation level in metastasis. The mediator genes involved in the metastasis are classified based on the tumour stage, localization, and biological functions in the body [69]. 'Metastasis initiation genes' are the genes that pave the way for the tumour cells to enter the circulation. This category includes most tumour cell movement, invasion, or angiogenesis genes. 'Metastasis progression' genes are involved in rate-limiting functions in the primary growth of the tumour and play a role in other specific functions in the colonization of metastasis. 'Metastasis virulence' genes impart selective advantage in secondary tumour sites. However, they don't participate in the primary tumour, thus being involved in metastatic colonization, not the primary tumour development. These genes promote metastasis after tumourigenic genes have produced a modified, locally aggressive tumour cell population. These genes add virulence to secondary tumour sites [69].

The metastasis-promoting genes such as WDNM-1, WDNM-2, MMP11 (stromelysin-3), MTA1, and ERBB2 have all been linked to the progression of metastasis in breast cancer [70]. The characteristics involving metastasis tumour initiation are unlimited growth, survival potential, and genomic instability. The genes involved in such processes include KRAS, BRAF, HER2, P13K, etc. The characteristics involving metastasis initiations are invasion, marrow mobilization, angiogenesis, epithelial to mesenchymal transition, and the genes involved are RHoC, LOX, VEGF, CSF-1, TWIST1, MET, FGFR, MMP-9, NEDD9. Vascular remodeling of tissues, immune extravasation, and evasions are the features of metastasis progression, and the genes engaged are EREG, COX-2, MMP-1, CCL5, and ANGPTL4. The other class of metastasis virulence genes is CXCR4, RANKL, CTGF, IL-11, and Endothelin-1, and these possess functions that are organ-specific [71].

There are many emerging technologies through which these genes can be targeted as therapeutic approaches. CRISPR/Cas is one of the most recent generations of gene editing technology. As an "immune system," it was initially discovered in bacteria and archaea to defend these species from phage and other viral invasion. The utilization of a guide RNA that binds to the DNA target site while a nuclease called CRISPR-associated caspase protein (Cas) cleaves specific DNA strands that are complementary to the gRNA of the CRISPR system is one intriguing aspect of CRISPR systems. This gene editing technique can be utilized for targeted mutation editing, cancer prevention, and enhancing adaptive immunity. It has been demonstrated that this gene editing approach can reduce tumour size, migratory potential, and medication resistance in pancreatic, prostate, colon, and other types of cancer [72].

5.2. Metastasis suppressor genes

Metastasis-suppressor genes prevent (spontaneous) macroscopic metastases at multiple stages in the metastatic cascade. These genes are distinct from oncogenes, which drive cellular transformation, and tumour-suppressor genes, which suppress tumour growth [70]. MSGs are characterized by their loss of function, which enhances metastasis without impacting the growth of the primary tumour. The distinctive feature of MSGs lies in their potential to restrain overt metastasis in secondary organs without exerting any influence on the development of the original tumour at its primary site. This unique capability sets MSGs apart, focusing their specific role in regulating the metastatic process while leaving the primary tumour growth unaffected. The only commonality among this group of genes is their ability to inhibit metastasis. They encode proteins with a wide range of biochemical functions and are components of several signaling pathways.

Furthermore, metastasis suppressors exert their suppressive actions at various phases of the metastatic cascade. Microcell-mediated

chromosome transfer approaches were used to identify metastasis suppressors. The metastasis suppressor genes mechanistically target cell adhesion, MAPK, G-protein-coupled receptor, transcriptional regulatory, cytoskeletal, and metastasis susceptibility pathways. Most MSGs are functionally multifactorial, inhibiting metastasis at multiple points in the cascade. Many operate in a context-dependent fashion [73].

Metastasis suppressors block one or more gene phases in the metastatic cascade and regulate various signaling pathways in the cancer pathophysiology [74]. Unlike their role in development and differentiation, where their pathways are turned on and off in a controlled manner, they act as metastasis suppressors in unstable cancer cells. Various genes have so far been identified as metastasis-suppressor genes, some of which are nm23 (NME1), KAI1, KiSS1, BRMS1, and MKK4 (MAP2K4) [70]. For instance, BRMS1 is localized on chromosome 11 and has been associated with suppressing metastasis in ovarian models, non-small cell carcinoma, melanoma, and bladder cancer models. KA1, which belongs to the tetraspanin family of suppressing metastasis in models of prostate and breast cancer. MAP2k4 belongs to the MAP kinase family localized in chromosome 17 and suppresses metastasis in prostate cancer. While, KISS1 acts as a suppressor in models of breast, ovarian, pancreatic, and melanoma cancers [75].

5.3. *Epigenetic regulation of metastasis*

DNA methylation, post-translational Histone modification, chromatin remodeling, and recently discovered microRNAs are the most common epigenetic markers (Fig. 4). Unlike genetic mutations, epigenetic alterations are potentially reversible; hence, these alterations can be used as targets for cancer therapy. Many miRNAs are deregulated for the manifestation of cancers and have a direct impact on tumour suppression and metastasis. For example, upregulation of miR24-2 promotes the malignant growth of liver cancer stem cells (LCSCs) by increasing the tyrosine-protein kinase sarcoma gene Src expression in human LCSCs and oncogenes like c-Myc [76]. Another miRNA, miR-639 which normally acts as a tumour suppressor, is downregulated by aberrant DNA methylation of CpG islands and helps in the proliferation, migration, and invasion of hepatocellular carcinoma cells (HCC) [77]. These findings indicate that miRNA can be cancer therapeutic targets and diagnostic biomarkers. Hypoxia in the tumour microenvironment causes the downregulation of DROSHA [78] and DICER. Loss of DICER and DROSHA play a major role regulating hypoxia-induced EMT and stimulating metastasis [79]; hence, targeting hypoxia is another potential therapeutic target. Other epigenetic modifications such as the overexpression of Zinc finger protein Snail2, represses E-cadherin expression through histone methylation and deacetylation boosting invasion and metastasis in CRC [80]. Another zinc finger protein ZBTB16, inhibits breast cancer proliferation and metastasis by forming complexes with ZBTB28 and BCL6 genes [81].

The expression of long non-coding RNA (lncRNA) may suppress and promote cancer metastasis. Many lncRNAs, such as HOTAIR, mediate epigenetic silencing of tumour suppressor genes. It was reported that CAFs promote metastasis in breast cancer by over-expression of HOTAIR, another lncRNA HUMT hypomethylation that promotes lymph angiogenesis and metastasis in TNBC [82]. It was recently reported that reduced m6A RNA modification by DNA hypermethylation increased the stability and expression of critical oncogenes such as lncRNA XIST [83]. Another study reported that METTL14, a m6A writer, suppresses the proliferation and metastasis

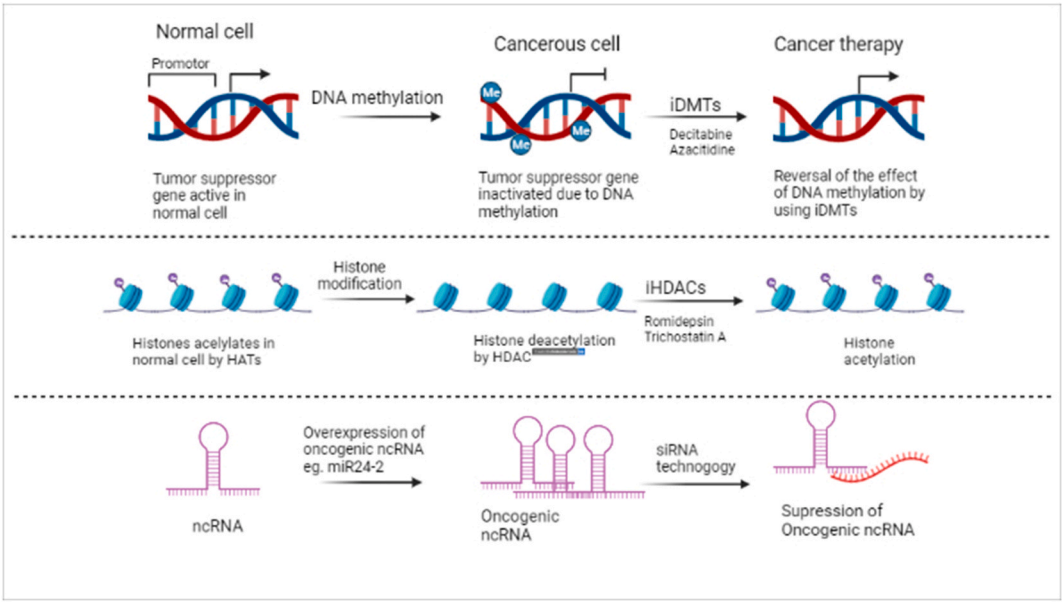

Fig. 4. Epigenetic modifications and role of epigenetic therapy: Major epigenetic alterations involved in tumourigenesis are DNA modifications, histone modifications, and non-coding RNAs (especially miRNAs). Targeting these epigenetic modifications using DNA methylation inhibitors such as Decitabine and Azacitidine reverses the initial alterations. Similarly, histone modification can be reversed using histone deacetylase inhibitors such as Romidepsin and Trichostatin A. Overexpression of oncogenic ncRNAs such as miR24, and HOTAIR can be suppressed by siRNA technology.

of CRC by down-regulating oncogenic lncRNA XIST [84]. Hence, various epigenetic factors are responsible for cancer progression and metastasis, which further need to be studied for efficient therapeutic use against metastasis.

A variety of drugs have been screened for epigenetic therapy. For example, Trichostatin A suppresses the migration and colony formation in human cancer cells, and several HDAC inhibitors have been demonstrated to have anti-proliferative effects in various cancer types, including gastric and breast cancer [85]. INK-128, a mTOR inhibitor, and JNJ-26481585, an HDAC inhibitor, were recently discovered to reduce gallbladder cancer (GBC) cell growth. It has been suggested that these medicines can be used against GBC in combination with gemcitabine to suppress tumour development and metastasis, as minimal doses of gemcitabine are required in combination therapy, improving therapeutic efficacy and reducing toxicity [86]. Similarly, in a genetically modified mouse model with tumours resulting from the knockout of PTEN and APC, researchers have tested therapeutics against endometrioid cancer. A combination of cisplatin and paclitaxel, along with mTOR and AKT signaling inhibitors, has proven effective in these mouse models [87].

The FDA has approved azacytidine and decitabine as DNMT inhibitors for the treatment of acute myeloid leukemia and myelodysplastic syndrome. Zebularine is an alternative derivative of cytidine and has the potential to be a better drug than azacytidine and decitabine for epigenetic cancer therapy [88]. Based on the above discussion, epigenetic control can be a therapeutic target for the treatment of metastatic cancer. Understanding the epigenetic aspects of cancer helps study various emerging issues like anticancer drug resistance, tumour relapse, the potential for combination therapy, prognosis, etc. (Fig. 5). Understanding the epigenetic modifiers is essential for investigating the possibility of HDAC inhibitors, demethylation agents, and similar therapeutics against cancer metastasis. Additionally, it also aids in assessing the risks associated with epigenetic drug treatment on metastatic tumour cells.

5.4. *Metastatic core program of gene expression*

The core programme and a site-specific element define the metastatic gene expression profile. The genetic core programme of metastasis encodes the four functional entities, which are activated in the primary tumour and maintained in the target site. They include angiogenesis, tissue remodeling, and reduction in extracellular matrix interactions with enhancing cell motility. These metabolic adaptations enhance the energy production of cancer cells, convey anchorage-independent survival, and change the equilibrium of inorganic ions. A notable potential druggable target in metastasis could be deregulating the proteasome pathway. Carfilzomib and bortezomib are proteasome inhibitors that block protein degradation and show anti-cancer activity. In metastasis, the signature of gene expression changes from primary tumours, and metastases from various origin sites converge in their gene expression patterns when reaching the same target organ. Therefore, emphasizing the selection of combination chemotherapy tailored for the target organ could be a promising strategy. For instance, treating all liver metastasis with similar drugs that target the genetic core program of metastasis, regardless of their organ of origin, would be more efficacious [89,90]. IL6 and CCL5 genes are overexpressed in basal breast cancer. IL6 also promotes the formation of cancer stem cells. CCL5 and IL6 might be potential therapeutic targets in basal breast cancer and metastasis [91]. In human osteosarcoma, overexpression of RPL17 results in the stabilization and activation of p53,

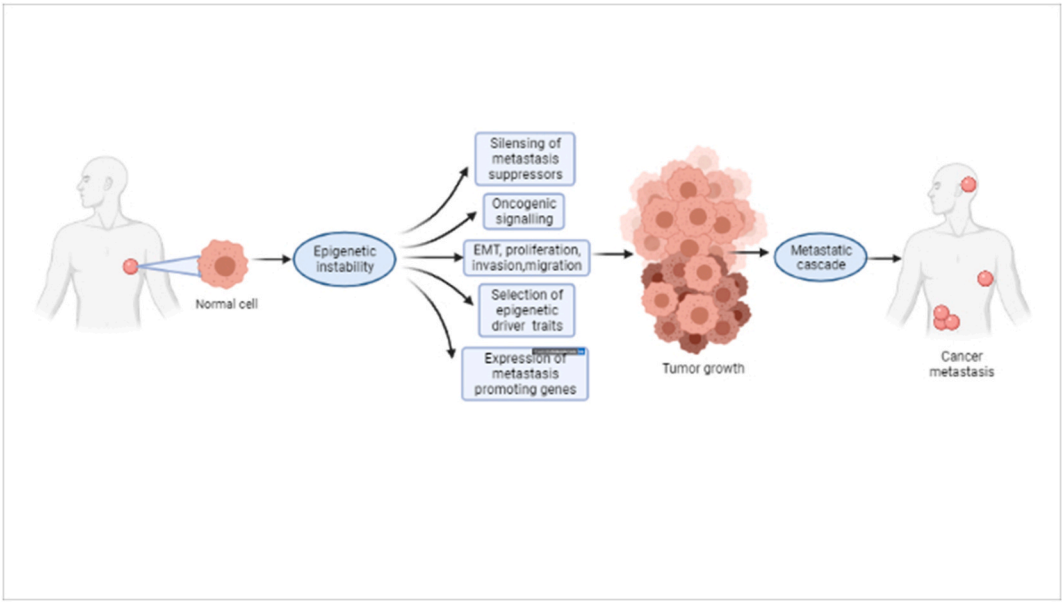

Fig. 5. Epigenetic changes during tumourigenesis leading to metastasis: The epigenetic instability leads to different changes in the metabolic pathways, such as the silencing of metastasis suppressor genes, expression of the metastasis promoting genes, enhancement of the oncogenic signaling, etc., which results in the tumour proliferation, invasion, migration, and EMT leads to promotion of tumourigenesis and thus results in the metastasis.

which, in turn, suppresses cancer cell proliferation [92]. Similarly, the in vivo study showed that the single knockouts of Tp53 or Rb1 were significantly less effective at inducing metastatic cancer, i.e., only 13 % of Tp53 knockout mice and 3 % of Rb1 knockout mice developed tumours. Notably, these studies demonstrate that Tp53 mutations alone are sufficient for the initiation of ovarian tumours, but concurrent mutations in both Tp53 and Rb1 are necessary to lead to metastatic ovarian cancer [93].

In TGF-β induced EMT, there is upregulation of FUT8 (fucosyltransferase 8) in breast carcinoma cells. The core fucosylation of cell surface targets such as TGF-β RI and RII form ligand binding complexes and promote downstream signaling. Inhibition of FUT8 by genetic or pharmacologic interruption suppresses breast carcinoma cell invasiveness and lung metastasis in mouse models [94]. In cancer cells, the levels of MALAT1 are high and facilitate cell and tumour progression and metastasis in triple-negative breast cancer cells. Depletion of MALAT1 in breast cancer and hepatocellular carcinoma which alters the expression and pre-mRNA splicing of genes that are involved in cancer progression and metastasis [95].

5.5. Site-specific gene expression programs in metastasis

To adapt to its environment, cancer metastasis induces site-specific changes in gene expression, suppressing the genetic characteristics of the original site and promoting an expression profile akin to the host environment. This adaptation challenges current immunotherapy approaches, directly emphasizing the need to target disseminated cells for effective anti-metastasis therapy in cancer [89]. Additionally, the gene expression of primary tumours varies with their locations; for instance, tumours with non-regional nodal metastases exhibit a high level of androgen receptors, while other metastatic tumours display comparatively low receptor levels. Leveraging these location-specific gene expression patterns in primary tumours presents a promising avenue for potential therapeutic targets [96].

Exploring metastasis-associated differential gene expression pathways in primary tumor and metastatic pancreatic neuroendocrine tumours (pNETs) involved a comprehensive analysis using Ingenuity Pathway Analysis and Connectivity Map. This approach allowed for identifying proliferation activities and drugs targeting these pathways. Notably, the mitogen-activated protein kinase and topoisomerase pathways emerged as highly active, and successful interventions with targeted drugs showcased significant efficacy against metastatic pNETs. This strategy can be used to discover the more effective treatment against metastasis in cancer therapy [97]. Differences in gene expression are observed in the primary and the metastatic colon adenocarcinoma, which can be considered the biomarker for the cancer and therapeutic targets. The expression profile of the genes LEP, DLX2, CLSTN2, and REG3A were significantly higher in tumour tissues than in normal tissues. Three drugs namely ajmaline, TTNPB, and dydrogesterone, were found to target these genes and were found to treat colon adenocarcinoma [98]. MDA-9/Syntenin is an essential gene for cancer progression and metastasis to diverse histologically distinct cancers. The gene comprises the four domains such as the N-terminal or NTD (1–109 aa) domain, two tandem PDZ domains, PDZ1 and PDZ2 (amino acid 110–193 and amino acid 194–273, respectively) domain, and a short carboxyl-terminal domain (CTD). Among these, the transcriptional relevance of PDZ functions stands out in relation to metastasis when compared to NTD and CTD. PDZ1i, a molecule specifically designed to target the PDZ1 domain of MDA-9/Syntenin, offers a strategic approach to address prostate and neuroblastoma cancers and combat metastasis associated with reduced MDA-9/Syntenin expression [99].

6. Immune modulators in metastasis

The adaptive and innate immune systems play a significant role in the metastasis of the cancerous cells. The tumour microenvironment remains immunosuppressive by targeting the cytotoxic T and NK cells. Cytotoxic T lymphocytes (CTLs), Natural killer (NK), dendritic cells, macrophages, myeloid-derived suppressor cells, regulatory T cells and fibroblasts modulate the function of the CTLs and NK cells, thus influencing the metastasis and tumour progression [100]. Tumour-associated macrophages (TAMs) produce growth factors, chemokines, cytokines, inflammatory mediators, and proteolytic enzymes, as well as activating immune checkpoint proteins in T cells that suppress immune responses, creating immunosuppressive TME. As a result, they facilitate all aspects of metastasis [101], including promoting tumour cell invasion and vascularization, developing a pre-metastatic niche, protecting CTCs, and promoting tumour cell extravasation. Tumour necrosis factor, interleukin (IL)-8, IL-1, and transforming growth factor [101], implicated in the EMT [102,103] are among the soluble substances released by the TAMs at the main sites. EMT is a critical cellular morphological change event that promotes the emergence of biological malignancies like invasion, angiogenesis, and metastasis. The majority of leukocytes, or neutrophils, are involved in almost every stage of the metastatic cascade, including the creation of the pre-metastasis niche, the escape of cancer cells from the primary tumour, intravasation into the blood and/or lymphatic system, survival in circulation, extravasation to distant sites, reactivation of dormant cancer cells, and metastatic growth [104]. By identifying and eliminating tumour cells, NK cells play an essential role in tumour immune surveillance and the control of metastasis [105]. To prevent cancer metastasis, they can interact with CTCs directly and indirectly [106]. However, platelets wrap CTCs, defending them from NK cell assault and shear stress [107]. NK cells interact with CTCs through specific ligands and receptors, influencing and regulating cancer spread through various mechanisms [106]. They also activate effector mechanisms that cause direct cytotoxicity by using the perforin and granzyme B exocytosis pathway [108].

In the evolving landscape of cancer therapeutics, remarkable success has been achieved by utilizing immune cell membrane-based nanoparticles (NPs) loaded with potent anticancer agents. This innovative strategy demonstrates unparalleled therapeutic efficacy in the targeted treatment of cancer metastasis, owing to the pivotal roles played by immune cells. Specifically, immune cells contribute significantly to the metastatic process by discerning cancer cell surface signals through intricate interactions facilitated by immune cell protein ligands. This strategic integration of immune cell membrane-coated nanoparticles not only capitalizes on the inherent

specificity of these cells but also orchestrates a sophisticated molecular ballet to home in on metastatic lesions, revolutionizing the landscape of precision medicine in oncology [109]. Engaging in a nuanced modification of NPs to amplify their targeting precision towards metastatic sites, alongside fortifying the host's immune defenses, presents a transformative avenue in cancer treatment. This entails the adept integration of a biomimetic immune cell-based nano-strategy, proficiently loaded with potent anti tumour agents encompassing chemotherapy, immunotherapy, or synergistic combinatorial therapies. These strategic adaptations promise heightened effectiveness and underscore a commitment to ensuring the safety and efficacy of interventions that staunchly suppress tumour metastasis. Beyond its proficiency in pinpointing metastatic tumour locations and CTCs, the immune cell membrane boasts inherent attributes, notably its capacity for immune evasion [110]. Simultaneously, the outer membrane envelope serves as a shield for pharmaceutical payloads from environmental degradation. This dual function fortifies structural integrity and curtails the risk of leakage, exemplifying a sophisticated synergy of molecular capabilities within the immune cell membrane for enhanced therapeutic precision [111]. Numerous preclinical and clinical studies have highlighted the significant role of miRNAs in immune suppression within tumours. Notably, circulating exosomal miRNAs such as miR-146a, miR-125a, miR-155, let-7e, miR-146b, miR-125b, miR-99b, and miR-100 have been identified as markers of immune resistance in melanoma patients treated with nivolumab and ipilimumab [112]. Additionally, miRNAs that target immune suppressors are often downregulated in tumours, further promoting an immune-suppressive tumour microenvironment. Research is actively exploring ways to target the immune system to prevent metastasis. For example, lenalidomide and pomalidomide, allow for multiple myeloma treatment and have broad immunostimulatory effects, improving NK cell functions such as ADCC. These drugs are now being studied in clinical trials for other blood cancers. Additionally, Indoximod and epacadostat, relatively non-selective IDO1 inhibitors that enhance NK cell activity, are being tested in combination with chemotherapy, radiotherapy, or immunotherapy for treating various cancers [113].

7. New treatment opportunities

Metastasis prevention has been demonstrated in pre-clinical settings; however, the development of clinical drugs has been hindered due to poor clinical trial design and therapeutic strategies. Currently, there are two complementary anti-metastasis strategies: preventing metastasis and suppressing the already metastases. Various treatment opportunities have been proposed recently, such as oncolytic virotherapy, which has rapidly advanced in recent years. The exciting approach is the use of viruses for the development of anti-cancer vaccines that target patient-specific mutations [114], and genome editing techniques such as CRISPR/Cas9 can also be used for metastasis treatment by restoration of metastasis suppressor genes, suppression of oncogenes, altering genes associated with drug resistance etc [115]. Genetically engineered bacteria such as *Salmonella* sp. and *E. coli* can er metastasis by enhancing the cytotoxicity of host immune cells and producing cytotoxic proteins, respectively [116,117]. These therapeutic approaches must be executor for various types of cancers to assess their possessiveness. Another advancement is that amino acid deprivation therapy is a potential therapy for auxotrophic tumours [118]. Amino acid deprivation, particularly arginine deprivation, has become therapeutic for cancer cell metastasis because utilization of L-arginine by NOS produces species that promote cell migration and activate the focal adhesion kinases [119]. The tumour-homing peptides can be used for in vivo tumour imaging. For example, a peptide probe chemical be used ally labeled with dyes like fluorescein, near-infrared dyes like indocyanine green, and 5-aminolevulinic acid can development of novel photodynamic diagnostic (PDD) techniques for cancer patients may result from such an application, mainly when PDD is used during surgery to assess the extent of cancer invasion or to locate microscopic metastatic foci by visualization with the probes [21].

The miRNAs are the non-coding RNAs that are 18–25 nucleotides long, which contributes to cell metabolism by regulating the post-transcriptional expressions of the gene through interaction with the mRNAs. There are various miRNAs; called oncomiR, which are highly expressed in the cancer, thus leading to tumour progression. Each miRNA can simultaneously target multiple genes, potentially enhancing therapeutic effects by influencing several nodes in a pathological pathway. For example, miR-21 expression increases in most cancers, and its targets include tumour suppressors like PDCD4, PTEN, and TPM1 [120]. There are some miRNAs. These miRNAs can be used as targets for cancer therapeutics. More than 30 clinical trials have focused on small ncRNA-based cancer therapeutics, with numerous innovative formulations currently being evaluated in preclinical studies. For example, TargomiRs - miR-16 mimics which target BCL2, CCND1, CDK1, JUN, and EST1, have completed the Phase I studies in malignant pleural mesothelioma and non-small cell lung cancer. Similarly, MRX34 and MRG-106 are under clinical trials (www.clinicaltrial.gov.in). The term tumour "self-homing" refers to the movement of CTCs to establish metastatic lesions and their recruitment to previously removed primary tumour sites. Self-homing CTCs have recently been used in preclinical primary tumour models as delivery systems for anti-cancer medicines. However, the capacity of CTCs to self-home and treat metastatic illness is little unknown. Research work illustrates the remarkable capacity of experimental CTCs to home the metastatic lesions of breast cancer. Additionally, it demonstrates encouraging progress towards effective and targeted delivery of gene-based treatments to treat both primary and metastatic lesions by integrating a prodrug gene therapy system into self-homing CTCs [121].

Engineered cell-based therapies are changing the cancer treatment by utilizing living cells with superior sensing and response capabilities for better therapeutic effect, targeting, and specificity. Recently, efforts have been directed towards engineering NK cells to express chimeric antigen receptors (CARs), which provide them with antigen-specific, MHC-unrestricted cytotoxic abilities. The clinical safety and efficacy of these CAR-expressing NK cells are under study. Similarly, T cell immunotherapies that are engineered, such as T cell receptor (TCR) and chimeric antigen receptor (CAR) engineered T (CAR-T) cell treatments, have been created since the immunological activity of T cells against tumours is commonly reduced during tumour progression. To activate T cells to kill tumour cells, CAR-T and TCR-T cell therapies use gene editing to express CARs or TCRs that recognize tumour cells on the T cell surface [122]. The excellent response rates of CD19-targeted CAR-T cell therapies have amply demonstrated the importance of cell engineering in cancer therapy. CARs are artificial receptors that enable the retargeting of T lymphocytes to identify and eradicate cells expressing

user-defined antigens without the need for the MHC. Despite the revolutionary effects of CAR-T therapy, there are still difficulties with the emergence of cytokine release syndrome, resistance brought on by antigen escape, and worries about on-target off-tumour effects that may cause severe toxicities, especially in the case of solid tumours [123]. AR-NK cells show promise in addressing metastatic solid tumours, which pose challenges for CAR-T cell therapy due to their limitations. They offer intrinsic benefits such as strong cytolytic activity, the ability to target antigens independent of MHC molecules, natural infiltration into tumour tissues, and minimal adverse effects, making them a viable treatment option for solid tumours. Preclinical studies have demonstrated their effectiveness against various solid tumours. However, clinical data on CAR-NK cells in treating solid tumours remain limited, with ongoing phase I/II trials indicating feasibility and potential effectiveness. Continued exploration through clinical trials is essential to fully understand the safety and efficacy of CAR-NK cells in the dynamic field of cancer therapy [124].

In summary, CAR-NK cell therapy is a promising alternative to CAR-T therapy, offering safety, flexibility, and efficacy advantages. Ongoing clinical trials investigating CAR-NK cell therapy for hematological and solid cancers underscore its potential to transform cancer treatment.

A new high-throughput technology called single-cell sequencing (SCS) can be used to analyze a single cell's genomes, transcriptomics, tumour heterogeneity, and epigenetics. Cancer is one of the disorders for which SCS is frequently used in diagnosis and treatment. The expression levels of genes involved in many biological processes connected to metastasis change dynamically throughout metastasis. SCS helps achieve this goal by revealing genetic, transcriptional, and metabolic heterogeneity between primary and metastatic tumours and the mechanisms underpinning gene expression dynamics [125]. The data on SCS might help tailor effective anti-metastasis therapeutic modalities.

8. Conclusion

Metastasis drives the systemic spread of cancer, resulting in new tumour formations in distant organs through a complex, multi-step process. This process involves cancer cells homing and invading target sites, surviving within the vascular environment, and eventually colonizing distant tissues. At each stage, cancer cells must evade immune detection and destruction, adding layers of complexity to our understanding of metastasis, especially in relation to the TME. Despite extensive research efforts, effectively targeting and halting metastasis remains challenging, making it a major cause of cancer-related deaths.

Recent advancements in sensitive detection methods have revealed that tumours can shed cells into the bloodstream at early stages, contradicting previous assumptions that tumour size was a prerequisite for metastasis initiation. Developing effective anti-metastatic agents necessitates a deep understanding of the metastatic cascade, including the interactions of genetic instability, gene expression, and tumour heterogeneity. Although recent research has identified several molecular mechanisms and potential targets for anti-metastatic therapies, successful strategies are still scarce.

A comprehensive understanding of exosome biology, alongside genetic and epigenetic mechanisms of metastasis, offers significant opportunities for advancing cancer diagnostics and therapeutics. Exosomes, with their diverse cargo and roles in intercellular communication, are poised to become integral components of personalized medicine in oncology. Future research must delve into the molecular pathways governing exosome production and function and develop novel therapeutic strategies targeting both genetic and epigenetic regulators of metastasis.

Metastatic gene expression profiles reveal crucial processes such as angiogenesis, tissue remodeling, cell motility, and metabolic adaptations. Targeting deregulated pathways, like the proteasome pathway, shows promise, with inhibitors such as carfilzomib and bortezomib already in use. Site-specific changes in metastasis necessitate tailored therapies, exemplified by targeting IL6 in basal breast cancer. The immune system, particularly tumour-associated macrophages, plays a vital role, with innovative strategies like immune cell membrane-based nanoparticles showing potential.

Emerging therapies include oncolytic virotherapy, CRISPR/Cas9 gene editing, and cell-based therapies like CAR-T and CAR-NK cells. Single-cell sequencing (SCS) provides detailed insights into the heterogeneity of cancer cells, aiding the development of effective anti-metastatic treatments.

Integrating these insights into clinical practice holds the potential to improve patient outcomes significantly, paving the way for more effective and targeted cancer treatments. This review emphasizes the necessity of a deeper understanding of the factors driving metastasis and highlights emerging treatment prospects. It explores tumour-host interactions, targeting specific molecules, angiogenesis, the role of exosomes, and genetic and epigenetic regulation, offering a refined understanding of cancer metastasis and potential therapeutic avenues.

CRediT authorship contribution statement

Manasi S. Pote: Writing – original draft, Writing – review & editing. **Deepshikha Singh:** Writing – original draft, Writing – review & editing. **Aparna M. A:** Writing – review & editing. **Jully Suchita:** Writing – review & editing. **Rajesh N. Gacche:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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