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Escape from Original Home: Do Metastatic Cells Stay Dormant or Destructive?

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ABSTRACT

Metastasis is defined as tumour implants discontinuous with the primary tumour. It is responsible for most cancer-related mortality. Many factors relating to the tumour and host factors are involved in the presence of metastasis and the long-term prognosis of the disease process. This study observed available literature and aims to emphasise tumours and their interaction with the tumour microenvironment. Epigenetic and genetic influences on pathogenesis, tumour and microenvironment interaction, role of epithelial-mesenchymal transition in metastasis are essential determinants of advanced malignant diseases. Early detection of metastatic disease is an essential part. The histopathological aggressiveness of a tumour and its biological behaviour determine the probability of metastasis and advanced disease. Understanding these factors has a benefit to improving the current therapies and diagnostic approaches to an advanced level, leading to the prevention of metastasis and more successful management of patients.

INTRODUCTION

Local invasion and metastasis constitute the primary hallmark of malignant neoplasms. Metastasis contributes to 90% of cancer-related mortality worldwide due to its effect and failure of cancer chemotherapy. The word metastasis comes from a Greek word meaning a change, which prefixes the word stasis

meaning an equilibrium state. Dissemination of cancer cells into the circulation can occur parallel or linear with the development of primary tumours. A unique subset of the cancer cell population forms metastasis-initiating cells (MICs) during the clinical course. MICs escape from the primary site disseminate in the bloodstream and overcome its pressure forces. These disseminating tumour cells (DTCs) enter the bloodstream as circulating tumour cells (CTCs) meet the challenges of the new microenvironment and local immunity of the secondary site before seeding there. Disseminating tumour cells (DTC) may remain in the secondary site as a dormant form for months to years or produce instantaneous and overt tumour formation. Depending on this, the latency period between the initial diagnosis and recurrence of metastasis may vary between different individuals.

Genetic and epigenetic signature of cancer cells and their metastatic clones

Tumour cells are genetically heterogeneous within a tumour (Welch et al., 2019). Intra-tumoral heterogeneity (ITH) represents the clonal evolution of a tumour and its progression. Even though malignant cells are monoclonal in origin, intratumoral genetic heterogeneity develops due to multiple mutations during their clonal evolution, leading to subclones with different biological characteristics. Initially, transformed cells resulted from inherited or acquired mutations that impaired DNA repair, and they are genetically unstable and prone to be affected by random spontaneous mutations in subsequent clonal evolution. The resultant genetic heterogeneity or diversity leads to different clonal genetic architecture within the subclones with variable behaviour, such as subclones capable of survival, growth, invasion and metastasis. Some studies explain the role of genetic heterogeneity in the clonal evolution of tumours. In the clonal evolution of plasma dyscrasia, genetic heterogeneity of selective clones undergoing primary genetic events such as hyperdiploid and chromosomal abnormality results in clonal expansion of plasma cells, which is called gammopathy of undermined significance (MGUS) or smouldering multiple myeloma which are pre-malignant conditions. Secondary genetic events such as MYC rearrangement, TP53 mutation, or DNA repair alteration results in malignant condition (multiple myeloma) (Petrilla et al., 2023). By studying ITH during lateral growth and downward growth (invasion) of tumour evolution, the hierarchy of ITH was seen as early and late branching subclones along the phylogenetic tree. It was observed that early clones with less aggressive potential spread horizontally, whereas later, more aggressive subclones led to deeper and more distant spread (Ryser et al., 2020).

A variety of genetic contributions is needed for the development of a tumour. Carcinogens can induce normal cells to undergo genetic changes called initiating or first-drive mutation. Additional driver mutations contributing to cancer hallmarks result in precursors with stem cell-like properties and later acquire hallmarks of cancer. Additional genetic evolution can form the subclones within a tumour. The resultant intratumoral subclones, known as phenotypic heterogeneity, differ in a given phenotype. Neoplasms having ITH result in different parts of a tumour having different phenotypes and behaviours, resulting in treatment unresponsiveness with poor outcomes and progression to the advanced stage (Jacquemin et al., 2022).

Epigenetic heterogeneity, such as DNA methylation, can cause changes in the behaviour and outcome of a tumour (Hunter, 2018). Tumour environments such as hypoxia, pH, oxygen availability, cytokines secreted by the microenvironment immune cells, and nutrient supply can influence epigenetic change (Flavahan et al., 2017), resulting in epigenetic changes such as aberrant DNA methylation. This results in abnormal control of the cell cycle, DNA damage repair, and cancer-related signalling pathways that can,

in turn, cause transcriptional changes and abnormal structure of DNA or chromatin, which are the early changes in tumour formation. Epigenetic dysregulation results in aberrant epigenetic changes, usually occurring in the early stage of cancer development. Commonly encountered epigenetic changes are DNA methylation, histone modification, and chromatin conformation during cancer initiation, progression and metastasis (Guo et al., 2019). Epigenetic changes can contribute to the onset of tumorigenesis by altering the expression pattern of transcriptional genes (transcriptional heterogeneity) (Jacquemin et al., 2022). Diverse routes drive towards epigenetic aberration during tumour progression and metastasis formation, giving rise to eITH (epigenetic intra-tumour heterogeneity) (Beyes et al., 2021). For example, epigenetic modifications result in tumour cells' adaptation to changing developmental or environmental needs. Subclones that acquire epigenetic heterogeneity, which develop within a primary tumour, acquire propensity to relapse, therapy resistance, dissemination and immune evasion. The aberrant epigenetic changes may serve as early detection, prognostic and chemo-sensitive markers in cancer. A large cohort study of IDH-wild-type glioblastoma cases revealed the presence of widespread epigenetic heterogeneity in DNA methylation (Klughammer et al., 2018). Disruption of the epigenetic regulator by mutation leads to the altered transcriptome, multiplying the effects of a single genetic alteration.

Large numbers of cancers show aneuploidy (Molina et al., 2020), microsatellite instability or chromosomal instability (Tijhuis et al., 2019) and telomere dysfunction (Makki et al., 2015), which are responsible for carcinogenesis and metastasis. During the early phase of carcinogenesis, human cells acquire mutations which alter their phenotypes, and repeated mutations will form new clones. Such clones expand to grow autonomously and disseminate to distant sites. Preexisting well-established oncogenic mutations in heterogeneous cancer cell populations such as KRAS and BRAF are associated with metastatic capability without additional mutation (Jacob et al., 2015).

Gene signatures of metastatic cells that enable them to survive in the journey of metastasis are derived from tumour subclones with microsatellite instability or CpG island methylation phenotypes (Setaffy et al., 2015). RNA binding proteins (RNABPs) such as LIN28A and LIN 28B are overexpressed and correlated with tumour invasiveness and unfavoured survival and recurrent colorectal cancers (Chatterji et al., 2018). These early mutations are supplemented with additional driver genes, such as MUC4 and SRC, for metastasis in tumour evolution (Masoodi et al., 2020; Poturnajova et al., 2020).

Cancer stem cells (CSC), a subpopulation of cancer cells, can undergo multi-lineage differentiation and self-renewal properties (Ayob et al., 2018). CSCs play a role in spread, recurrence and resistance to primary chemotherapy (Zhou et al., 2017). CSC markers such as ALDH1 and CD26 expression are correlated with tumour angiogenesis, tumour progression and metastatic capacities (Ng et al., 2022), and these CSC markers, Notch1 and ALDH1, are associated with perineural invasion, advanced disease in lymph nodes and recurrence (*de* Freitas et al., 2021). Dynamic bidirectional plasticity of tumour cells, which are interchangeable between CSC and non-CSC states, is required for metastasis. Colonic cancer cells with leucine-rich repeat-containing G protein-coupled receptor Lgr5+ (Lgr5), which initiate tumour, change into Lgr5- cells for metastasis, survival in their journey and seeding in the niche sites. These Lgr5- cells regain their Lgr5+ states to continue the expansion of secondary microscopic seeding into larger metastatic clusters (Ganesh et al., 2020). The extent of plasticity may be determined by epigenetic modifications such as DNA methylation and histone modifications

(Kumar et al., 2022). Enzymes such as DNA methyltransferases that modify epigenome are genetically altered in malignancies, such as DNMT3B in pancreatic and breast cancer cells (Yuan et al., 2019).

The journey of metastatic cells and their behaviour at secondary sites

Dissemination of tumour cells to distant sites involves a cascade of events. With the effect of genetic mutation and environmental carcinogens, neoplastic cells grow at the primary sites. For survival and growth, tumour angiogenesis is an essential process which may vary in extent based on the tumour type. Metastasising tumour cells may have the same molecular features as the primary or different properties from those at the primary site (Poturnajova et al., 2021; Welch et al., 2019). For their survival in a new site, MICs possess properties for autonomous renewal chemotherapy resistance.

Vascular endothelial growth factor receptor (VEGFR2) and endothelial receptor tyrosine kinases TIE1 and TIE2 are core signatures that regulate pro-angiogenic VEGF and angiopoietin signalling (Lugano et al., 2020). Mutant clones of tumour-initiating cells capable of migration also proliferate at high rates. They invade through nearby stroma by individual cells or in collective migration (Welch et al., 2019). The balance between antitumour immune functions and pro-tumour (budding) determines the extent of tumour spread.

Large numbers of cancer cells are shed in the bloodstream daily, but only < 0.1% of tumour cells metastasise (Fares et al., 2020). The metastasising cells must leave their original sites through the basement membrane. Metastatic cells can re-infiltrate the original tumour (self–seeding) and metastasis to metastasis spread. Many processes are occurring in TME, including matrix degradation and acquired adjustment of cytoskeletal activity. Membrane protrusions called invadopodia have high proteolytic properties, enabling the cancer cells to invade the dense scaffold of stroma (Augoff et al., 2020; Welch et al., 2019). Cancer cells produce ECM niche periostin and tenascin C to transform fibroblasts in MET into cancer-associated fibroblasts (CAF) that promote invasion and metastasis (Asif et al., 2021). TGF signaling render CAFs secrete cytokine such as IL-11 to activate STAT3 signaling to intensify the ability of metastatic cells to survive in secondary sites (Lai et al., 2020). Cancer cells optimise their environment during their journey to secondary sites by increasing NADPH through various pathways to overcome oxidative stress (Hayes et al., 2020). Tumour cells form emboli among themselves or with some platelets and immune cells within the circulation or acquire certain mesenchymal traits through epithelial-mesenchymal (EMT) (Makki et al., 2015). EMT enables invasive front cells to have better motility ability to degrade extracellular matrix than epithelial cells (Poturnajova et al., 2021).

After surviving the haemodynamic forces within the vessels and reaching niche secondary sites, tumour cells arrest in areas of microcapillaries start their extravasation and settle as microfoci at the site to remain dormant or progressive to form macroscopic tumours (Welch et al., 2019). Early Metastatic cancer cells show cancer-derived specific microRNAs (miRNAs) that can modify the tumour microenvironment (Loo et al., 2016) and the level of mRNAs correlated with grading and recurrences (Fletcher et al., 2019) and suggested miRNAs as a prognostic biomarker and deregulated mRNAs are used as trials in cancer treatment (Chakraborty et al., 2021).

Colorectal cancers with microsatellite instability CRC can initiate a MHC–mediated immune response of T cells, thus showing more intralesional lymphocyte infiltration (Taylor et al., 2022). EMT transcription factors, including *SNAI1*, *ZEB1* and *TGF-β*, have been shown to suppress the functioning of the immune system of TME (Wu et al., 2020). Immune surveillance functions at the tumour

microenvironment (TME) account for more than half of the arrest metastases (Cheng et al., 2020). Some genetic expression controls the dormancy of metastatic cancer cells. Genes such as *Cfh*, *Gas6* and *Ogn* are up-regulated in dormant breast cancer cells compared to proliferative cells (Ren et al., 2022).

After settling in secondary sites, tumour cells remain as non-detectable single cells or tiny clusters of quiescent cells in a dormant stage before the development of macrometastasis (Blasco, et al. 2022). The balance between proliferation rate and cell death determines the time of awakening of cellular dormancy. In addition, there is a necessity for maturation with further genomic alteration to form overt cancer, which explains the latency of detectable secondary formation (Klein et al., 2020).

Organotropism and Metastasis

Various cancers display different spread patterns and preferred locations for secondary seeding. Cells that can intrigue the mechanical permissiveness of the capillary endothelial barrier will seed at the target distant organs. Endothelial cells (ECs) vascular endothelial growth factor (VEGF) regulates angiogenesis and new vessel formation and it is up-regulated in human cancers. ECs control the transmigration of circulating tumour cells, an important step in spreading tumour through surface receptor expression. ECs are divided into subpopulations based on their morphology and functions (Hennigs et al., 2021). Colorectal cancers most likely metastasise to the liver due to their fenestrated endothelial cells of liver sinusoids, allowing higher permeability of cancer cells (Martin et al., 2022). It may be explained by the fact that metastasis is a possibility of the anatomical location and sharing portal venous system between the organs. One theory explains that a rich sinusoidal network and slow blood flow through the liver make it more permeable to cells and other metabolites (Mielgo et al., 2020).

Pre-metastatic niche concept postulates that chemoattractants, extracellular vesicles (EVs) and growth factors produced by primary tumour cells may modify and prime the tumour microenvironment such as increased vascular permeability and matrix remodelling to enhance the seeding and growth (Dong et al., 2021). Cancer-derived EVs elicit pro-inflammation and profibrotic reactions after being taken up by tissue macrophages, leading to fibrous tissue formation and supporting further metastasis (Taboada et al., 2022). Due to their important role in metastasis, therapeutics that inhibit EV bio-formation and secretion may be an alternative to cancer treatment.

The research found an interaction between the brain's blood-brain barrier (BBB) and circulating breast cancer cells (BCC). Invadopodia formation of BCCs by FAK and β4-integrin favours the invasion of distant tissues and BBB endothelial remodelling with cytoskeleton, leading to paracellular intra and transcellular permeability (Godinho et al., 2021). This fact explains why metastasis commonly occurs in the brain instead of having a highly selective blood-brain barrier. Early Metastatic cancer cells show cancer-derived specific microRNAs (miRNAs) that can modify the tumour microenvironment (Loo et al., 2016).

Metabolic reprogramming is an adaptive change used by cancer cells to survive. Cancer cells can induce the expression of OXCT1 enzymes for ketone metabolism, rendering the ketones usable for energy and progression (Hwang et al., 2022). This study stated that dietary intervention with keto diets may target metabolic changes and give benefits as a support for chemotherapy. The metabolic phenotype of a tumour is determined by genetic mutation through oncogenic signalling pathways. Conversely, oncogene-driven metabolic programming also affects the metabolism–related gene expression. Modifying these epigenomic–metabolic

interactions enhances cell proliferation even in conditions with restricted growth factors and metastasis (Goncalves et al., 2018). Organ-specific metabolic adaptations render the cancer cells to survive in distant organs as organo-tropic phenotypes (Schild et al., 2018).

Histologic grading influencing the staging of cancer

Histologic grading is a simple method to determine the disease prognosis. Its reproducibility and strong correlation with disease prognosis are demonstrated in 1813 breast cancer patients (Boiesen et al., 2000). Morphological features with immunohistochemical studies help to improve the prediction values for prognosis. Cell proliferation markers such as Ki-67 protein, positive for all cell cycles except for resting cells S phase and phosphohistone H3 (PHH3), showed great promise (van Steenhoven et al., 2022). Artificial intelligence helps to better assess the metastatic lymph node status, mitoses counting and facilitates expert communications (Kim et al., 2022). These tests are comparable to an expert pathologist without time pressure and constraints. Molecular and gene profile studies are new tools to predict tumour behaviour. They give added value to classic biomarkers for the decision to start adjuvant therapy and facilitate expert communications (Gyanchandani et al., 2016). Many malignant tumours, regardless of early diagnosis, complete resection and staging at the time of diagnosis, can give rise to either local recurrence or distant metastasis. Standardised pathological reports, using newly developed algorithms and report systems for large cancer registry data, provide more precise information on cancer behaviour and epidemiology of sites of metastasis (Soysal et al., 2017).

Epithelial-mesenchymal transition (EMT) and its role in metastasis

Epithelial-mesenchymal transition (EMT) is a cellular process which plays an essential part in cancer progression and advanced disease. After initiated by signalling through growth factors, Notch ligands, and tumour microenvironment factors such as hypoxia, cancer cells acquire phenotypical and biological behaviour changes into mesenchymal cells, which is called epithelial-mesenchymal plasticity. The expression of N-cadherin virement histologically evidences cancer cells undergoing EMT in cancer progression as mesenchymal markers and suppression of E-cadherin and cytokeratin as epithelial markers (Jørgensen et al., 2020; Makki et al., 2015). These transformed mesenchymal cells lose their cellular adhesion and acquire strong cytoskeleton, favouring more resistance to sustained injury during migration. Through EMT, cells acquired an increased ability to migrate and invade tissues by changing cell polarity from basal–apical to frontal polarity (Jung et al., 2019). Epigenetic regulators such as methylation of E-cadherin (CDH1), a calcium-dependent cell adhesion protein seen in most cancers, are the EMT process's main regulators. Downregulation of E-cadherin triggers partial EMT and increases the migratory of human embryonic stem cells (hESC) (Aban et al., 2021). In addition, EMT endows cancer cells with resistance during cancer chemotherapy.

Ferroptosis is a cell death induced by lethal lipid peroxidation. Epigenetic reprogramming of E-cadherin of EMT process inhibition may modify the cancer cell plasticity. Studies showed that therapy-resistant cancers are associated with a mesenchymal or metastatic property that is apt to be and they are more susceptible to ferroptosis inducers. Ferroptosis is also regulated by E-cadherin-mediated intercellular interaction, resulting in suppressing ferroptosis. This suggests E-cadherin inhibition or EMT induction in cancer cells might enhance ferroptosis. Experiments showed CDH1 down-regulation increases the ferroptosis susceptibility in cancer cells, showing epithelial markers, whereas overexpression of CDH1 reduces the susceptibility (Lee et al., 2020).

Advanced diagnostic strategies

Molecular alteration in cancer genes results in the formation of cancer driver genes and non-driver mutations. Cancer-driver genes have acquired mutations commonly linked to cancer initiation, progression and metastasis and have selective advantages, whereas non-driver genes lack this property. These driver genes can be identified and predicted risk by computational methods. Such computational predictors use data sets and predict cancer pathogenic and non-pathogenic somatic mutations (Feizi et al., 2022). Methods are generally based on mutational frequency for mutation significance, functional impact of mutation and structural consequences (Active Driver) (Reimand et al., 2013). Network analysis for identifying pathways creates a gene network for each patient. It detects the minimal set of mutated genes controlling the maximal differentially expressed (Guo et al., 2018) and functional multiomic integration to predict response to treatment and cancer subtypes (Pham et al., 2021). The identified driver genes are listed in data sets such as the network of cancer genes (NCG) and database (Repana et al., 2019) and FI-net (Gu et al., 2020).

As metastasis is a most dangerous tribute of malignancy, it is mandatory to exclude metastasis at first diagnosis before the decision of treatment and at follow-up visits. A new non-invasive test in clinical oncology is the liquid biopsy, which uses blood or body fluids such as urine or pleural fluid to detect circulating tumour cells (CTCs), DNA (ctDNA), or tumour extracellular vesicles. The tumour's molecular profile is obtained through single or repeated sampling by liquid biopsy, and individually personalised therapy can be arranged for real-time monitoring of therapy and screening for chemotherapy resistance in the management course (Lone et al., 2022). Precise genomic atlas for various cancers provide more information on the molecular profile of the tumour and is advantageous for the decision of treatment modalities such as targeting angiogenesis or triggering cancer death by apoptosis (Li et al., 2021). CTCs can be tested for intra and inter-patient variable expression of epidermal growth factor receptor (EGFR)-related genes like KRAS and PIK3CA to determine colorectal cancer response and therapeutic outcomes (Luo et al., 2020).

A rapid autopsy is a post-mortem examination performed on an urgent basis after the death of a patient. Large and adequate tissue samples can be taken from many body sites at autopsy and are analysed for molecular sequencing, proteomic analysis or immunological analysis in various types of cancer. This procedure allows the study of the diseases after aggressive local or distant spread. A sufficient amount of tissue sampling enhances the study by multiple disciplines (Hooper et al., 2021). Scientists discovered a new strategy for patients' avatars using animal avatars, xenografting in immunocompromised mice models or in vitro 2D cell line cultures. This method can provide multidisciplinary studies on tumour behaviour and treatment response based on genomic, proteomic and epigenetic analysis are now in advance (Fazio et al., 2020).

Minimal residual diseases (MRDs) are multicellular secondary tumour cell clusters or disseminated single tumour cells (DTCs) after treatment. The aim of detecting MRD is to monitor response to therapy and possible relapse (Kruse et al., 2020). MRD is assessed by detecting phenotypes or gene expression using flow cytometry, polymerase chain reaction or next-generation sequencing. Multiple levels of MRD testing are used to identify risk profile for adjusting the chemotherapy duration. The molecular sequencing method detects cell-free circulating tumour DNA (ctDNA) after neoadjuvant systemic therapy in triple-negative breast cancer. Several study results showed that ctDNA positivity rate and 3-year event–free survival and overall survival are positively correlated (Stecklein et al., 2023). Advances in multidisciplinary sections such as clinical, pathology, and laboratory

investigations are crucial for comprehensively treating primary and secondary malignancies (Parker et al., 2022).

CONCLUSION

The study of key biological features and the process of disease progression of malignant tumours is essential for predicting prognosis and management plans. Identifying high-risk patients who can develop metastasis is challenging in real practice. Further research should be performed to understand more about the role of genetic and epigenetic factors, biological behaviour of tumours and their reactions with tumour environment in progression of disease. Understanding the mechanism of advanced disease and ways to detect it before well-established seeding in distant sites will help improve existing treatment, leading to more effective, timely control of malignant diseases.

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CONFLICT INTEREST

We have no conflict of interest to disclose.

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