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Biosensors for metastatic cancer cell detection

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ABSTRACT

Early detection and effective cancer treatment are critical to improving metastatic cancer cell diagnosis and management today. In particular, accurate qualitative diagnosis of metastatic cancer cell represents an important step in the diagnosis of cancer. Today, biosensors have been widely developed due to the daily need to measure different chemical and biological species. Biosensors are utilized to quantify chemical and biological phenomena by generating signals that are directly proportional to the quantity of the analyte present in the reaction. Biosensors are widely used in disease control, drug delivery, infection detection, detection of pathogenic microorganisms, and markers that indicate a specific disease in the body. These devices have been especially popular in the field of metastatic cancer cell diagnosis and treatment due to their portability, high sensitivity, high specificity, ease of use and short response time. This article examines biosensors for metastatic cancer cells. It also studies metastatic cancer cells and the mechanism of metastasis. Finally, the function of biosensors and biomarkers in metastatic cancer cells is investigated.

1. Introduction

In certain nations, cancer is the second largest cause of mortality behind cardiovascular disease [1–3]. While for Iran, it comes out to be third leading factor for deaths, falling behind only the cardiovascular disease, and accidents [4] and is regarded as one the most important problem faced in many developed and developing countries [5–8]. The International Agency for Research on Cancer estimated 9.7 million deaths from cancer in the year 2022 alone and 20 million new cases. They also estimate that about 1 in 5 people will develop cancer in their lifetime. The number of cancers in a year is predicted to have a 77 % increase from 20 million in 2022 to 35 million in 2050 [9]. As a result, the World Health Organization considers cancer as a significant chronic disorder that requires continuing and diligent self-care [10]. Hence, cancer is a broad word encompassing a diverse array of illnesses capable of impacting many anatomical regions inside the human body [11,12]. Cancer cells are abnormal tissue masses that grow asymmetrically and larger than normal tissue due to their inability to respond to normal growth regulators and signals. They originate from cells with genetic damage caused by factors like heredity, chemicals, radiation, or viruses. The transformation from a normal cell to cancer involves a multi-stage process where damaged DNA replicates, mutations activate oncogenes, alter regulatory genes, or deactivate cancer-inhibiting genes. These changes lead to abnormal gene expression and malignant tumor growth [13–15]. The most prominent feature of malignant tumors is the invasive spread and metastatic capacity of cancer cells [16,17]. Metastasis is a complex, multi-stage process in which cancer cells acquire the ability to move from their original location (primary tumor) to distant areas.

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Metastatic is the deadliest stage and cause 90 % of cancer deaths [18–21]. Cancer metastasis begins with invasion, where cancer cells alter their connections with surrounding tissue components like the extracellular matrix (ECM). Proteases like matrix metalloproteinases (MMP), urokinase plasminogen activator (uPA), and others break down tissue, allowing cancer cells to move. During invasion, the expression of E-Cadherin (an epithelial factor) decreases while N-Cadherin (a mesenchymal factor) increases, aiding in cellular motility and attachment to new sites. These detached cancer cells then enter circulation or the lymphatic system (intravasation), forming emboli by binding to platelets and lymphocytes. As they reach small vessels in distant organs, cancer cells exit the circulation (extravasation) to initiate secondary tumor growth [22–25]. Thus, increasing demands for early, accurate and highly sensitive diagnosis of metastatic cancer cells demonstrate the importance of developing new diagnostic technologies [26,27]. Metastatic cancer cells provide a substantial global health challenge and represent a prominent contributor to mortality on a global scale. Prompt detection of these sophisticated cancer cells is imperative for efficient therapy. Detecting cancer biomarkers, molecules, genes, or other measurable traits in blood or tissue can indicate the presence of cancer at an early stage. This early detection allows for prompt treatment, potentially extending the patient's lifespan by addressing the disease before it progresses to later, more critical stages [28,29]. It is essential to make use of biosensors in order to accurately diagnose and manage cancer cells that have spread to other parts of the body. Emerging biomarkers can be detected by designing a suitable biosensor, and the effect of the drug on target sites can be determined [30,31]. In comparison with other diagnostic methods, biosensors are among the early and economical diagnostic tools that have high sensitivity, reduction potential and usability in home applications [32,33]. Zhang et al. [34] evaluated that traditional tumor detection methods, like immunological and histopathological techniques, pose challenges including high costs, complexity, and prolonged turnaround time. Electrochemical technique provides quick, sensitive, and specific detection, allowing for early tumor identification and prognosis. This review focuses on recent advancements and applications of electrochemical biosensors in tumor cell detection [34]. A sophisticated electrochemiluminescence (ECL) sensing device was developed by Ye et al. [35] for the purpose of diagnosing breast cancer and identifying metastatic breast cancer. They discovered microRNA-21 (miR-21) as a breast cancer biomarker by using enzyme-free DNA amplification in conjunction with ECL. To suppress ECL signals in the presence of miR-21, the system employs a catalytic three-hairpin assembly (CTHA) circuit, and miR-105 levels are measured using toehold-mediated strand displacement reactions (TSDRs). Validated using cellular and serum samples, the ECL biosensor displays large linear detection ranges and low detection limits for miR-21 and miR-105. It efficiently identifies breast cancer cell lines (MCF-7 and MDA-MB-231 cells) from non-breast cancer cells (HepG2, TPC-1, and HeLa), as well as malignant MCF-7 and metastatic MDA-MB-231 cells [35]. Premachandran et al. [36] has developed a SERS-functionalized L-MISC (Lung-Metastasis Initiating Stem Cells) nanosensor to detect metastatic signatures in patient blood. Their research characterized cancer stem cell populations in lung cancer, revealing distinct profiles. The nanosensor, with single-cell sensitivity, detects MISCs accurately, aided by machine learning. Their method diagnoses metastatic lung cancer with high sensitivity from just 5 μl of blood, validated with clinical samples achieving 100 % sensitivity. The L-MISC nanosensor provides a quick, non-invasive, and accurate detection of lung cancer metastases [36]. The aim of this article was to use biosensors for metastatic cancer cells. In addition, this article covers current research on biosensors as a device for detecting metastatic cancer cells, to enable the use of biosensors in the development of metastatic cancer cell diagnosis in the future. Also, metastatic cancer cells, metastasis mechanism, biosensors and biomarkers were evaluated for metastatic cancer cells.

2. Metastatic cancer cell

The most fatal and advanced stage of cancer is metastasis, which refers to the spread of cancer cells to distant organs from their original site. The vast majority of cancer-related fatalities are caused by metastatic illness rather than the initial tumor itself. Metastasis involves a sequence of biological processes where cells from the original tumor gain the ability to invade surrounding tissues, move through blood vessels, lymphatic channels, or adjacent structures, establish in distant organs, and then resume growing to form new tumors at these distant sites [37–39]. The aggressive spread of cancer (metastasis) is primarily linked to the degree of malignancy of the original tumor. However, a common feature across all metastases is the progression through a series of steps known as the "invasion-metastasis cascade" [40]. The initiation of this process occurs when neoplastic cells undergo invasiveness and experience a loss of adhesion to the adjacent matrix, comprising the basement membrane (BM) and extracellular matrix. As a result, these tumor cells move away from the main tumor and infiltrate adjacent organs [41]. Consequently, infiltrating blood arteries or lymph vessels, disseminated tumor cells undergo a response to many resistance conditions, including shear stress, anoikis, and immune surveillance inside the circulatory system [42]. A restricted proportion of neoplastic cells are capable of enduring the adverse conditions present in the bloodstream. Once tumor cells have effectively invaded the secondary site, they adhere to the endothelium of the target organ, release fluid, and migrate into the organ parenchyma, which serves as the "pre-metastatic niche" [43–45]. They either start out as a single cell in a long-term latent state or as several cells in micrometastasis, and later they start to grow constantly to produce clinical metastases (Fig. 1) [46]. Tumor cells may take on several phenotypic cell states and manipulate surrounding stromal and immune cells in the tumor environment to facilitate their growth and evade the immune system, which powers each of these activities [47]. Metastatic cancer differs from ordinary primary tumors in that either it can cause direct disruption to an organ by colonizing it, or might cause mortality via changing the organ's metabolism through changed secretomes [37,48]. Even in the same patient, the response to systemic therapy might vary greatly between primary and metastatic illness. Clinically visible metastasis is typically incurable, with rare exceptions, due to metastatic cancers' acquired resistance to conventional therapy. Clinical trials targeting different events in tumor metastasis are presented in Table 1.

3. Metastatic mechanism

The complex process of metastatic disease involves the spread of cancerous cells from the primary tumor, their infiltration of nearby tissues and organs, and the development of new tumors [54]. To get a better understanding of the cellular and molecular causes of metastasis, Isaiah J. Fidler presented the invasion-metastasis cascade concept in 2003. S. Valasytan later accepted this theory. The formation of micrometastases, metastatic colonization, arrest at distant places and extravasation, intravasation and survival in the circulation, and local invasion are the mechanisms that lead to distant metastasis from the primary tumor, as shown in Fig. 2 [55]. The complicated connections between malignant and non-malignant cells, the extracellular matrix (ECM) biochemistry, biomechanics, and a variety of secreted chemicals all play a role in the multifaceted process of cancer spread [56]. Fig. 2 depicts crucial steps of this process. 1. ***Local Invasion** The onset and maintenance of cancer invasion are assisted by modulating cytoskeletal dynamics in cancer cells and the turnover of cell-ECM and cell–cell junctions [56]. Epithelial-mesenchymal transition (EMT), induced by stimuli like hypoxia, cytokines, and growth factors, enables cancer cells to migrate and invade [55,57]. EMT is regulated by transcriptional factors (Twist, Snail, Slug, ZEB1, ZEB2) or by epigenetic processes [57,58]. Vimentin and N-cadherin (the cadherin switch) are overexpressed while E-cadherin is downregulated in EMT [59]. Through

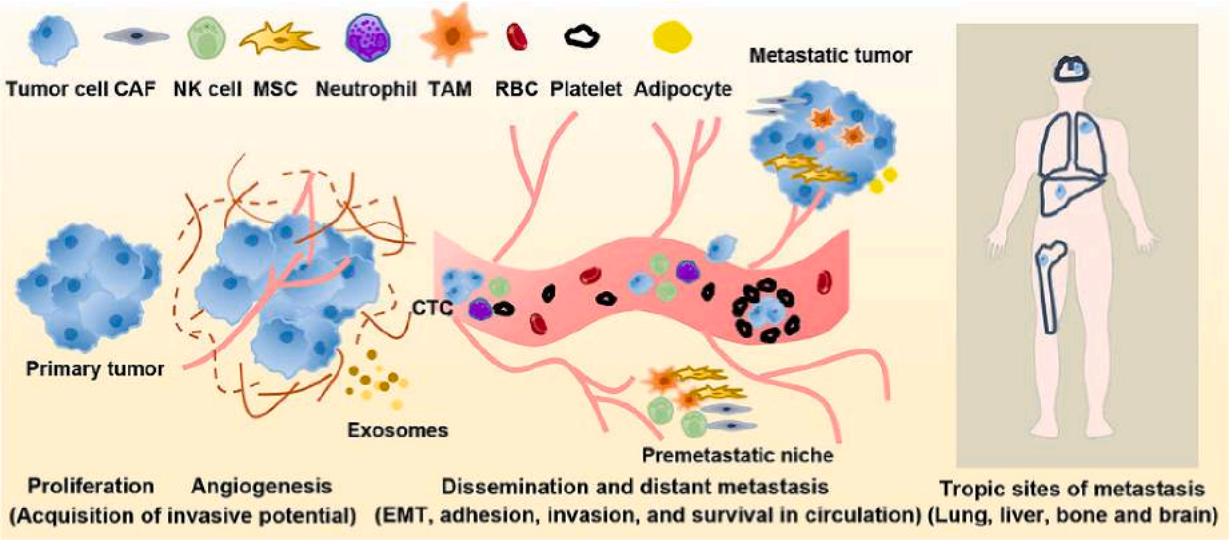

Fig. 1. The metastatic cascade in summary. After breaking free from the main tumor, cancer cells travel and infiltrate through the extracellular matrix and basement membrane. They then enter the blood or lymphatic vessels, intravasate into the bloodstream, pierce the blood or lymphatic vessels (extravasation), attach, and grow in secondary locations. The signals that surround the tumor from a variety of stromal cells, immune cells, and other molecular elements enhance the ability of cancer cells to spread. Platelets and neutrophils shield tumor cells from shear stress, secrete TGF-β, neutralize NK cell cytotoxicity, and promote immune escape. Abbreviations: BM, basement membrane; CAF, cancer-associated fibroblast; CTC, circulating tumor cell; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; MSC, mesenchymal stem cell; NK cell, natural killer cell; RBC, red blood cell; TAM, tumor-associated macrophage (Reprinted with permission [46]).

Table 1
Clinical trials to target different events in tumor metastasis.

Type of cancer	Factor's name	Mechanism of action	Consequences	Ref.
Advanced hepatocellular carcinoma	Galunisertib	Galunisertib is a selective inhibitor of transforming growth factor-β receptor type I. The drug changed the plasma levels of related proteins	Median overall survival was improved in the treated patients	[49]
Advanced solid tumors	Chiauranib	Chiauranib is a multi-target kinase inhibitor. Chiauranib suppresses simultaneously suppresses kinases related to angiogenesis, mitosis and chronic inflammation	A majority of patients (66.7 %) receiving chiauranib showed stable disease	[50]
Metastatic non-small cell lung cancer	hydroxychloroquine	Hydroxychloroquine is an inhibitor of autophagy. Hydroxychloroquine combination with chemotherapy (paclitaxel, carboplatin with/without bevacizumab) improved objective response rate and progression-free survival more in KRAS+ tumors	Addition of Hydroxychloroquine may overcome resistance to chemotherapy	[51]
Metastatic breast cancer	Eribulin	Eribulin is a microtubule dynamic suppressor. Eribulin treatment increased epithelial–mesenchymal transition conversion (enhanced E-cadherin expression in cancer cells) and improve vascular normality (decreased CA9 expression in tumor vasculature)	Patients showed higher rate and durable responses, explained partially by decreasing the evolving of new metastatic foci in cancer patients	[52]
Melanoma	AuNPs	Gold NPs (AuNPs) facilitated vascular normalization, enhanced blood perfusion and reduced hypoxia, and reversed epithelial–mesenchymal transition	Patients receiving AuNPs represented lower rates of lung metastasis	[53]

integrin clustering and intracellular kinase signaling pathway activation, which alter EMT, cancer migration, and invasion, ECM remodeling plays a role in the causation of cancer [56]. After separation from the initial lesions, EMT, migration, and invasion through the basement membrane, MMPs (−1, −2, −9) and uPA/uPAR break down the extracellular matrix (ECM) [55,60]. 2. **Intravasation and Survival in Circulation:** Tumor cells actively enter the circulation, facilitated by MMPs or uPA/uPAR [55]. Tumor neovascularization and lymphangiogenesis are linked to metastasis; both processes are fueled by the production of pro-angiogenic stimuli and the downregulation of anti-angiogenic proteins [56,61]. Circulating tumor cells (CTCs) overexpressing TrkB or Wnt2 avoid anoikis (death due to anchorage detachment). Staying alive in the bloodstream requires avoiding natural killer cells, generating platelet clusters (a process called tumor cell-induced platelet aggregation), and defending against physical shear pressures [55,62]. 3. **Arrest at Distant Sites and Extravasation:** Cancer cells leaving circulation (extravasation) invade distant organs through disruption of vascular junctions, facilitated by various factors like epiregulin, MMPs, and COX-2 [62]. Metastatic colonization is site-specific, involving organ-specific chemokines and receptors on tumor cells [55]. Cancer cells trapped in emboli release substances such as CCL2 to attract inflammatory monocytes that facilitate metastatic colonization [63]. 4. **Micrometastasis Formation and Colonization:** Cancer cells encounter difficulties in novel settings because of variations in the stromal constituents, tissue configuration, and cytokine milieu [62]. Tissue-specific adaptations are necessary for survival and colonization. Cancer cells mimic non-cancerous resident cells, expressing markers like serpins to evade cell death [56]. Metastasis relies on epigenetic variables, soluble signals, cell–cell interactions, and ECM dynamics [64]. Metastasis involves proteolytic systems like MMPs, regulated by uPA/uPAR and tissue inhibitors of metalloproteinases (TIMPs) [65,66]. Despite numerous cancer cells entering circulation, only a fraction survives to extravasate and form metastases [56]. The "seed and soil" hypothesis by Steven Paget emphasizes the importance

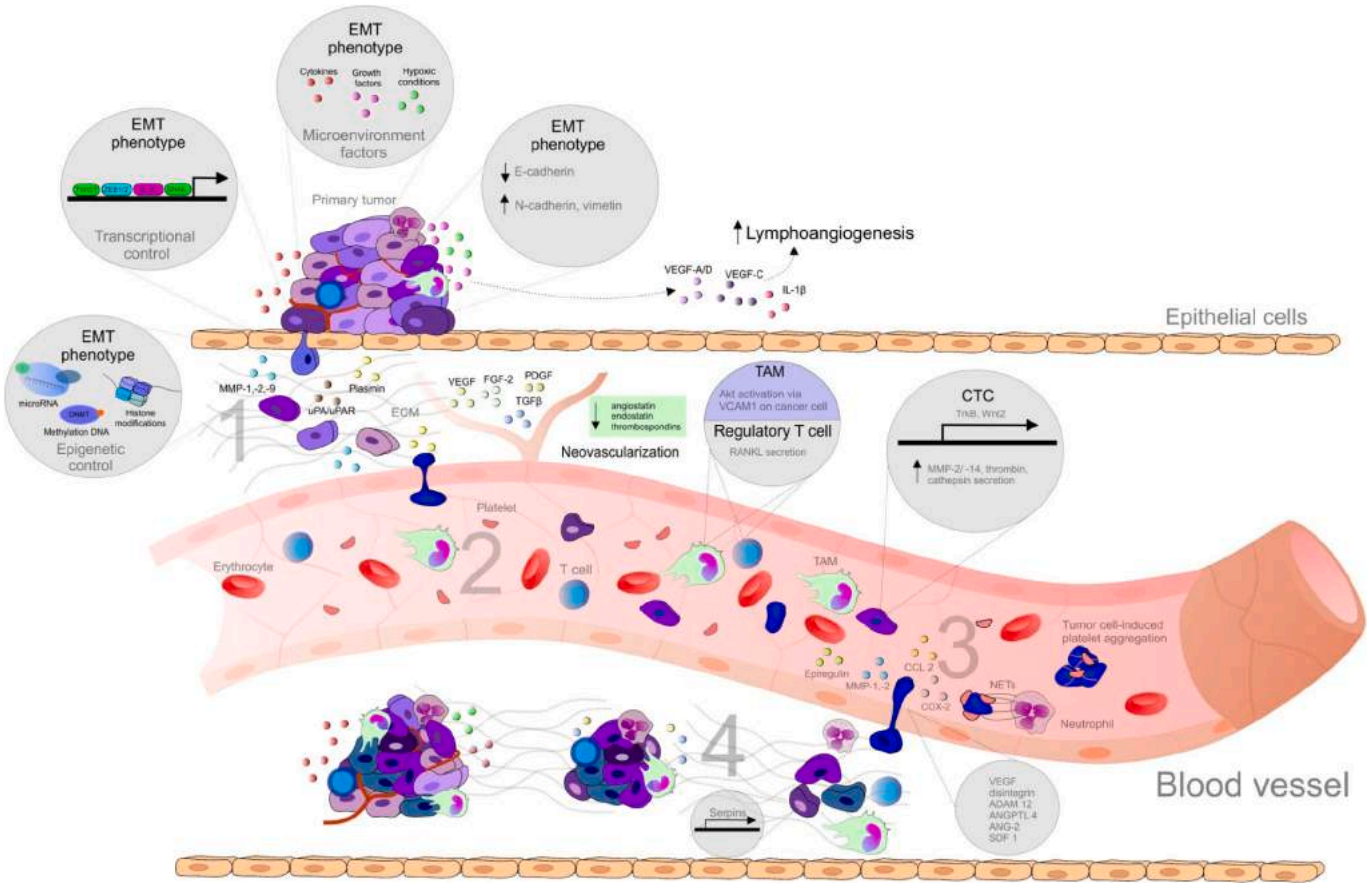

Fig. 2. The process of metastatic spread from the primary tumor involves several key steps facilitated by various molecular factors and cellular processes. These include the following components: ADAM12 (a metalloproteinase domain-containing protein), ANG-2 (angiotensin II), ANGPTL4 (angiopoietin-like 4), CCL2 (CC-chemokine ligand 2), COX-2 (cyclooxygenase-2), CTCs (circulating tumor cells), DNMT (DNA methyltransferase), DTCs (disseminated tumor cells), ECM (extracellular matrix), EMT (epithelial-mesenchymal transition), FGF (fibroblast growth factor), IL (interleukin), MAMs (metastasis-associated macrophages), MMPs (matrix metalloproteinase), NET (neutrophil extracellular traps), PDGF (platelet-derived growth factor), RANKL (regulatory T cells producing receptor activator of nuclear factor-κB ligand), SDF1 (stromal cell-derived factor 1), Snail and Slug (transcription factors of the Snail family), TAM (tumor-associated macrophages), TCs (tumor cells), TGFβ (transforming growth factor beta), Twist (basic helix-loop-helix factors), uPA/uPAR (urokinase plasminogen activator/urokinase plasminogen activator receptor), VCAM1 (vascular cell adhesion molecule 1), VEGF (vascular endothelial growth factor), and ZEB (zinc-finger E-box-binding factors) such as dEF1/ZEB homeobox 1 and Smad-interacting protein 1/ZEB2. These elements collectively contribute to the progression of metastasis, a complex and coordinated process critical in the dissemination and establishment of secondary tumors at distant sites in the body. (Reprinted with permission [70] Copyright © 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

of both cancer cell properties (seed) and the microenvironment (soil) for successful metastasis [67]. Tumors modify future metastatic sites prior to CTC arrival, creating a pre-metastatic niche through secreted factors and extracellular vesicles [56]. Chronic inflammation plays a critical role in tumor progression and metastasis by altering tissue homeostasis and immune response [68]. Immune cells exhibit diversity and plasticity, influencing metastasis either positively or negatively. Cancer-derived cytokines drive immune cells toward a tumor-promoting phenotype, contributing to immune evasion [69].

4. Stages of metastatic

The three overlapping stages of metastasis—dormancy, colonization, and dispersion—allow cancer cells to enter tissues, endure while in transit, and settle within organs. This entire process is known as the metastatic cascade (Fig. 3) [37,38]. Dissemination occurs when certain oncogenic mutations from tumors penetrate the basement membrane and move into deeper tissue layers, where they acquire the ability to survive in the lack of specific growth triggers. They then intrude into nearby blood vessels or lymphatic vessels (a process known as intravasation) and later exit these vessels (extravasation) to enter distant organs. This exit can happen through crossing endothelial cell barriers, disrupting capillaries, migrating alongside nerves, or directly spreading into nearby spaces like the peritoneal or pleural cavities [37,38,71]. During circulation, circulating tumor cells (CTCs) endure considerable decrease owing to physical, redox, and immunological stressors, as proven in mice studies and shown by the low concentration of CTCs in the bloodstream quickly after the original tumor excision (Fig. 3) [72–74]. CTCs circulate either as individual cells or in small groups containing stem-like cancer cells. These groups are often covered with platelets, neutrophils, or stromal cells derived from the tumor itself. This shielding can help CTC clusters evade immune detection and also enhances their ability to spread to other parts of the body compared to individual CTCs [72]. When disseminated tumor cells (DTCs) reach distant organs, they are usually eliminated because of high levels of oxidative stress, inadequate growth factors or nutrients, and active immune defenses, which include natural killer (NK) cells, infiltrating T cells, tissue-specific macrophages, and other immune surveillance mechanisms [47,71]. Some DTCs that survive can undergo a variable period of dormancy (Fig. 3). During this time, they may stop dividing or reach a state of balance where occasional bursts of growth are balanced by immune responses or containment within the tumor

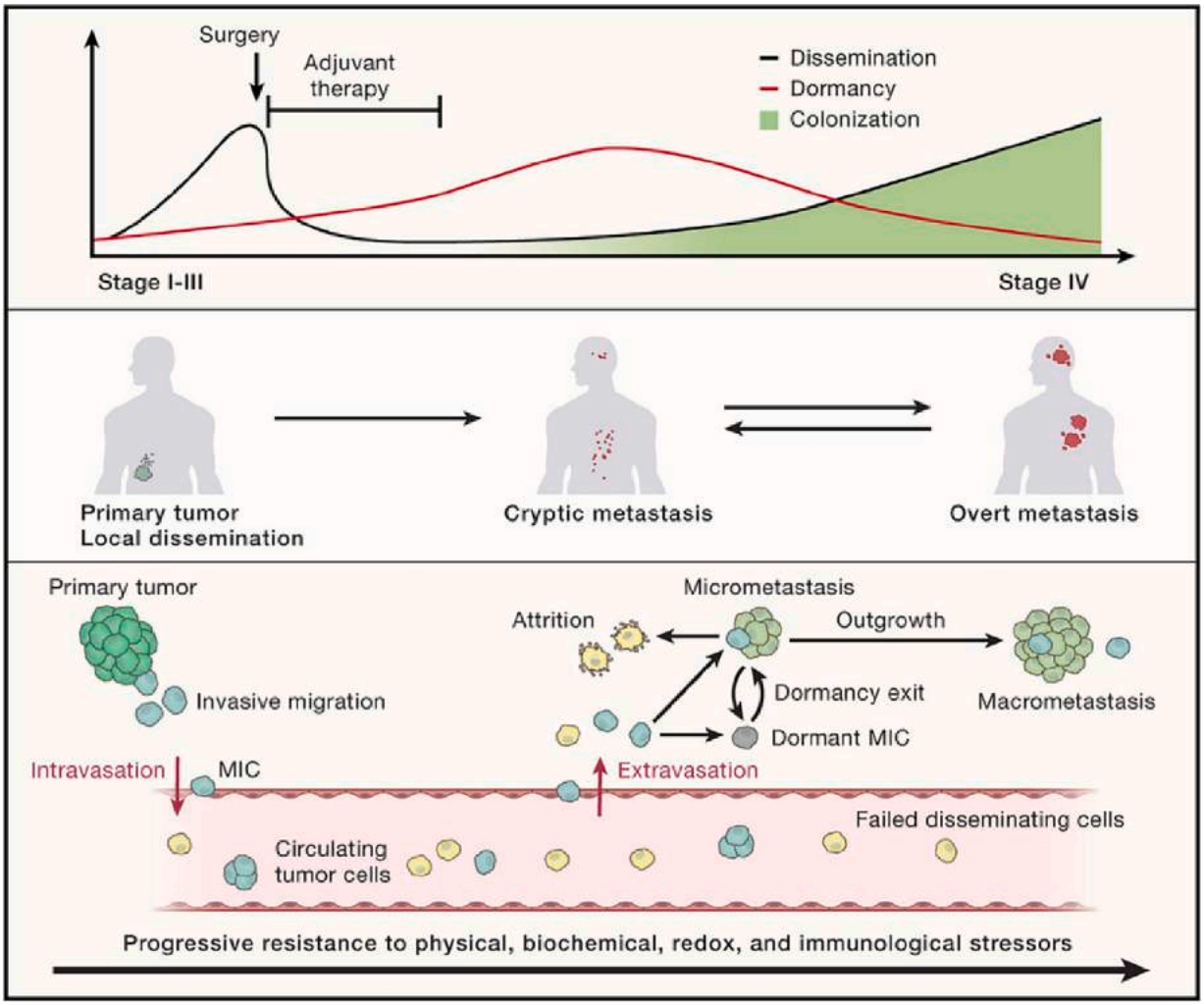

Fig. 3. Metastasis consists of three stages: diffusion, dormancy, and colonization, all of which can coexist and overlap over time. MICs are derived from primary tumors and can move invasively before disseminating as CTCs via the blood or lymphatics. Physical, metabolic, and immunological stresses drive the clearance of the majority of CTCs. CTCs, which are trapped in distant organ capillary beds, extravasate and move into organ parenchyma as DTCs, seeding nascent metastases. DTCs reproduce in organ-specific perivascular habitats. The majority are eliminated by niche-specific or systemic immune responses, but a few MICs persist, undergoing reversible growth arrest and immune-evasive quiescence, acquiring organ-specific growth adaptations, and co-opting their TME to elude immune detection. Environmental cues cause MICs to emerge from dormancy and generate clinically identifiable macrometastases. (Reprinted with permission [76] Copyright © 2023 Elsevier Inc.)

microenvironment (TME). This dynamic process limits significant metastatic growth [37,75]. Since dormant tumor cells (DTCs) cannot be seen by standard clinical imaging and patients are not aware of the existence of this silent disease, dissemination and dormancy are categorized as early-stage micrometastatic illnesses. Metastasis-initiating cells (MICs) that are specific to a tumor and take advantage of its microenvironment (TME) are the source of clinically detectable macrometastases. This adaptability eventually permits them to expand and colonize distant organs by exploiting regenerative, angiogenic, and immunosuppressive mechanisms. The metastatic cascade depicts a continuing evolutionary shift including cellular and microenvironmental alterations, as well as the selective survival of particular cancer cell subpopulations capable of resisting environmental stressors [37]. This leads to unchecked tumor development, which eventually causes organ failure, a systemic deterioration in all body functions, and death.

5. Models of metastasis

5.1. Progression model

The most widely recognized model of metastasis is the progression model [77]. This hypothesis was first introduced by Nowell, suggesting that a series of mutational events occur within the original tumor subpopulations or disseminated cells. This cycle eventually allows a tiny number of cells to achieve complete metastatic capacity [78]. This model shows the constraints of metastasis, as it is unlikely that any one cell inside the initial tumor would acquire all of the essential modifications for effective metastasis. Studies have demonstrated that clonal descendants of cell lines can display different metastatic characteristics [79], indicating the presence of distinct metastatic subgroups, at least in vitro. The clonal evolution model became known when the progression linear model was first proposed for cancer cells (Fig. 4). Also in this model, by a linear clonal evolution process, full metastatic potential is obtained through the spread of tumors, in which a small part of the cells is created through the accumulation of physical genetic changes. Many laboratory and clinical observations confirm this model [80–83]. Undoubtedly, one of the strong reasons for the existence of metastatic subpopulations is the difference in the metastatic potential of clonal derivation of cultured cell lines [79,84]. On the other hand, primary tumor-associated colonies are mainly related to cancer ovarian metastases [81]. Not following metastatic progression to a linear clonal evolution can be seen in early ovarian cancers that have a common clonal

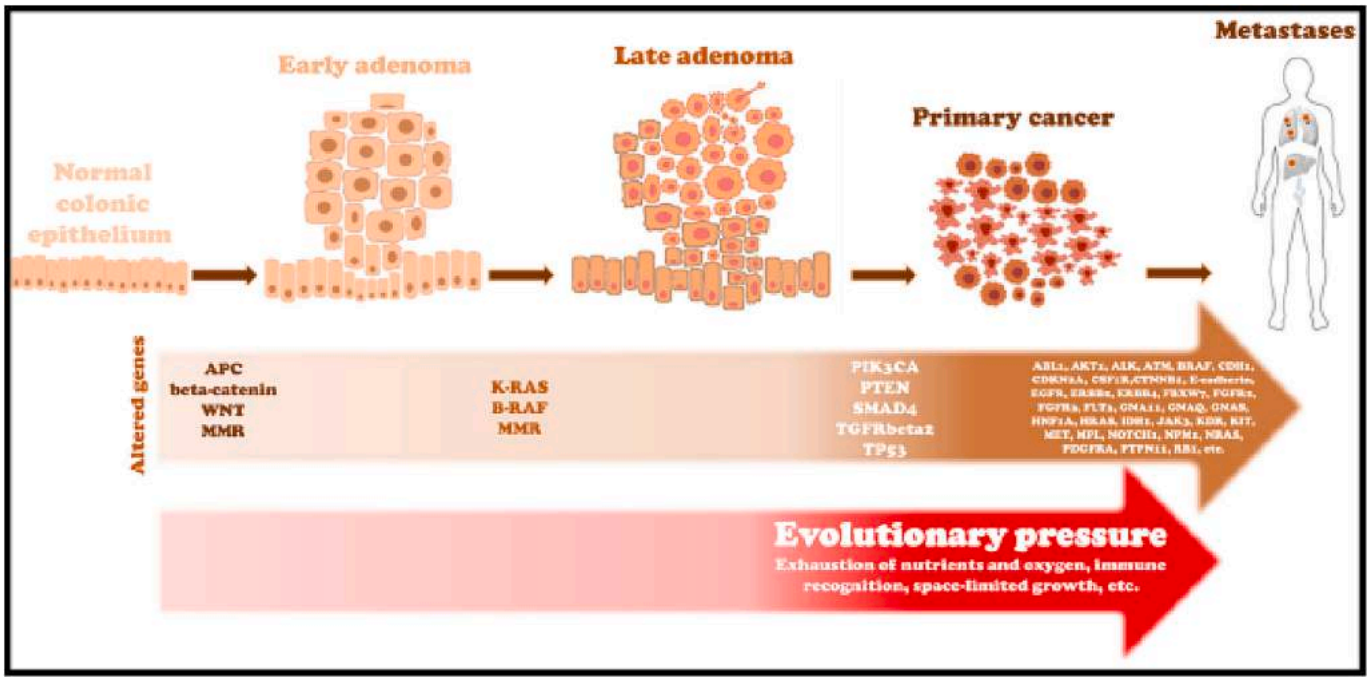

Fig. 4. Progressive aggregation of specific genetic changes and environmental factors, evolution from adenocarcinoma precursors to malignant lesions (Reprinted with permission [83]. Copyright © 2021 The Authors. Published by Elsevier Inc.).

origin pattern according to the data shown. But the metastatic potential obtained by polycloning with various clones in both the initial and final stages is due to genetic divergence. This model became known as the parallel progression model [82,85]. Although a number of studies support progressive models, this model cannot be generalized to all types of metastases. Significantly, reduction of metastatic capacity variability (susceptibility) occurs after several generations by identifying various clones with metastatic potential in metastatic cell populations [86,87]. The clonal progression model predicts metastatic events when the metastatic potential is inherited, not rapidly diminished. However, although this model may be acceptable to most metastases, it cannot be considered a comprehensive model. Given that it is possible to explain the inadequacy and inefficiency of metastatic potential with this low probability in the linear progression model, consequently, a particular cell in the original tumor undergoes all the many modifications necessary to go through the various phases of the metastatic cascade [88,89]. Recent experiments have shown that changes in genetic makeup within cell populations can influence target organ tropism. By employing cloning and selection methods on a cell line derived from human tumors, researchers have identified distinct subpopulations of cells with unique gene expression patterns that increase their likelihood of metastasizing to particular organs. These findings suggest that certain somatic alterations may contribute to organ-specific metastasis [90–92]. The idea that somatic processes have a significant influence on the formation of metastases is supported by the identification of genes that prevent metastasis. These suppressor genes are responsible for inhibiting the ability of cells from metastatic cell lines to form large-scale metastases, without significantly impacting the progression of the primary tumor [93,94]. Reduced expression of metastasis suppressor genes in malignancies has been linked to loss of heterozygosity (LOH) [95] or transcriptional silencing [96], which does not usually involve mutational inactivation. Despite increasing evidence supporting this idea, uncertainties remain, including cases where individuals develop metastatic disease with an unknown primary tumor site. The stochastically guided progression model states that a primary tumor needs a lot of cells to start the necessary sequence of events that eventually lead to metastasis. As a result, the lack of big initial tumors in individuals with metastatic cancer calls into question this notion [86,97]. The notion of progression states that physiological activities that are continuing and result in the potential to spread should be inherited permanently instead of being lost instantly.

5.2. Transient model

The metastatic transient model explains why relative to the primary tumor, the metastatic capacity of the secondary tumor does not increase [98,99]. According to this model, although the full metastatic potential is achieved by many cells in the neoplasm, only a small number of them produce secondary clonal sites; Because epigenetic events are randomly induced in the microenvironment (Fig. 5) [100]. Confirmation of this model is possible with findings that indicate the necessary for angiogenesis for metastatic induction as well as modulation the metastatic capacity of cells by inhibiting methylation of cell lines [80,101,102]. Chromosomal abnormalities caused by the inhibition of methylation by global de-methylation have become the most important areas of this model. This increases the likelihood of epigenetic events due to metastatic modulation by induction of these inhibitors due to mutations [103,104]. The dynamic heterogeneity model was proposed to explain why secondary tumors do not continually advance in their metastatic capability compared to primary tumors [86]. According to the progression theory, if the capacity to metastasis is caused by a sequence of inherited genetic alterations, cells that have successfully traveled through the metastatic cascade should potentially be more efficient at producing new metastatic tumors than the initial tumor. However, this

Fig. 5. Transient part model. Obtaining metastatic potential by all cells in the tumor (Reprinted with permission [100] Copyright © 2009, Springer Science Business Media B.V.).

predicted result was not consistently detected across different experimental circumstances [105]. According to the Weiss transitory metastatic compartment model, living cells within a tumor develop the ability to metastasis, but only a small proportion of these cells ultimately complete the metastatic process [105]. Studies demonstrating the ability of methylation inhibitors to alter the metastatic capabilities of cell lines provide further evidence supporting this concept [106–108]. Global demethylation may share similarities with certain hypothesized epigenetic processes, but these agents have the capacity to induce chromosomal abnormalities. This raises the possibility that mutational events, rather than epigenetic changes, may be responsible for modulating metastatic potential. Additionally, solid tumors typically exhibit genomic instability, with a higher incidence of chromosomal abnormalities often indicating a poor prognosis [103,109]. The clonality of metastases is also not taken into consideration by the transient compartment model [110–112]. Given the significant diversity observed in primary tumors, it is unlikely that a large portion of secondary cancers would originate from a single clonal source, solely governed by temporary epigenetic mechanisms, if every cell has metastatic potential [113–115].

5.3. Early oncogenesis model

Two separate research teams found that they could use microarrays to analyze gene expression across large amounts of human tumor tissues. This approach made it possible to develop gene signature profiles capable of distinguishing between metastatic and non-metastatic cancers [116,117]. Due to these findings, the progression model had to be revised, and it was suggested that only a few percentages of the original tumor cells would develop all the phenotypic traits necessary for effective colonization of distant organs. Consequently, several researchers have shifted their theories towards the idea that metastatic potential is established early in cancer development, possibly through similar patterns of genetic activation or inactivation seen in the original tumor. This challenges the traditional somatic evolution paradigm [117,118] (Fig. 6). f the metastatic gene expression profile is established early, most tumor cells would exhibit this profile. This may assist to explain metastatic illness of unclear etiology. If the same cancer-causing activities lead to metastasis, it's clear how small tumors could quickly spread and colonize distant sites. However, there are limitations to this model. Initially, if the tendency for metastasis is primarily determined by the initial cancer-causing activities, then predicting the metastatic potential of most tumor epithelial cells becomes feasible. Consequently, the efficiency of these cells to colonize distant organs should be significantly greater than what is observed in clinical studies. Moreover, the results of the microarray research do not exclude the possibility that the parent cancers have unusual cellular subpopulations. An extensive tumor sample's average cell may be found in the gene expression profiles. This implies that certain tumor subpopulations could exhibit distinctive features of the metastatic profile, although this depiction is but a portion of the full scheme. Moreover, the premise behind this theory is that patterns of gene expression in metastases are driven by somatic oncogenic processes. However, it does not account for genetic variations, such as hereditary polymorphisms, which also contribute significantly to genomic diversity observed in cancer patients [117,119–123].

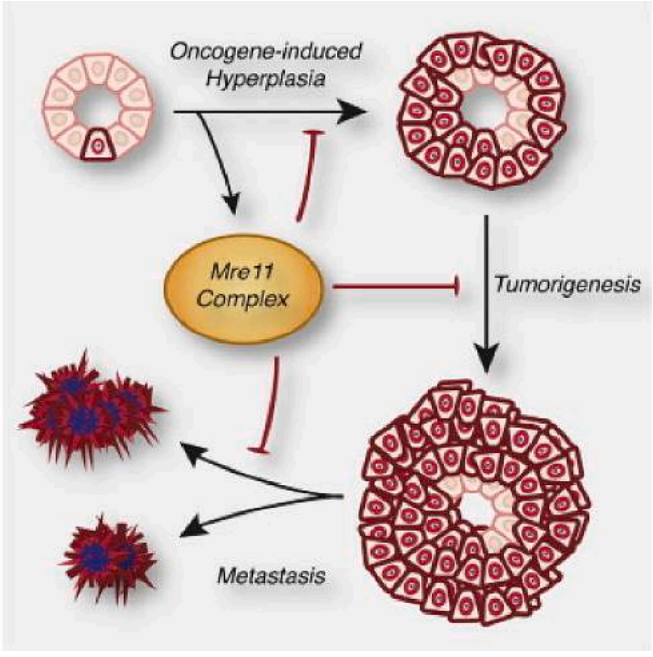

Fig. 6. Early oncogenesis model. Development of metastatic potential of primary neoplasm due to somatic mutations in the same early stage of tumorigenesis (Reprinted with permission [119]. Copyright © 2013 Elsevier Inc. All rights reserved.).

5.4. Fusion model

According to the progression model, as somatic alterations accumulate, cells undergo de-differentiation leading to a more embryonic-like phenotype. In solid tumors, different cell types coexist, prompting various alternative theories on how epithelial cells in tumors acquire the ability to metastasize. Many of these theories suggest that metastatic tumor cells acquire properties resembling lymphoid cells. Tumors often contain high concentrations of tumor-associated macrophages (TAMs), which significantly correlate with disease prognosis [124]. The presence of numerous cells in tumors that possess characteristics such as leukocytic, phagocytic, and fusogenic abilities has led certain researchers to suggest that these cells might serve as partners for tumor cell fusion. This speculation proposes that these cells are responsible for imparting multiple properties to tumor epithelial cells, enabling them to spread and colonize distant areas [125,126]. How frequently cancer patients experience cell fusion, which results in the spread of the disease, is an unsolved subject. Subclones with varying capacities for metastasis can be created in laboratory conditions by cell fusion [126–128]. Therefore, it is unclear whether the enhanced metastatic abilities observed in these hybrids can be specifically attributed to fusion events or if they are the outcome of random subcloning and selection processes. Considering that some of the cell lines used in this study were originally taken from metastatic tumors, this uncertainty is very significant [129]. Metastatic cells, by acquiring several phenotypic features, differentiate themselves from the parent cells, some of which are lymphoid in nature. These observations initiated fusion theory. According to this theory, metastatic phenotype acquisition occurs when immune system leukocytes attach to primary tumor cells (Fig. 7) [130]. A metastatic cell becomes a hybrid with a white blood cell that can move naturally in all parts of the body [131,132]. There is currently inadequate information to prove the significance of cellular fusion in the development of metastatic capacity. This shows that cellular fusion may not be a mode of metastatic dissemination and development at this time [77].

5.5. Gene transfer model

Another important topic to consider while building metastatic capacity is horizontal gene transfer. When circulating tumor DNA (ctDNA) was discovered in animal tumor samples and cancer patients, the long-held theory that metastatic potential may be acquired by horizontal transmission of tumor characteristics was resurrected [133,134]. This notion has been reintroduced as the "geno-metastasis theory," based on data proving horizontal genetic transmission in experimental animals under particular conditions. [135]. The theory suggests that metastases

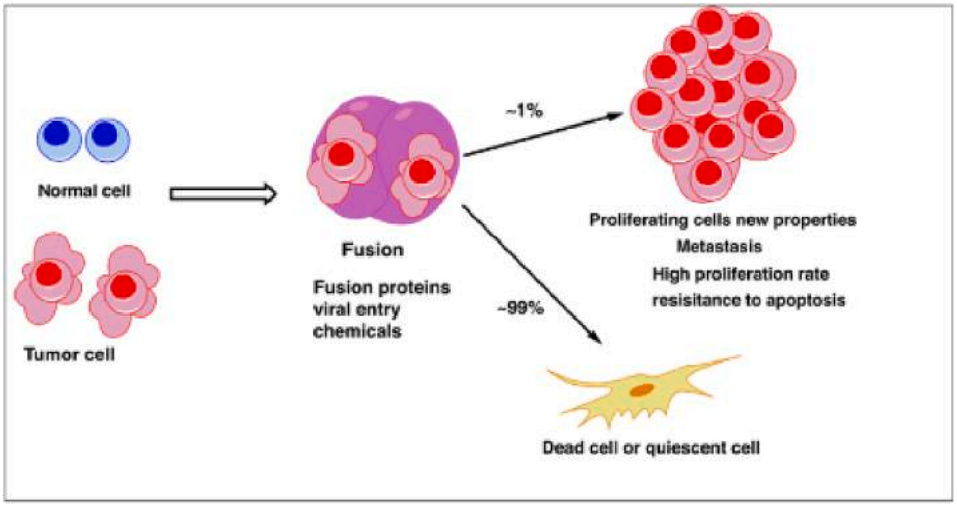

Fig. 7. Fusion model. Metastatic cell formation with hybrid lymphoid cells (Reprinted with permission [130]. Copyright © 2019 Elsevier Ltd. All rights reserved. License: 5287910823994).

may not be initiated by circulating cells, but rather by stem cells acquiring circulating DNA in secondary locations within the body (Fig. 8) [136]. Therefore, metastasis might occur due to new cancers developing within cancer patients rather than originating directly from primary tumors. However, this concept has faced skepticism due to certain observations. Primarily, this theory fails to explain why metastases show specific organ preferences [137]. The geno-metastasis theory proposes that carcinogenic DNA must be transcribed tissue-specifically. While this concept is logical in principle, there is currently no data supporting these phenomena in vivo [138–140].

5.6. Genetic predisposition model

The susceptibility of each primary tumor to being a metastatic is determined by its genetic background. As a result, people's susceptibility to metastatic will be different because their single nucleotide polymorphism is different. All aspects of metastatic cascade in primary germ cells are affected by the presence of these differences, which include the expression of pre-metastatic genes in the primary tumor. Hunter and colleagues in 1998 used transgenic mice to show that their ability to metastasize lung cancer was different [142]. These findings indicate that inherited polymorphisms are involved as a significant factor in the development of the metastatic process, which are distinct from the somatic mutations in tumors (Fig. 9) [83]. These studies showed that the genetic background of people with cancer as a key determining factor in the ability of the primary tumor to metastatic process plays a role [143]. Undoubtedly, polymorphism of codon 71 of the P53 gene is associated with cancer susceptibility in the Korean

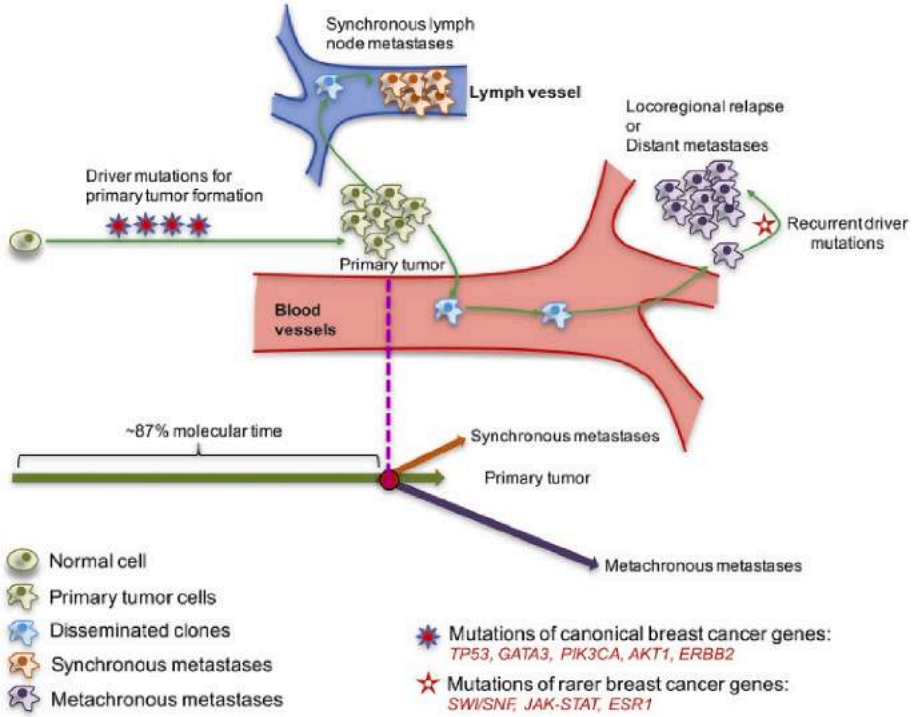

Fig. 8. Gene transfer model. Metastatic DNA that emerges from the primary tumor and is absorbed through the bloodstream by stem cells into an organ, causing metastatic (Reprinted with permission [141]. Copyright © 2017 Elsevier Inc.).

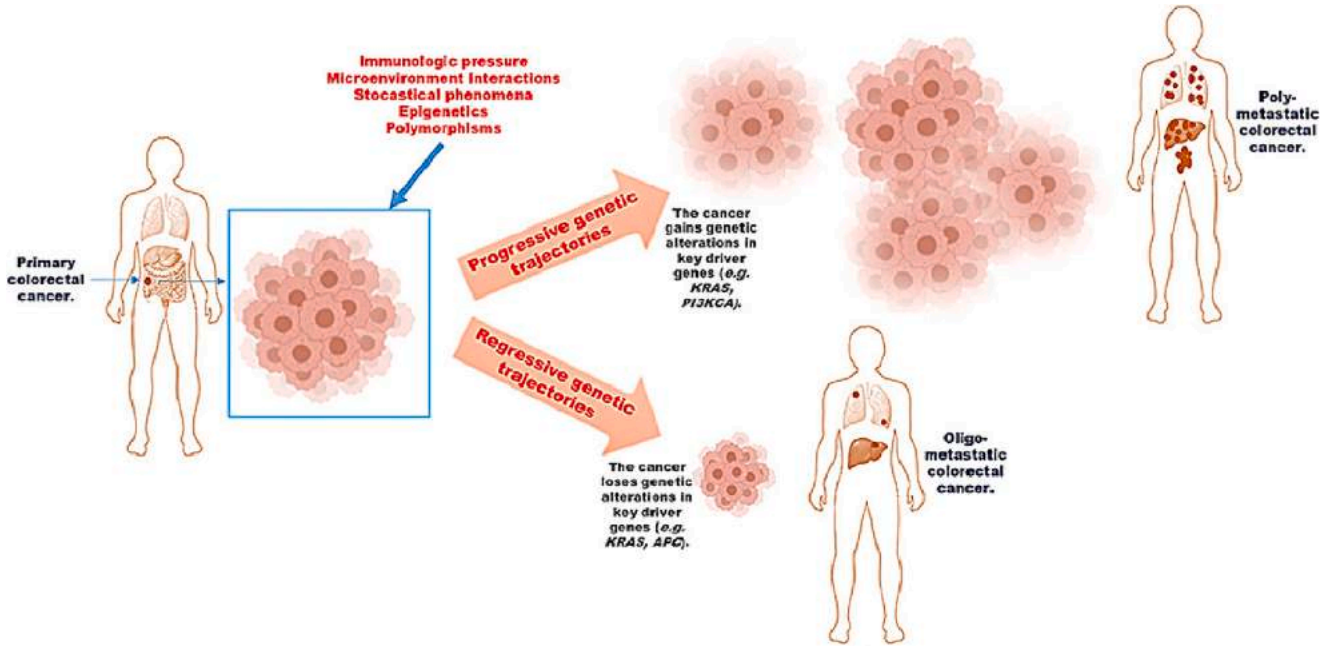

Fig. 9. Genetic predisposition model. Exposure to metastatic potential in any tumor under the influence of individual genetic predisposition (Reprinted with permission [83]. Copyright © 2021 The Authors. Published by Elsevier Inc.).

population [144]. A mouse model was created using transgenesis of a highly aggressive breast tumor, demonstrating that the genetic profile of the tumor significantly influenced its ability to efficiently spread to the lungs [142]. Given that all tumors stem from the same oncogenic source, which is transgene activation, research findings demonstrate that hereditary polymorphism plays a significant role alongside somatic events that induce metastasis within the tumor. Moreover, the presence of constitutional polymorphisms across all tissues of an individual suggests that the impact of polymorphisms affecting metastasis could manifest in tissues beyond the tumor epithelium. For instance, slight changes in lymphocyte activity due to inherited germline-encoded abnormalities in cellular function could profoundly affect immunosurveillance. Consequently, the ability to remove spread tumor cells at another site may be affected positively or negatively. Numerous studies have demonstrated the gene transcription-altering effects of inherited polymorphisms [145–147], forming the basis for evaluating expression quantitative trait loci. This research indicates that certain genes within a prognostic profile exhibit altered expression patterns between high and low-metastatic genotypes [148]. Therefore, it is likely that predictive gene expression profiles for metastasis not only indicate mutations that drive cancer spread but also reflect the inherited vulnerability to metastasis present across the human population. Importantly, incorporating genetic background in these models shows that prognosis evaluation using non-tumor tissue should be viable, perhaps even before cancer arises. If germline polymorphisms determine a significant portion of the metastatic risk instead of distinct somatic processes inside the tumor, then this risk may be detectable in any bodily tissue. While genetic variations may vary among tissues, the existence of universally fundamental susceptibility polymorphisms may make it possible to determine a patient's susceptibility status using any tissue [148].

6. Biosensors and metastatic cancer cell

Today, the growing need to detect and measure various biological and chemical species has led to the widespread use of biosensors [149]. To identify a biological analyte using a biological organism such as proteins, RNA, and DNA, a device called a biosensor is designed to produce a detectable and measurable signal [30]. From another point of view, biosensors are analytical devices with the ability to measure components related to biomolecules that produce measurable signals from a sample using appropriate transducers [150]. These devices can be used for applications such as food health, medicine and environmental applications [151]. Biosensors in the field of metastatic cancer cell can measure the biomarkers of metastatic cancer cells and thus diagnose and measure the progression of metastatic cancer cell [30]. Biosensors are divided into five subgroups: thermal-detector biosensors, electrochemical biosensors, ion-sensitive field effect transistors biosensors, resonant biosensors and optical biosensors [149]. Table 2 shows the biosensor for metastatic cancer cells. Among these, electrochemical biosensors are among the devices that have the ability to test systems without damaging them [30]. A biosensor consists of three components: a signal processor, a signal converter, and a diagnostic element. The diagnostic component views the signal from the environment or analyte and then converts this signal into an electrical or digital output [151–153]. Components of the diagnostic element include biological molecules such as enzymes, polypeptides, antibodies, cells, etc. That these biomolecules must be able to bind specifically to the analyte in question. In order to use biosensors, it must first be possible to stabilize the desired biomolecule on it in an appropriate way. There are several ways to do this, such as covalent bonding, physical adsorption, langmuir blodgett (molecular) depositon, confinement, crosslinking, electropolymerization, and lamellar aggregation, including crosslinking, strong

Table 2
The biosensor for metastatic cancer cells.

Type of metastatic cancer cell	Biosensor	Surface ligand	Detection limit	Ref.
Lung	Electrochemical	Antibody	–	[159]
Lung	Surface plasmon resonance and quartz crystal microbalance	single-stranded DNA	0.03 μM	[160]
Pancreatic	Surface plasmon resonance	Antibody	66.7 U/mL	[161]
Liver	Double-stranded DNA and antibody	Antibody	10.6 pM and 1.06 pM	[162]
Prostate	Electrochemical	Antibody	0.02 ng/mL	[163]
Prostate	Surface plasmon resonance	Antibody	2.3 ng/mL	[164]

protein-surface bonding. Which, of course, may also cause problems such as decreased enzyme activity [154]. Fig. 10 shows a schematic of a simple biosensor consisting of bioreceptors attached to a transducer. The mechanism of operation of biosensors is that a characteristic of the sensors, such as their resistance or conductivity, is measured before the electrode is placed in contact with the target species and after placement, and changes in output signal changes. Thus, the electrode's particular surface area plays a crucial role in determining the biosensor's sensitivity. Furthermore, it is stated that the biosensor may react more quickly the greater the electrode's specific surface area [151]. The primary obstacles and restrictions facing biosensor advancements are (i) the successful acquisition of biorecognition signals and their subsequent transduction into electrochemical, electrical, optical, gravimetric, or acoustic signals; (ii) improving transducer performance, meaning sensitivity can be increased, response times can be shortened, reproducibility can be ensured, and detection limits can be lowered even for individual molecules; and (iii) micro- and nanofabrication technologies can be used to miniaturize biosensing devices [155]. Zhang and colleagues [156] introduced a worm-based (WB) microfluidic biosensor designed to swiftly monitor biochemical signals linked to metastasis within a controlled setting. Unlike traditional biomarker-based techniques, the WB biosensor enabled efficient high-throughput screening at a low cost, relying solely on visual assessment of results. They established a chemotaxis index (CI) to standardize the quantitative evaluation from the WB biosensor. CI levels between 3.24 and 6.5 indicated moderate risk of metastasis, while CI levels above 6.5 indicated the presence of metastasis. Their study revealed that the metabolite glutamate, when secreted, acted as a chemorepellent. Additionally, larger clusters associated with higher metastatic potential were shown to elevate CI levels [156]. Cristina et al. [157] studied a novel peptide-based electrochemical biosensor for the identification of a protease associated with metastasis in pancreatic cancer cells. The findings reveal that the biosensor delivered highly consistent readings (with a relative standard deviation of 3.4 % based on 10 repetitions) and was selective to various proteins and proteases found in biological materials. They published the first quantitative results on trypsin expression in human cell lysates [157]. Yuan et al. [158] investigated the in vivo interaction of breast cancer metastasis and mitochondrial autophagy using the rational design of mitochondria-targeted fluorescence biosensors. They created four fluorescent biosensors with varying alkyl chains to track mitochondrial autophagy. PMV-12 had the highest sensitivity to viscosity changes, the lowest sensitivity to polarity changes, and the longest imaging duration. The addition of the C12-chain allowed PMV-12 to persistently adhere to the mitochondrial membrane, regardless of variations in mitochondrial membrane potential (MMP), allowing for long-term in situ monitoring of mitochondrial autophagy. When mitochondria were labeled with PMV-12 and treated with apigenin, they exhibited swelling and increased viscosity, indicating apigenin's potential to induce mitochondrial autophagy. Subsequent experiments confirmed that apigenin inhibits cancer cell invasion by 92 % [158].

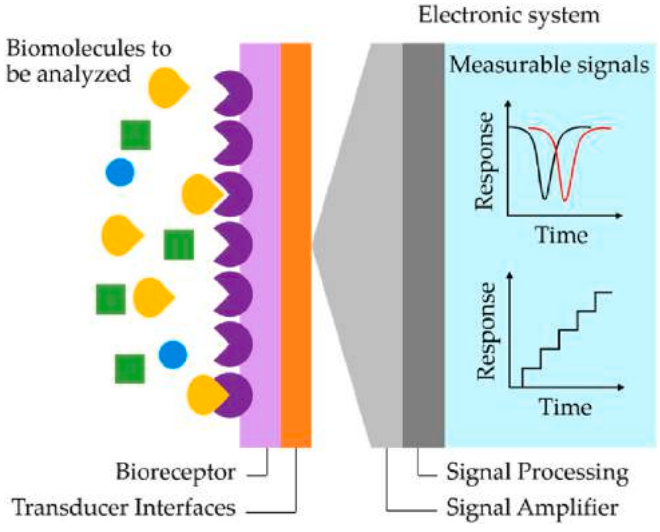

Fig. 10. Schematic of a typical biosensor consisting of biosensors connected to a converter (Reprinted with permission [150] from MDPI).

7. Metastatic cancer cell and biomarkers

Metastatic cancer cell is an abnormal and uncontrolled cell growth that results from a group of genetic or epigenetic defects. Tumor formation is due to abnormal growth. Against programmed cell death (apoptosis) and other anti-growth defenses, tumor cells become resistant in vivo. The tumor begins to spread to other parts of the body through the growth of a metastatic cancer cell, which causes the metastatic cancer cell to spread throughout the body. Biomarkers, according to the National Cancer Center (NCI) in the United States, are molecules that indicate a normal or abnormal process in the body and may be a sign of disease. Biomarkers are found in a variety of molecules such as proteins, DNA, hormones and genes, all of which provide a wealth of information about health. Biomarkers are substances that are present in body fluids like body tissues, blood, serum and urine as well as are increased in people with cancer in various tissues. Metastatic cancer cell biomarkers are among the most suitable tools for correct diagnosis of metastatic cancer cell stage for treatment, early diagnosis of metastatic cancer cell, measuring the effectiveness of treatments and drugs on metastatic cancer cell. Biomarkers are found in body fluids like the blood, urine and serum (blood), but can also be present in or on a tumor. Table 3 presents the biomarkers of metastatic cancer cells. Diagnostic components of antibody- and antigen-based biosensors are among the fastest diagnosis systems. One of the most important advantages of this system is the inherent specificity of the antigen- antibody bond. Also, in this type of system, there is no need to purify the target molecule before the diagnosis operation [165–167]. The difference between healthy cells and some types of breast cancer cells with MCF-7 biomarker overexpression is shown schematically in Fig. 11. The usefulness of circulating tumor cell (CTC) status as a prognostic indicator following enzalutamide therapy was examined by Nakamura et al. [168]. They performed a prognostic assessment and retrospective subgroup analysis on 43 patients who had bone metastases from metastatic castration-resistant prostate cancer (mCRPC). Patients received a daily dose of 160 mg of enzalutamide. Blood samples for CTC analysis were taken before treatment and every three months thereafter. Patients who had no identifiable CTCs at the start of the research had a considerably longer overall survival time than those who did. Furthermore, individuals who demonstrated a negative conversion of CTCs following enzalutamide therapy had a considerably longer OS than those who remained CTC positive. Higher baseline hemoglobin levels and negative CTC conversion were shown to be substantially associated with longer OS. The findings show that individuals with improved long-term OS who achieve negative conversion of CTCs following treatment for mCRPC with bone metastases [168]. Smabers et al. [169] evaluated the potential of organoids as a biomarker for customized therapy of metastatic colorectal cancer. They improved drug screening procedures by removing N-acetylcysteine from the growth medium and used biphasic curve fitting

Table 3
The biomarkers of metastatic cancer cells [167,171,172].

	Type of metastatic cancer cell	Biomarker
1	Liver	CEA
2	Ovarian	CEA, CA 549, CASA, CA 19-9, CA 15-3
3	Breast	NY-BR-1, ING-1, HER2/NEU
4	Melanoma	Tyrosinase
5	Esophageal	SCC

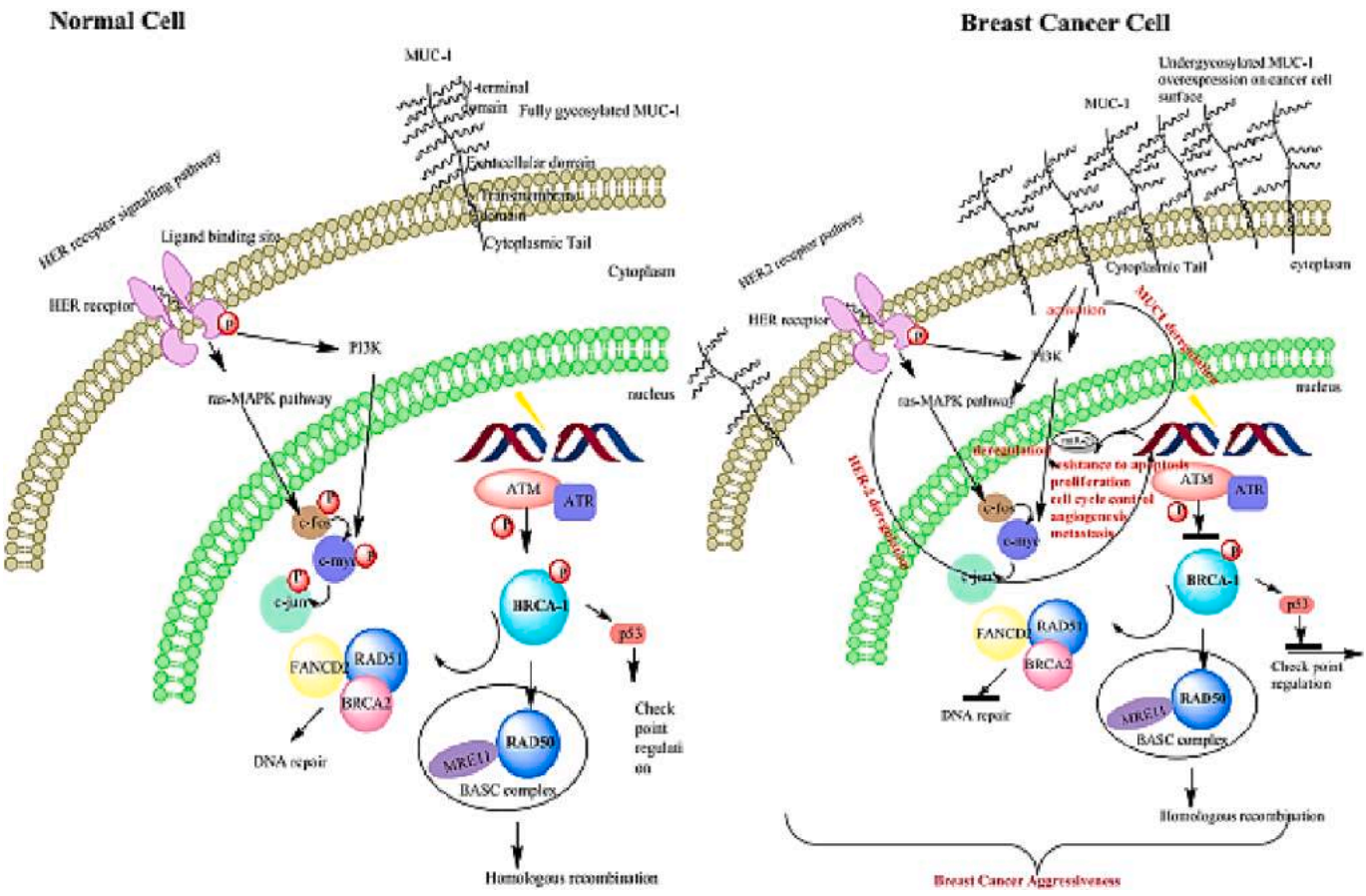

Fig. 11. The difference between healthy cells and a type of breast cancer cell with MCF-7 biomarker overexpression in terms of biomarkers (Reprinted with permission [173]. Copyright © 2016 Elsevier B.V. All rights reserved. License: 5287871044166).

for 5-FU-oxaliplatin combos. After optimization, there was a link between organoid response and patient outcomes with correlation values of 0.58 for 5-FU (n = 6, 95 % CI −0.44,0.95), 0.61 for irinotecan (n = 10, 95 % CI −0.03,0.90), and 0.60 for oxaliplatin-based chemotherapy (n = 11, 95 % CI −0.01,0.88). Patients with resistant organoids following oxaliplatin-based chemotherapy exhibited a substantially lower median progression-free survival than those with sensitive organoids (3.3 vs 10.9 months, p = 0.007). Additionally, increased resistance to 5-FU in patients previously treated with 5-FU/capecitabine was accurately mirrored in the organoids (p = 0.003) [169]. Liu and colleagues [170] analyzed data from the Cancer Genome Atlas Program (TCGA) and Gene Expression Omnibus (GEO) databases to look for possible biomarkers for osteosarcoma (OS) metastasis. Their examination of datasets DS1, DS2, and DS3 with the IML method revealed 53, 45, and 46 characteristics, respectively. By combining these gene sets, scientists were able to generate 79 interpretable prediction criteria for OS metastatic disease. Importantly, their findings demonstrated statistically significant changes in survival rates based on TRIP4, S100A9, SELL, and SLC11A1 expression levels. Furthermore, scientists discovered associations between these genes and numerous immune cells, totaling 22 unique kinds [170].

8. Biosensors in metastatic cancer cell detection

Nanotechnology-based therapeutics improve diagnostic testing and can help create tailored therapeutic delivery systems to reduce treatment-related systemic adverse effects. In general, breakthroughs in nanotechnology can contribute to creating innovative and cost-effective treatment options for various diseases, including the ability to monitor COVID-19 [174]. Biosensors are regarded as potential early-stage cancer detection techniques when compared to genomic, proteomic, and other methodologies. Among them, electrochemical (EC) sensors have shown to be both economically and operationally sophisticated. The timely detection of certain biomarkers associated with diseases has the advantage of preventing potential instances, whereas delayed reporting results in insufficient management of infectious diseases. Currently, there are several methods for detecting nucleic acids and proteins. However, there is a notable need for point-of-care (POC) technologies that are rapid, cost-effective, and self-diagnostic. In this context, nanotechnology assumes a pivotal role in the development of biosensors exhibiting exceptional characteristics and in the production of proof-of-concept (POC) devices [174]. Nano-conjugated hybrid materials, which serve as a transducing platform for the detection of minute quantities of ambient or human body proteins, are the building blocks of biosensors. A variety of methods are employed to gather data as an output. A molecularly imprinted polymer (MIP) sensor with voltammetric capabilities was developed to identify the HER2-ECD biomarker for breast cancer. Thus, using a screen-printed gold electrode (Au SPE), phenol and HER2-ECD were electropolymerized [175]. Rajaji and colleagues [176] created a novel nanocomposite by decorating reduced graphene oxide (rGO) with iron nitride nanoparticles (Fe2N NPs) using a solvothermal process followed by nitridation. The fabricated sensor exhibited a wide linear detection range for 4-nitroquinoline-1-oxide (4-NQO) from 0.05 to 574.2 μM with a low detection limit of 9.24 nM. Furthermore, the Fe2N NPs@rGO/SPCE sensor was employed with near-100 percent recovery rates to successfully detect 4-NQO in human blood and urine samples [176]. Loyez et al. [177] have shown that optical fiber-based surface plasmon resonance (OF-SPR) sensors have exhibited great versatility and performance in recent years, making this technique central to many innovative biosensing concepts. To improve sensitivity

to surface refractive index changes, 1 cm-long optical fibers with a core diameter of 400 μm were coated with a sputtered gold coating. They evaluated their efforts in two ways: by measuring the plasmon resonance's center wavelengths and assessing their influence on bulk refractive index sensitivity. In this work, they effectively identified HER2 biomarkers at 0.6 μg/mL (equal to 5.16 nM) without labels. Using HER2 antibodies to boost the signal resulted in a roughly hundredfold increase, allowing for detection of concentrations as low as 9.3 ng/mL (77.4 pM) [177]. Sun et al. [178] used silica microfibre interferometry to identify a breast cancer biomarker without the need of labels. They developed a small and label-free optical fiber sensor for detecting HER2 in serum using silica microfiber interferometry. In this sensor, antibodies bound on the microfibre surface function as specialized receptors for trapping HER2 targets. The optical fiber sensor detects changes in surface refractive index caused by immunoreactions, resulting in a large wavelength shift in the interferometric fringe. Even in a serum matrix, the suggested fiber-optic biosensor has enhanced sensitivity to 0.1 nm/(ng/mL) [178]. Li et al. [179] created a microcantilever array biosensor with a sandwich construction to detect CEA and α-fetoprotein (AFP) simultaneously. The biosensor uses an optical readout approach with real-time monitoring of the cantilever profile. The results show that the connection between the cantilever's deflection value at 90 % position and the target concentration functions as a calibration curve. The biosensor attained a detection sensitivity of 0.6 ng/mL for AFP and 1.3 ng/mL for CEA [179]. Recent research suggests that optical sensors might be able to identify cancer biomarkers like miRNAs and cysteine. Biomolecule-modified micro/nano-dimensional cantilevers undergo frequency shifts that cause mass changes in response to stimulation, which is how mass-sensitive biosensors work. When combined with SPR, electrochemistry, dual-polarization interferometry (DPI), and microfluidic chips, mass-based biosensors such as acoustic and piezoelectric crystal-based sensors can yield sensitive results [180]. Calorimetric biosensor's function based on changes in the heat energy released due to biomolecule interactions at various stages. A point-of-care immunoassay was developed by Celikbas et al. [181] whereby nitrocellulose membranes are coated with gold nanoparticles (AuNP-Cys) coupled with cysteamines within the detecting pad. This method was employed to identify AFP and MUC16 biomarkers in the samples. According to the findings, the linear detection ranges for AFP and MUC16 were respectively 0.1 ng/mL to 100 ng/mL and 0.1 ng/mL to 10 ng/mL. 1.054 ng/mL was the limit of detection (LOD) for AFP and 0.413 ng/mL for MUC16 [181]. Colorimetric pH sensing is a promising method for detecting cancer biomarkers due to its ease of use and visibility. Its practical application has been hindered, meanwhile, by low target concentrations and interference from complex sample compositions. Using glucose oxidase (GOD) enrichment and catalysis, Miao et al. created a new pH-based colorimetric approach that enhances cancer biomarker detection while minimizing interference from sample components and analytical methods. They used this method in their study to find human platelet-derived growth factor-BB (human PDGF-BB), achieving a low detection limit of 0.94 pM and remarkable specificity as a model protein biomarker [182]. Additionally, there are whole-cell, enzymatic, DNA/RNA, and immunosensor types of bio-recognition biosensors. Amplification of nucleic acid or aptamer hybridization produces signals that are detected by DNA/RNA sensors. Enzymatic sensors detect particular analytes by catalytic activity, whereas whole-cell biosensors detect intracellular and extracellular indications using organisms or bacteria as bio-ligands. Antigen and antibody immunosensors attach to the analyte of interest in a specific biological way, generating a measurable signal. Non-enzymatic technologies, like enzymatic sensors, are capable of selective, sensitive, and simultaneous detection [183].

9. Conclusion

Cancer is a complex and multifactorial disease. Traditional cancer classification systems face many challenges and require more accurate data, including molecular data. Conclusively, the latest developments in biosensor technology for identifying metastatic cancer cells signify a noteworthy progression in the domain of cancer diagnosis and therapy tracking. The development and refinement of these biosensors have enabled researchers and clinicians to detect metastatic cancer cells with higher sensitivity, specificity, and efficiency compared to conventional methods. One key area of progress is the improvement in biosensor sensitivity. Newer biosensors can detect even trace amounts of metastatic cancer cells, which is critical for early diagnosis and intervention. This enhanced sensitivity allows for the identification of cancer cells circulating in the bloodstream or migrating to distant sites, providing valuable prognostic information and guiding personalized treatment strategies. Furthermore, biosensors have shown remarkable specificity in differentiating cancer cells from normal cells based on unique biomarkers. This specificity minimizes false-positive results and ensures accurate cancer detection, essential for timely and targeted therapeutic interventions. The integration of biosensors with advanced technologies such as microfluidics, and nanotechnology has increased their capabilities. These interdisciplinary approaches have led to the development of miniaturized, portable biosensors capable of real-time, point-of-care cancer cell detection. Such devices hold immense promise for improving patient outcomes through early detection and monitoring of metastatic disease. In addition to their diagnostic potential, biosensors are facilitating research in understanding cancer biology and therapeutic response. By enabling the analysis of cancer cells at a molecular level, biosensors contribute to the identification of new drug targets and the assessment of treatment efficacy, thus supporting the development of personalized cancer therapies. Looking to the future, continued research and innovation in biosensor technology will likely lead to even more sophisticated devices with enhanced performance characteristics. These future biosensors could revolutionize cancer management by providing rapid, accurate, and cost-effective tools for detecting metastatic cancer cells at various stages of disease progression.

CRediT authorship contribution statement

Masoomeh Yari Kalashgrani: Writing – original draft, Resources, Methodology, Investigation, Formal analysis. **Seyyed Mojtaba Mousavi:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization. **Muhammad Hussnain Akmal:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Ahmad Gholami:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Navid Omidifar:** Writing – review & editing, Resources, Methodology, Investigation, Formal analysis. **Wei-Hung Chiang:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Chin Wei Lai:** Writing – review & editing, Resources, Methodology, Investigation, Formal analysis, Data curation. **Md. Ripaj Uddin:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Raed H. Althomali:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Formal analysis. **Mohammed M. Rahman:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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