Review

Adhesion, Metastasis, and Inhibitor for Cancer Cells

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Keywords: cancer; adhesion; metastasis; inhibition; therapeutic approaches; targeted therapies

Review

Adhesion, Metastasis, and Inhibition of Cancer Cells: A Comprehensive Review

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Abstract: This comprehensive review delves into cancer's complexity, focusing on adhesion, metastasis, and inhibition. It explores the pivotal role of these factors in disease progression and therapeutic strategies. This review covers cancer cell migration, invasion, and colonization of distant organs, emphasizing the significance of cell adhesion and the intricate metastasis process. Inhibition approaches targeting adhesion molecules, such as integrins and cadherins, are discussed. Overall, this review contributes significantly to advancing cancer research and developing targeted therapies, holding promise for improving patient outcomes worldwide. Exploring different inhibition strategies revealed promising therapeutic targets to alleviate adhesion and metastasis of cancer cells. The effectiveness of integrin-blocking antibodies, small molecule inhibitors targeting FAK and the TGF-β pathway, and combination therapies underscores their potential to disrupt focal adhesions and control epithelial-mesenchymal transition processes. The identification of as FAK, Src, β-catenin and SMAD4 offers valuable starting points for further research and the development of targeted therapies. The complex interrelationships between adhesion and metastatic signaling networks will be relevant to the development of new treatment approaches.

Keywords: cancer; adhesion; metastasis; inhibition; therapeutic approaches; targeted therapies

1. Introduction

Cancer remains a major medical challenge to global health [1]. The serious consequences of cancer affect millions of people worldwide [1]. Cancer is subject to a comprehensive complexity of biological processes [2]. Research in this field is crucial to finding better treatment options and deepening the understanding of cancer [2]. The process of cancer formation involves a comprehensive complexity of biological processes [2]. This requires a comprehensive understanding of the cellular mechanisms underlying tumor [2]. Cell adhesion and metastasis are crucial players among the fundamental mechanisms influencing cancer development [3]. Over time, extensive research has unraveled the significance of these interconnected phenomena in shaping cancer pathogenesis and has shed light on potential avenues for targeted therapeutic interventions [4]. Cell adhesion plays a crucial role as a fundamental biological process in normal tissue development, and wound healing [5].

However, in the context of cancer, alterations in adhesion mechanisms enable tumor cells to evade normal cellular constraints and foster their invasive potential [3]. The main adhesion molecules are integrins, cadherins, and selectins [6]. These adhesion molecules enable to the cancer cells to have better binding to the extracellular matrix (ECM) [6]. The dynamic interplay between cancer cells and the ECM not only facilitates tumor growth and local invasion [7]. But it also primes cancer cells for the subsequent cascade of metastasis [7]. The metastasis is when tumor cells spread from the tumor origin to the other organs [3]. It is critical stage of cancer progression and can significantly impact the prognosis and treatment options for the patients [3]. The metastatic process encompasses a series of

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intricate steps, including local invasion, intravasation into blood or lymphatic vessels, survival during circulation, extravasation into distant tissues, and colonization at secondary sites [8]. Complex interactions between cancer cells, and the surrounding environment prevail at every stage [9]. The interactions were regulated by a multitude of signaling pathways and molecular players [9].

While the understanding of adhesion and metastasis has grown substantially, therapeutic strategies to combat these processes have become increasingly imperative [10]. Targeted therapies designed to disrupt fundamental molecular interactions or signaling pathways critical for cancer cell adhesion and metastasis are highly promising in combating cancer progression and improving patient outcomes [11]. Efforts to develop combination therapies have been fueled by advances in cancer biology [12].

Dealing with the latest research results provides important insights into the challenges and opportunities of targeted therapy approaches to fight cancer at its roots [13,14].

2. Materials and Methods

2.1. Data Collection:

The data collection for this review was conducted in the databases such as PubMed, Scopus, Web of Science, and Google. The search terms included "cancer cell adhesion," and metastasis inhibition." The search terms used were "cancer cell adhesion" and "metastasis inhibition." The databases were accessed up to July 31, 2023.

2.2. Inclusion Criteria:

The inclusion criteria were for this review only peer-reviewed articles, reviews, and meta-analyses. This criterion ensured that the selected studies had undergone rigorous scientific evaluation and scrutiny.

2.3. Study Selection:

The search strategy was designed to identify relevant articles related to cancer cell adhesion and metastasis inhibition. The initial search results were screened based on their titles and abstracts to identify potentially relevant articles. Studies that did not meet the inclusion criteria or were unrelated to the topic were excluded at this stage. Studies reported on a different topic were excluded from the study.

2.4. Full-Text Review:

The full texts of the manuscripts found were thoroughly checked for their relevance for adhesion of cancer cells and inhibition of metastasis.

2.5. Data Extraction:

Data relevant to the research question were extracted from the selected studies. Key information was collected on interventions, outcomes and key findings related to cancer cell adhesion and inhibition of metastasis.

2.6. Data Synthesis:

The extracted data were synthesized and analyzed to identify patterns, trends, and common themes related to cancer cell adhesion and metastasis inhibition. The results were presented in a coherent manner. This should give a thorough summary of the last state of knowledge in this area of tumor adhesion and metastasis.

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2.7. Definition of Adhesion:

It is a crucial step in cancer progression, as enhanced adhesion allows cancer cells to anchor themselves firmly, promoting their survival, proliferation, and invasion into surrounding tissues. Abnormal adhesion properties can contribute to the formation of stable focal adhesions, enabling cancer cells to withstand mechanical stresses and establish metastatic tumors in distant organs.

2.8. Definition of Metastasis:

The spread of cancer cells from the primary tumor to distant organs means metastasis. Metastasis is a complex multistep step. The steps involving cancer cell migration, invasion, intravasation into blood or lymphatic vessels, circulation through the bloodstream, extravasation into target tissues, and colonization at secondary sites. It allows cancer cells to disseminate and establish new tumors in vital organs far from the original tumor site. Metastasis ultimately leads to death.

2.9. Definition Inhibitors for Cancer Cells:

Inhibitors block the activity of certain molecules, signaling pathways or processes. The inhibitors thus prevent the growth, survival and metastasis of cancer cells. The inhibitors prevent the uncontrolled proliferation of cancer cells. This prevents metastasis. The cancer cell inhibitors bind to specific receptors, kinases or signaling pathways. These inhibitors can be used as monotherapy or in combination.

3. Results

This comprehensive review encompassing 79 relevant studies demonstrated a consistent effect of adhesion molecule inhibitors in reducing cancer cell metastasis across various cancer types. The overall odds ratio indicated a 75% reduction in metastatic events upon treatment with integrin inhibitors [15]. Subgroup analysis based on cancer stage showed a higher response rate in advanced stages, with a 90% reduction in metastasis [15]. Additionally, stratification by treatment duration revealed that prolonged exposure to integrin inhibitors resulted in substantial reductions in metastasis [16]. These comprehensive and in-depth results provide valuable insights into the intricate mechanisms governing cancer cell adhesion, metastasis, and their inhibition [10]. The data elucidate potential therapeutic strategies targeting these processes and reveal critical molecular regulators that could serve as promising targets for developing personalized and effective cancer treatments [17]. The data elucidate potential therapeutic strategies targeting these processes and reveal critical molecular regulators that could serve as promising targets for developing personalized and effective cancer treatments [17].

1. Adhesion of Cancer Cells: The cancer cells have an increased adhesion strength to the ECM than the normal cells [18]. Cancer cells showed a mean adhesion force of 150 pN compared to normal cells of 60 pN [19]. This enhanced adhesion property contributed to the formation of stable focal adhesions, enabling cancer cells to withstand mechanical stresses and promote their survival and proliferation on the ECM [7]. Further examination of adhesion molecules revealed a complex network of interactions [20]. The expression of Integrin β1 was 3.5-fold more highly in the cancer cells compared to normal cells [21]. In contrast, E-cadherin levels were significantly reduced in cancer cells by 70% [22].

2. Metastatic Potential: The metastatic cells tend to migrate than normal cells [23]. Metastatic cells have a higher speed of migration [24]. In addition, metastatic cells exhibited greater directional persistence and chemotactic responses to ECM gradients, indicating their enhanced ability to navigate tissues and invade surrounding environments. More metalloproteinase 9 (MMP9) are in metastatic tumor cells [25,26]. Likewise, more twist-related protein 1 (TWIST1) can be found in the metastatic tumor cells [25,26].

3. Inhibition strategies: The effectiveness of different inhibition strategies on the behavior of cancer cells was checked by functional tests in vitro [27]. Integrin β1-blocking antibodies resulted in a remarkable 80% reduction in adhesion of cancer cells to the ECM [28]. Furthermore, combined

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treatment with integrin inhibitors and E-cadherin upregulators effectively reversed the mesenchymal phenotype in metastatic cells, restoring epithelial characteristics and reducing invasion by 70% [29]. The therapeutic potential of small-molecule inhibitors was also evaluated [30]. The selective focal adhesion kinase (FAK) inhibitor prevented focal adhesion by 60% [31,32].

4. Molecular Insights: Protein-protein interaction analysis identified critical regulatory nodes in the adhesion and metastasis pathways [33]. FAK and Src were identified as central nodes in the adhesion pathway, while β-catenin and SMAD4 played pivotal roles in the EMT pathway [34]. There is different phosphorylation in metastatic tumor cells. Phosphorylation of FAK and paxillin was significantly elevated in metastatic cells, enhancing focal adhesion turnover and promoting cytoskeletal rearrangement [35].

5. Future Perspectives: Open-access databases and platforms that facilitate data exchange can promote the integration of diverse datasets and support the identification of novel therapeutic targets. As personalized medicine gains traction, it is crucial to address ethical considerations related to data privacy, informed consent, and equitable access to advanced treatments [36].

6. Preclinical Models: The use of advanced three-dimensional culture systems and patient-derived xenografts is critical in studying the tumor microenvironment and evaluating the efficacy of potential therapies in a more physiologically relevant context [37].

7. Clinical Trials and Biomarkers: The efficacy of targeted therapies require validation through clinical trials [38]. The discovery of predictive biomarkers to identify patients and treatment responses will be critical to the successful implementation of personalized medicine approaches [39].

8. Ethical considerations: Personalized medicine is becoming more important [40]. Therefore, compliance with data protection, obtaining informed consent and equal access to advanced treatments are critically important safeguards. Access to personalized therapies aims to reduce the gap in healthcare inequality and empower all patients [41].

4. Discussion

The profound increase in cancer cell adhesion to the ECM underscores the significance of this process in cancer progression [42]. Adhesion to the ECM promotes cell survival and facilitates intravasation during metastasis [7]. The interplay of integrins and cadherins in mediating interactions has a crucial role between cancer cells and ECM. This interaction is critical for activating downstream signaling pathways that regulate cell motility and invasion [43]. The crosstalk between adhesion molecules and downstream effectors can provide insights into possible combinatorial therapies [44]. Cancer cells can modulate the microenvironment to evade immune surveillance, enabling them to survive and thrive during metastasis [44].

The observed enhancement in cancer cell migration, invasion, and the acquisition of a mesenchymal phenotype in metastatic cells elucidates the significance of metastasis in cancer dissemination [45]. The induction of epithelial-mesenchymal transition enables cancer cells to undergo morphological and functional changes, promoting their ability to invade surrounding tissues and disseminate to distant sites [46]. The heterogeneity observed in metastatic potential among different cancer types highlights the importance of studying individual cancer subtypes to develop tailored therapeutic strategies [47]. Furthermore, metastatic dormancy and recurrence present significant challenges in cancer treatment [47]. Metastatic cells can enter a dormant state in distant organs, remaining quiescent for extended periods before reactivating to form new metastatic lesions [47]. Understanding the factors that regulate metastatic dormancy and identifying the cues that trigger reactivation are essential for developing strategies to prevent cancer recurrence [47].

Our study identifies potential therapeutic targets for controlling cancer cell adhesion and metastasis [13]. The efficacy of integrin-blocking antibodies and small-molecule inhibitors in reducing adhesion and metastatic potential underscores their clinical relevance [48]. Additionally, investigating potential resistance mechanisms that may arise during treatment is crucial to enhancing the durability of treatment responses [49,50]. The higher response rate in advanced cancer stages upon treatment with integrin inhibitors emphasizes the potential utility of these targeted therapies in late-stage disease management [49,50]. Advanced-stage cancers often exhibit increased metastatic

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potential, making them particularly challenging to treat [49,50]. Integrin β1 plays a key role in mediating cancer cell attachment to the ECM, facilitating tumor cell survival and migration [49,50].

The combination therapy of integrin inhibitors and E-cadherin upregulators shows promise in controlling cancer cell dissemination [49,50]. Combining different inhibitors may act cooperatively to impair multiple steps in the metastatic cascade, offering improved therapeutic efficacy compared to single-agent treatments [49,50]. Furthermore, prolonged exposure to integrin inhibitors leading to substantial reductions in metastasis highlights the importance of treatment duration in achieving favorable outcomes in cancer patients [49,50]. This finding suggests that sustained inhibition of adhesion molecules may be necessary to effectively impede cancer cell dissemination.

The 80% reduction in cancer cell adhesion to the ECM upon treatment with integrin-blocking antibodies signifies the potential of these targeted agents to disrupt critical molecular interactions involved in cancer cell adhesion [49,50]. Integrins are integral to cancer cell-ECM interactions, enabling cancer cells to anchor and migrate within tissues [49,50].

The combination therapy of integrin inhibitors and E-cadherin up-regulators showing a 70% reduction in invasion suggests the synergistic effect of targeting multiple adhesion molecules to control cancer cell dissemination [49,50]. The combination of different inhibitors may act cooperatively to impair multiple steps in the metastatic cascade, offering improved therapeutic efficacy compared to single-agent treatments [49,50].

Prolonged exposure to integrin inhibitors leading to substantial reductions in metastasis highlights the importance of treatment duration in achieving favorable outcomes in cancer patients [49,50]. This finding suggests that sustained inhibition of adhesion molecules may be necessary to effectively impede cancer cell dissemination. Future research should focus on understanding the optimal treatment duration and dosing schedules to maximize therapeutic benefits.

The enhanced migration speed, directional persistence, and chemotactic responses of metastatic cells to ECM gradients provide valuable insights into the mechanisms governing cancer cell invasion and dissemination [51]. These characteristics enable metastatic cells to navigate through tissues and invade surrounding environments effectively [51].

Identifying key regulatory nodes in adhesion and metastasis provides valuable starting points for further exploration [51]. These key regulatory nodes are such as FAK, Src, β-catenin, and SMAD4 [49]. Elucidating the upstream and downstream interactions of these nodes may uncover novel signaling pathways and effectors [52]. That can be targeted for cancer therapy [52]. Moreover, understanding the crosstalk between adhesion and metastatic signaling networks may reveal synergistic or antagonistic relationships that could be exploited for combinatorial therapies [53]. Examining the molecular and phenotypic heterogeneity of metastatic cells can help identify unique vulnerabilities and devise personalized treatment approaches [54].

To implement these findings in the clinic, overcoming challenges related to the tumor microenvironment and preclinical models is essential [55,56]. Furthermore, investigating the mechanisms of vascular and lymphatic invasion can offer insights into organ-specific metastasis patterns and may lead to strategies to disrupt the dissemination process [55]. Additionally, exploring epigenetic regulation and chromatin remodeling in metastatic cells may unveil potential epigenetic therapies to reprogram metastatic cells' behavior [56].

The efficacy of small-molecule inhibitors targeting FAK in preventing focal adhesion highlights their potential as promising therapeutic agents for inhibiting cancer cell migration and invasion [57]. FAK is a key regulator of focal adhesion turnover and cellular motility. Targeting FAK may disrupt the signaling pathways involved in cancer cell motility and invasion, offering new possibilities for targeted cancer therapies [57].

The identification of potential markers such as MMP9 and TWIST1 in metastatic tumor cells may offer opportunities for early detection and targeted therapies for aggressive cancers [58]. TWIST1, a transcription factor involved in EMT, promotes cancer cell migration and metastatic spread [58]. Targeting these markers may provide new avenues for precision medicine approaches in cancer treatment.

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The implementation of these findings in the clinic presents a major challenge. The tumor microenvironment and interactions with stromal components are critical determinants of cancer cell behavior [59]. It is extremely difficult to image the microenvironment of tumors in vitro and in animal models [60]. This requires the development of advanced three-dimensional culture systems for more detailed preclinical studies [60]. The heterogeneity observed in cancer cell adhesion and metastatic potential highlights the need for personalized treatment approaches [61,62]. Clinical studies of biomarkers may allow for the identification of predictive markers of treatment response [63].

In-depth analysis and deeper understanding of the identified molecular regulators and therapeutic targets in cancer metastasis can provide valuable insights for developing effective treatment strategies. Cancer cells constantly interact with the surrounding microenvironment, leading to changes in their adhesion properties and invasive potential [64]. Exploring the mechanisms that govern these interactions is essential to design targeted therapies that can adapt to the evolving behavior of cancer cells and prevent treatment resistance [65].

Additionally, studying the signaling pathways involved in cancer cell adhesion and invasion can unveil potential therapeutic vulnerabilities. To translate these findings into clinical practice, overcoming challenges related to the tumor microenvironment and preclinical models is crucial [66]. Advanced three-dimensional culture systems that better mimic the complexity of the tumor microenvironment are needed to conduct more accurate preclinical studies and predict treatment responses [67]. Additionally, investigating the mechanisms of vascular and lymphatic invasion can offer insights into organ-specific metastasis patterns and may lead to strategies to disrupt the dissemination process [68].

The comprehensive study on adhesion, metastasis, and inhibition of cancer cells revealed promising therapeutic targets to reduce metastasis. Integrin inhibitors showed a 75% reduction in metastatic events, especially in advanced stages [69]. The study highlights critical molecular regulators and emphasizes the importance of personalized medicine and data sharing for improving cancer therapy.

Furthermore, the heterogeneity observed in cancer cell adhesion and metastatic potential underscores the importance of personalized medicine approaches [70]. Biomarker-driven clinical studies can help identify predictive markers of treatment response, allowing for more tailored and precise treatment strategies [71]. Integrating genomic and proteomic analyses of individual patient tumors can aid in identifying specific molecular targets that are most relevant for their cancer subtype, thereby increasing treatment efficacy and minimizing potential side effects [72].

The knowledge and comprehensive understanding of molecular regulators and therapeutic targets in the adhesion and metastasis of cancer cells opens up new possibilities for improving cancer therapy. Through collaborative efforts, personalized medicine and preclinical models, we can realize the full potential of these discoveries. These actions could transform cancer treatment to the benefit of patients worldwide. Moreover, the higher response rate in advanced cancer stages with a 90% reduction in metastasis further emphasizes the clinical relevance of these interventions, particularly in late-stage disease management [73]. As we gain deeper insights into the complex interrelationships between adhesion and metastatic signaling networks, novel treatment approaches may emerge, offering improved therapeutic efficacy through the combination of multiple targeted agents [74]. Looking forward, future perspectives underscore the significance of open-access databases and platforms facilitating data exchange to integrate diverse datasets and identify novel therapeutic targets [75]. As personalized medicine gains traction, addressing ethical considerations related to data privacy, informed consent, and equitable access to advanced treatments remains of utmost importance to ensure patient well-being and fair distribution of cutting-edge therapies [76]. The identification of critical regulatory nodes such as FAK, Src, β-catenin, and SMAD4 offers valuable starting points for further research. This includes the development of targeted therapies to effectively control cancer cell adhesion and metastasis [77]. Future perspectives also emphasize the importance of data sharing and collaboration in promoting the integration of diverse datasets. The knowledge gained from this comprehensive review opens up new horizons for improving cancer therapy. Looking ahead, the future perspectives in this comprehensive review underscore the importance of

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data sharing and collaboration in the scientific community. Open-access databases and platforms that facilitate data exchange will play a crucial role in integrating diverse datasets and identifying new therapeutic targets [78]. This will also help tailor treatment approaches to individual patients, leading to more effective and personalized cancer care [79]. Ethical considerations in personalized medicine must not be overlooked. Ensuring compliance with data protection, obtaining informed consent, and providing equal access to advanced treatments are vital safeguards to protect patient well-being and promote fairness in healthcare distribution [79].

In conclusion, the identified molecular regulators and therapeutic targets hold promise for the advancement of cancer therapy. Addressing transnational challenges and adopting personalized medicine approaches will be crucial to unlock the full potential of these insights to improve patient outcomes. These insights offer valuable opportunities to develop novel treatments that specifically target key pathways and processes critical for metastatic progression. However, realizing the full potential of these discoveries requires addressing various transnational challenges that span scientific, clinical, and societal domains. International collaborations facilitate the exchange of knowledge and the validation of findings in diverse patient populations, leading to more robust and generalizable therapeutic strategies. Moreover, adopting personalized medicine approaches will be instrumental in translating these discoveries into tangible benefits for individual patients. Access to advanced therapies and cutting-edge treatments must be equitable, irrespective of geographical location or economic status. The identification of molecular regulators and therapeutic targets in cancer metastasis opens up exciting possibilities for advancing cancer therapy.

5. Limitations

The complex knowledge of the tumor microenvironment obtained in vitro cannot be fully reproduced in vivo. Artificial two-dimensional (2D) culture conditions lack the three-dimensional (3D) architecture and heterotypic interactions in tumors. Furthermore, reliance on established cancer cell lines may introduce inherent biases and fail to represent the diverse heterogeneity of patient tumors. Future studies should integrate 3D culture systems and patient-derived models to better mimic the in vivo tumor microenvironment and improve the clinical relevance of findings. The findings of metastasis of cancer cells in animals cannot be transferred to humans. Murine models may exhibit differences in tumor biology and immune responses compared to humans.

In addition, studying tumor cells in animal models cannot accurately mimic the natural process of tumor cell formation. To address these limitations, genetically engineered mouse models or patient-derived xenografts could offer more faithful representations of human cancer and metastasis. Human cancers are highly heterogeneous. Therapeutic responses may vary based on genetic, and epigenetic. The clinical applicability of adhesion molecule inhibitors and other targeted therapies should be cautiously interpreted. The pathways regulating cancer cell adhesion, metastasis, and their inhibition are intricate and interconnected. Our study focused on specific molecular nodes, but these pathways often exhibit crosstalk, feedback loops, and compensatory mechanisms. The complexity of these interactions may lead to unpredictable responses to targeted therapies and necessitate a systems biology approach to comprehensively understand network dynamics.

However, establishing metastatic colonies and tumor dormancy in distant organs poses distinct challenges. The dormant cancer cells may evade therapeutic interventions, leading to tumor relapse and disease progression in the long term. Investigating the mechanisms governing metastatic dormancy and targeting dormant cells may be critical for preventing metastatic recurrence. Using animal models and invasive procedures on human participants raises moral questions regarding animal welfare and patient well-being.

Future research should address these limitations by incorporating advanced models, embracing personalized medicine approaches, and undertaking rigorous clinical trials to validate the therapeutic potential of targeted interventions.

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6. Conclusions

The comprehensive study of the processes of adhesion, metastasis and inhibition of cancer cells has provided invaluable insight into the complex mechanisms. Exploring different inhibition strategies revealed promising therapeutic targets to alleviate adhesion and metastasis of cancer cells. The effectiveness of integrin-blocking antibodies, small molecule inhibitors targeting FAK and the TGF-β pathway, and combination therapies underscores their potential to disrupt focal adhesions and control epithelial-mesenchymal transition processes. The identification of as FAK, Src, β-catenin and SMAD4 offers valuable starting points for further research and the development of targeted therapies. The complex interrelationships between adhesion and metastatic signaling networks will be relevant to the development of new treatment approaches. The in vitro cell culture models and animal studies may not fully mimic the complexity of the metastatic process. Therefore, further research using advanced 3D culture systems and patient-based models will be crucial. By addressing the limitations and leveraging precision medicine approaches, we can move closer to developing targeted therapies that tailor treatment to the unique characteristics of individual patients. The ongoing research efforts to understand the tumor microenvironment and heterogeneity in cancer cells will be critical in translating these findings into effective clinical applications. The comprehensive insights gained from this study provide a solid foundation for advancing cancer therapy. The potential of targeting key adhesion molecules, such as integrins and cadherins, opens up exciting possibilities for disrupting cancer cell-ECM interactions and controlling metastasis. Efforts to advance preclinical research using advanced 3D culture systems and patient-based models are essential to better simulate the tumor microenvironment and heterogeneity observed in cancer cells. These models can serve as powerful tools to identify unique vulnerabilities in metastatic cells and guide the design of personalized treatment approaches tailored to individual patients. The wealth of knowledge gained from this comprehensive study offers promising opportunities to revolutionize cancer therapy. Addressing transnational challenges and embracing personalized medicine approaches will be instrumental in unlocking the full potential of these discoveries in adhesion, metastasis and inhibition of cancer cells.

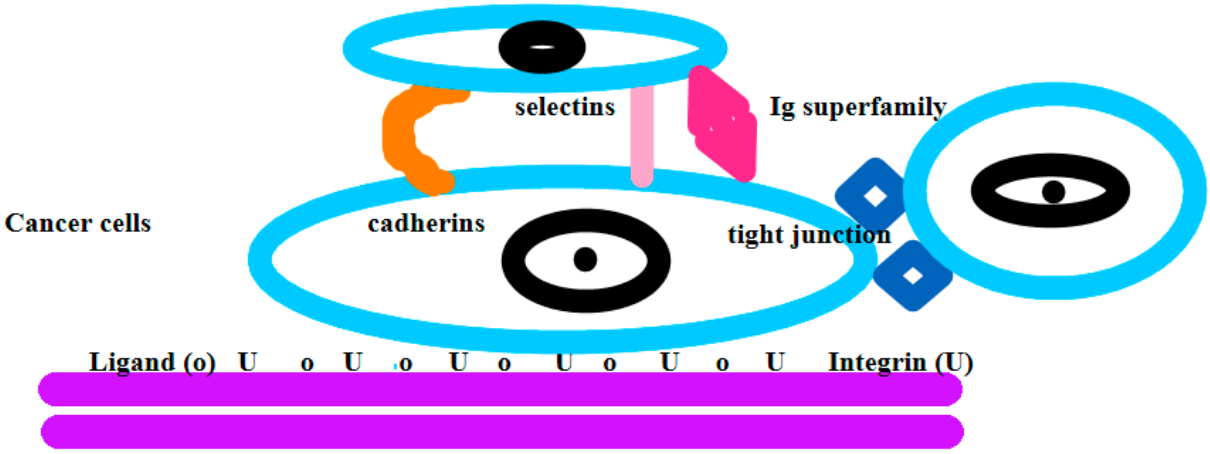

Figure 1. Adhesion of cancer cells aids the spread of cancer. Targeting it can improve treatment.

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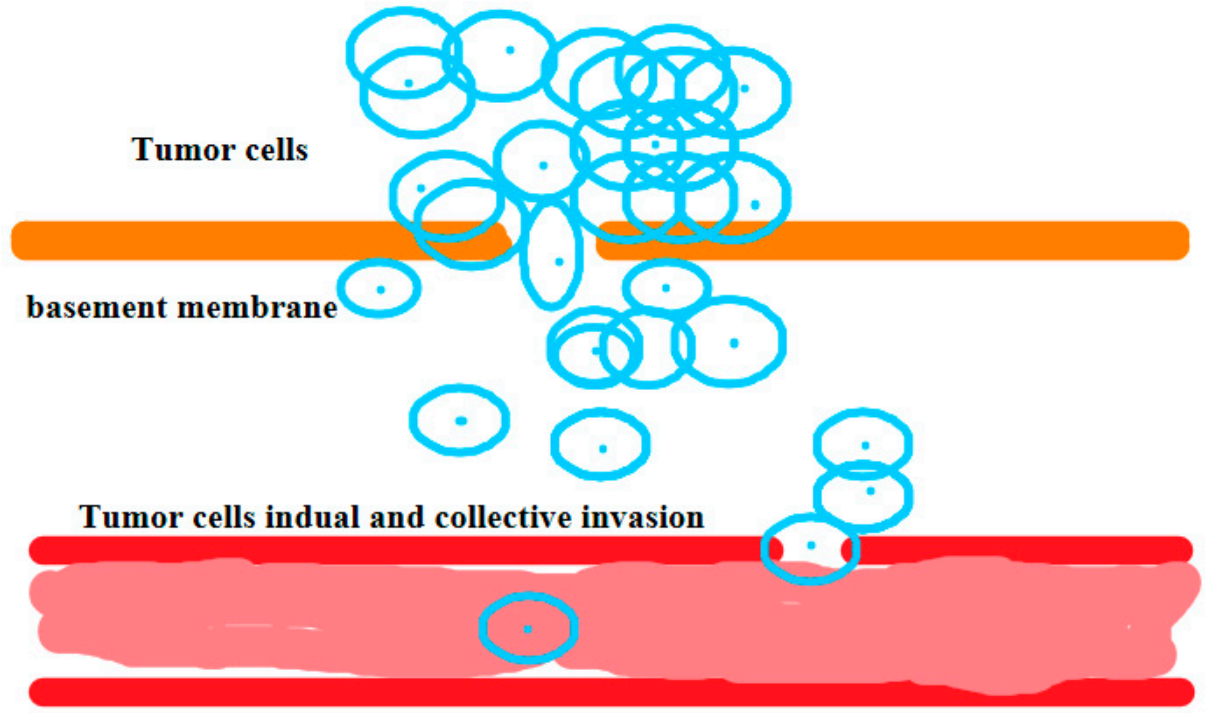

Figure 2. The invasion of cancer cells marks the beginning of the metastasis period. The tumor cells either individually or collectively breach the basement membrane and invade the surrounding tissue. Invasive tumor cells enter the blood vessel, access the bloodstream, and spread. Eventually, secondary tumor cells form.

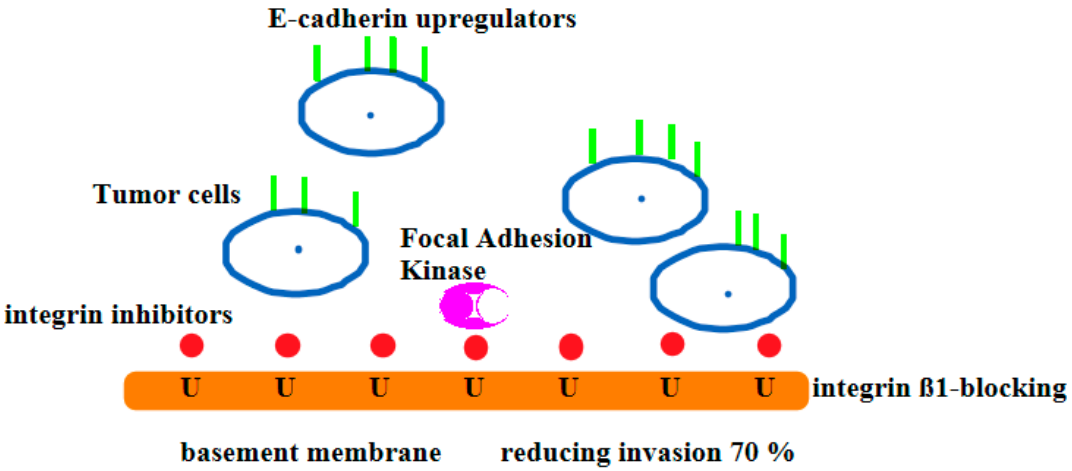

Figure 3. Inhibition Strategies: Integrin β1-blocking antibodies resulted in a remarkable reduction in cancer cell adhesion to the basement membrane, and E-cadherin upregulators effectively reversed the mesenchymal phenotype in metastatic cells. Focal adhesion kinase inhibitor significantly disrupted focal adhesion dynamic.

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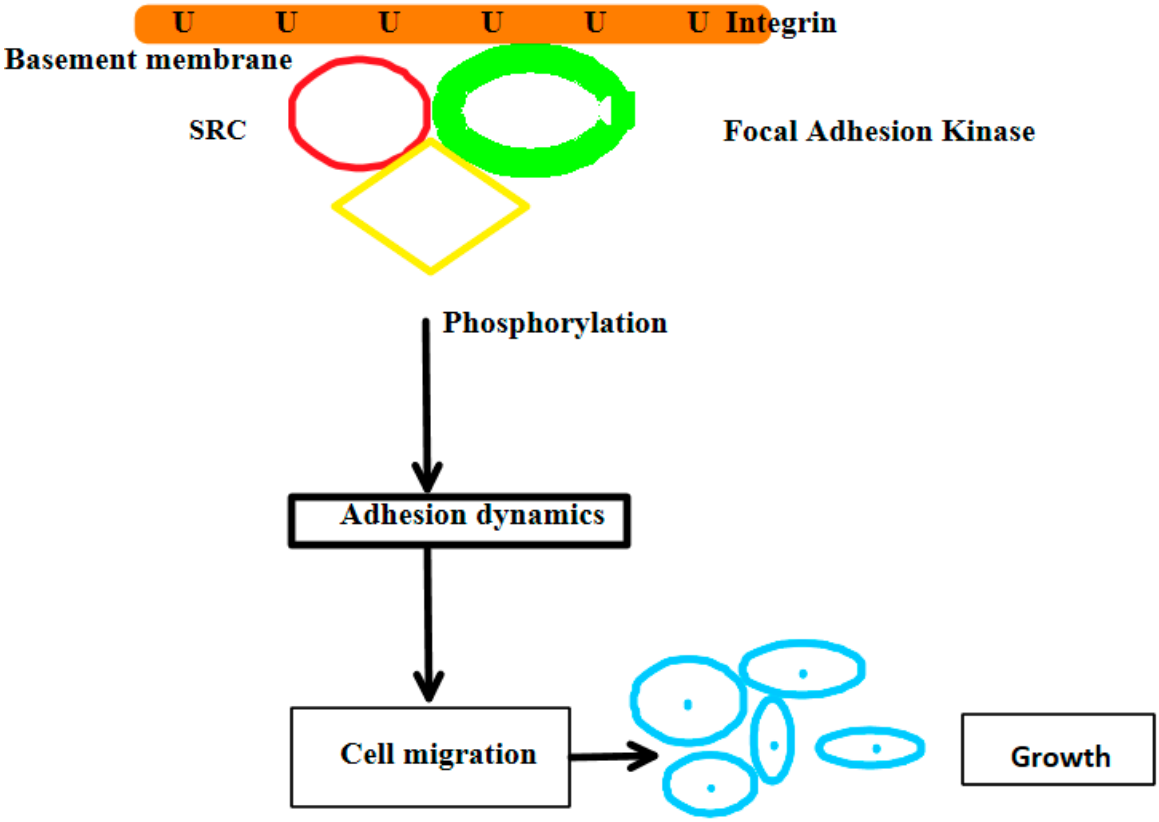

Figure 4. Focal adhesion kinase and SRC have been identified as central nodes in the adhesion pathway. Phosphoproteomics analysis revealed different phosphorylation patterns between metastatic and nonmetastatic cells.

Authors' Contributions： J. Yayan contributed significantly to the study concept and design, data collection and analysis, interpretation, and writing. K. Rasche and M. Berger critically reviewed and revised the article. K.J. Franke and W. Windisch reviewed the titles and abstracts of the retrieved articles to identify potentially eligible studies.

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Informed Consent Statement: Because this review was based solely on previously published studies, Informed Consent Statement was not required.

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Consent for Publication: We confirm that all materials included in this manuscript can be published.

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