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[Review] Investigating the Role of Urokinase in Cancer Metastasis: A Review

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Abstract

The greatest cause of cancer-related mortality is cancer metastasis, which is the spread of cancer cells from the original tumour to distant areas. Urokinase (uPA) is one of the important proteases involved in this process. By encouraging cell migration, invasion, and angiogenesis, uPA plays a critical part in the spread of cancer. Numerous cancers have an overexpressed uPA system, which is linked to a poor prognosis and a higher chance of metastasis. The project focuses on the state of the science around uPA inhibitors as a possible therapeutic for preventing or treating cancer metastasis. Different kinds of uPA inhibitors, including as monoclonal antibodies, small molecule inhibitors, and plasminogen activator inhibitors (PAIs), have been created and have showed promise in preclinical investigations. To prove their effectiveness in treating cancer patients, more study is necessary. A promising strategy for preventing or treating cancer metastasis involves targeting the uPA system with specific inhibitors or through techniques like gene therapy, anti-uPA/uPAR antibodies, uPA-targeted nanoparticles, and dual inhibitors that target multiple proteases involved in cancer metastasis. uPA inhibitors have also been researched as potential indicators for estimating the likelihood of cancer spread.

Keywords: uPA, cancer metastasis, Extracellular Matrix Protein Degradation, chemoresistance, uPA inhibitors.

Introduction

The most common reason for cancer-related mortality is cancer metastasis, which is the spread of cancer cells from the main tumour to distant areas. A number of proteases, such as urokinase (uPA), are involved in the complicated process by which cancer cells can move and infect nearby tissue. A serine protease known as urokinase is essential for the spread of cancer. Cancer cells can move through the extracellular matrix (ECM) and infiltrate neighbouring tissue because of the protease activity of uPA, which cleaves ECM proteins including plasminogen. Additionally, it has been demonstrated that uPA stimulates angiogenesis, which is important for the development and survival of malignancies. Breast, lung, and prostate cancer have all been reported to have elevated levels of the uPA system, which consists of the

uPA protein and its receptor (uPAR). A worse prognosis and a higher likelihood of metastasis are linked to this overexpression. A promising strategy for preventing or treating cancer metastasis may therefore involve targeting the uPA system, whether through specific inhibitors or through techniques like gene therapy, anti-uPA/uPAR antibodies, uPA-targeted nanoparticles, or dual inhibitors targeting multiple proteases involved in cancer metastasis. I will examine the present state of research on uPA inhibitors as a possible medication for preventing or treating cancer metastasis in this review of the literature. I will talk about how uPA affects cancer metastasis, the several types of uPA inhibitors that have been created and their potential to treat cancer, as well as the difficulties and potential future paths in the research and development of uPA inhibitors as a cancer treatment. I will also talk about the possibility of using uPA inhibitors as biomarkers to assess the likelihood of cancer spread.

Role of Urokinase in Cancer Metastasis

Cell migration, invasion, and angiogenesis are only a few of the critical stages of the metastatic process in which urokinase plays a role. Cancer cells can move through the extracellular matrix (ECM) and infiltrate neighbouring tissue because the protease activity of uPA cleaves ECM proteins including plasminogen [1]. uPA has been demonstrated to support angiogenesis, the creation of new blood vessels required for the survival and growth of malignancies [2]. Numerous cancers, including breast, lung, and prostate cancer, have been discovered to overexpress the uPA system, which consists of the uPA protein and its receptor (uPAR) [3]. A poor prognosis and an elevated chance of metastasis are linked to this overexpression [4]. Urokinase has a complicated and diversified involvement in the spread of cancer. Cell migration, invasion, and angiogenesis are a few of the critical stages of the metastatic process in which uPA is implicated. Cancer cells can move through the extracellular matrix (ECM) and infiltrate neighbouring tissue because of the protease activity of uPA, which cleaves ECM proteins including plasminogen. Cancer cell invasion and migration are made possible by the ECM proteins that are cleaved by uPA. Studies have revealed that uPA encourages cancer cells to migrate both in vitro and in vivo [1][2]. uPA is also essential for the invasion of cancer cells. In order to facilitate cancer cell invasion, it cleaves ECM proteins. Other proteases, such as matrix metalloproteinases (MMPs), are activated by uPA-mediated cleavage of ECM proteins, further promoting cancer cell invasion [3]. uPA has been found to support angiogenesis, the growth and survival of cancers depend on the development of new blood vessels. Vascular endothelial growth factor (VEGF) and other pro-angiogenic factors are released when uPA cleaves ECM proteins, activating other pro-angiogenic pathways. uPA increases angiogenesis both in vivo and in vitro, according to studies [4][5]. Breast, lung, and prostate cancer have all been reported to have elevated levels of the uPA system, which consists of the uPA protein and its receptor (uPAR). A worse prognosis and a higher likelihood of metastasis are linked to this overexpression. Therefore, preventing or treating cancer metastasis may be possible by targeting the uPA system with particular inhibitors or by techniques like gene therapy, anti-uPA/uPAR antibodies, uPA-targeted nanoparticles, or dual inhibitors that target several proteases.

The capacity of uPA to affect the immune system is a crucial factor in the spread of cancer. According to research, uPA helps the tumour microenvironment attract and activate immune cells including neutrophils and macrophages. By

releasing proteases and growth factors, these immune cells can encourage the invasion and migration of cancer cells [6]. It has been demonstrated that uPA facilitates the development of immunosuppressive tumour microenvironments, which increases cancer cells' capacity to elude the immune system [5]. It has also been discovered that uPA functions in the control of cancer stem cells (CSCs), a subset of cancer cells that initiates and maintains tumours. uPA encourages CSC self-renewal and proliferation, which helps metastases form [2]. Also discovered is uPA's role in the growth and development of primary tumours, in addition to its role in metastatic processes. A number of studies have shown that uPA enhances the growth and survival of primary malignancies by stimulating angiogenesis and modifying the immune system [5]. uPA's participation in the epithelial-to-mesenchymal transition is a crucial feature of its function in cancer metastasis (EMT). Cancer cells undergo a process called EMT when they lose their epithelial properties and develop a mesenchymal phenotype that enables them to move and infiltrate nearby tissue.

By encouraging the activation of transcription factors linked to EMT and the suppression of epithelial markers, it has been discovered that uPA is an important element in the production of EMT in cancer cells [7]. uPA also has an impact on cancer-associated stroma and fibroblasts (CAFs). A particular subtype of fibroblast known as cancer-associated fibroblasts invades the tumour microenvironment and aids in the migration, invasion, and angiogenesis of cancer cells. It has been discovered that uPA encourages CAF activation, which helps metastases form [8][9]. The extracellular vesicles (EVs) that cancer cells release can also be impacted by uPA. By encouraging angiogenesis, cancer cell migration, and invasion, these vesicles, which have the capacity to contain proteins, lipids, and RNA molecules, may contribute to the development and spread of cancer. uPA has been discovered to alter the composition and release of EVs, which may have an impact on the ability of cancer cells to metastasize [5]. As uPA promotes the development of immunosuppressive tumour microenvironments and the recruitment and activation of immune cells, it contributes to tumour microenvironment control. uPA is a viable target for cancer therapy due to its capacity to control several elements of the tumour microenvironment, such as ECM breakdown, angiogenesis, immune evasion, and cancer stem cells. Additional studies have revealed that genetic and epigenetic variables may have an impact on how uPA affects cancer spread.

Genetic changes in the uPA gene and its receptor (uPAR) have been linked to a higher risk of cancer growth and metastasis, according to studies [7]. Similar to this, it has been discovered that epigenetic changes such DNA methylation control the production of uPA and uPAR in cancer cells and aid in the formation of metastasis [7]. Targeting uPA could stop the growth and spread of the original tumour as well as the metastatic process. Additionally, genetic and epigenetic variables may have an impact on uPA's function in cancer metastasis, emphasising the significance of tailored approaches to the treatment of cancer metastasis. Hematogenous metastasis, or the spread of cancer cells through the circulation, is another significant feature of uPA's participation in cancer metastasis. Cancer cell clusters known as emboli that can separate from the original tumour and move via the circulation to other organs have been discovered to be significantly influenced by uPA. Cancer cells can separate from the primary tumour thanks to the protease activity of uPA, which has been demonstrated to enhance the development of emboli by cleaving ECM proteins [10].

Additionally, it has been discovered that uPA contributes to the development of metastatic colonies in distant organs and the survival of cancer cells in the bloodstream. Apoptosis (planned cell death) is discovered to be inhibited by uPA, which

also promotes the establishment of metastatic colonies by encouraging angiogenesis in distant organs [11]. Likewise, it has been shown that uPA contributes to the spread of cancer cells through the lymphatic system, a process known as lymphatic metastasis. Through the cleavage of ECM proteins and the activation of other proteases, uPA has been reported to facilitate the invasion and migration of cancer cells through lymphatic channels [12]. Targeting uPA could stop the growth and spread of the original tumour as well as the metastatic process. Genetic and epigenetic variables may have an impact on uPA's function in cancer metastasis, emphasising the significance of tailored approaches to the treatment of cancer metastasis.

The participation of uPA in the angiogenic switch process is a crucial component of its function in cancer spread. Cancer cells can create more energy and encourage angiogenesis by switching from oxidative phosphorylation to aerobic glycolysis during a process known as the "angiogenic switch." By encouraging the activation of transcription factors like HIF-1, which controls the expression of genes involved in the angiogenic switch, uPA has been revealed to play a crucial part in this process [13]. The process of cancer dormancy, in which cancer cells are dormant for protracted periods of time before becoming active and producing new metastases, has also been revealed to include uPA. By altering the expression of genes related to cell cycle control and apoptosis, uPA has been demonstrated to support cancer dormancy [14]. Additionally, it has been shown that uPA contributes to chemoresistance, or the capacity of cancer cells to fend off the effects of chemotherapy. By regulating the expression of genes involved in drug metabolism and drug efflux, uPA has been demonstrated to increase chemoresistance [15]. The participation of uPA in the process of epigenetic regulation is a crucial component of its function in cancer spread. The term "epigenetics" describes heritable changes in gene expression that take place without underlying DNA sequence alterations. The control of epigenetic processes including DNA methylation and histone modification, which can influence the expression of genes implicated in cancer metastasis, has been discovered to be critically dependent on uPA [8]. uPA also functions in autophagy, the process of cellular self-degradation. Cancer cells employ autophagy as a survival strategy to adjust to numerous stressful situations such hypoxia, food restriction, and chemotherapy. By regulating the expression of genes related to autophagy, uPA has been demonstrated to facilitate this process [16].

Moreover, uPA has been found to promote self-renewal and differentiation of cancer stem cells in the milieu known as the cancer stem cell niche. By encouraging the development of extracellular matrix, the attraction of cancer-associated fibroblasts, and the release of growth factors and cytokines, uPA has been demonstrated to modify the cancer stem cell niche [17]. Additional studies have revealed that the tumour microenvironment may play a part in uPA's participation in cancer spreading. Studies have demonstrated that elements including hypoxia, inflammation, and the presence of other proteases in the tumour microenvironment can affect the production and activity of uPA [18]. These findings imply a more potent strategy for preventing or treating cancer metastasis may involve targeting uPA in the context of the tumour microenvironment. The emergence of therapeutic resistance has also been linked to uPA. Studies have revealed a number of processes by which cancer cells might become resistant to uPA inhibitors, including the activation of alternative signalling pathways, the overexpression of other proteases, and the acquisition of genetic abnormalities [19]. To overcome resistance and improve the effectiveness of therapy, it is crucial to devise combination medicines that focus on several routes. Targeting uPA could stop the growth and spread of the original tumour as well as the metastatic process. The

tumour microenvironment, the development of therapeutic resistance, genetic and epigenetic variables, and uPA's function in cancer spread may all also have an impact. To overcome resistance and improve the effectiveness of therapy, it is crucial to devise combination medicines that take these aspects into account and focus on numerous routes. The participation of uPA in the process of cell-to-cell communication is a crucial component of its function in cancer metastasis. Exosomes are signalling molecules that can be released by cancer cells to communicate with other cancer cells as well as with other cells in the tumour microenvironment.

Cancer cells may produce and release exosomes that include uPA, uPAR, as well as other signalling molecules such miRNAs and mRNAs. It has been discovered that uPA is essential for this process (messenger RNAs). The development of a pro-metastatic milieu is facilitated by the ability of these exosomes to transmit these chemicals to additional cancer cells and cells in the tumour microenvironment [20]. uPA has been identified as one of the factors that contribute to the adaptability of cancer cells. Because uPA regulates the expression of genes involved in cell plasticity, it has been discovered that cancer cells can alter their phenotypic or functional properties in response to changes in the microenvironment [21]. uPA's participation in the invasion of cancer cells is a crucial feature of its function in cancer metastasis. By modifying the activity of matrix metalloproteinases (MMPs) and other proteases that break down the extracellular matrix (ECM) and basement membrane, uPA has been discovered to facilitate the invasion of cancer cells [22]. By altering the activation of integrins, transmembrane receptors that control cell-matrix interactions and cell migration, uPA can also encourage cancer cell invasion. It has been discovered that uPA encourages integrin activation, which aids in the invasive aggressiveness of cancer cells [23].

uPA contributes to the adherence of cancer cells. As cancer cells must adhere to the endothelial cells lining the blood arteries in order to enter the circulation and develop metastases, adhesion is a crucial stage in the metastatic process. By altering the activity of integrins and other adhesion molecules, it has been discovered that uPA increases the adherence of cancer cells to endothelial cells [23]. It also contributes to the movement of cancer cells. As cancer cells must migrate across the ECM and basement membrane in order to infect surrounding tissue and produce metastases, migration is a crucial phase in the metastatic process. It has been discovered that uPA stimulates the migration of cancer cells through regulating the activity of enzymes involved in cell migration, such as proteases [24]. In the interactions between cancer cells and endothelial cells, uPA is an essential component. In order to enter the bloodstream and develop metastases, cancer cells must interact with the endothelial cells lining the blood arteries. By altering the activity of integrins and other adhesion molecules on cancer cells and endothelial cells, it has been discovered that uPA promotes these interactions [23]. Additionally, it has been discovered that uPA contributes to the intravasation of cancer cells. Cancer cells enter blood arteries and lymphatic vessels through the process of intravasation to create metastases.

The activity of proteases and other molecules involved in cancer cell migration and invasion, as well as the production of emboli, have all been discovered to be modulated by uPA, which has been proven to enhance intravasation [25]. uPA's participation in the process of cancer cell extravasation is a key feature of its function in cancer metastasis. Cancer cells spread to distant organs by the process of extravasation, which occurs when they leave the blood arteries and lymphatic vessels. By regulating the activity of proteases and other enzymes involved in cancer cell migration and invasion, as well as by encouraging angiogenesis in the distant organs, uPA has been reported to increase extravasation [26]. Targeting

uPA could stop the growth and spread of the original tumour as well as the metastatic process. To overcome resistance and improve the effectiveness of therapy, it is crucial to devise combination medicines that take these aspects into account and focus on numerous routes. uPA's participation in the process of cancer cell survival in the circulation is an essential component of its function in cancer metastasis. Cancer cells must be able to last long enough in the circulatory system to spread to another organ. By regulating the action of molecules that are both pro- and anti-apoptotic and by encouraging the development of protective microenvironments like emboli, uPA has been demonstrated to increase the survival of cancer cells in the circulation [25].

As well as contributing to cancer cell spread, uPA can influence the growth and spread of other tissues as well. Cancer cells must be able to colonise and create a metastasis after they have reached a distant organ. By regulating the activities of proteases and other enzymes involved in cell migration and invasion, as well as by encouraging angiation in the distant organ, uPA has been demonstrated to increase cancer cell colonisation in distant organs. uPA also stimulates the development of pre-metastatic niches in distant organs by drawing in fibroblasts linked to cancer and altering the extracellular matrix [27]. It also contributes to the immune system evasion of cancer cells. Cancer cells must be able to avoid detection by the immune system in order to spread and thrive. By altering the activity of molecules involved in immune cell recruitment and activation as well as by encouraging the development of immunosuppressive microenvironments, uPA has been demonstrated to support cancer cells' evasion of the immune system [28]. Targeting uPA could stop the growth and spread of the original tumour as well as the metastatic process. The tumour microenvironment, the development of therapeutic resistance, genetic and epigenetic variables, and uPA's function in cancer spread may all have an impact. To overcome resistance and improve the effectiveness of therapy, it is crucial to devise combination medicines that take these aspects into account and focus on numerous routes.

The participation of uPA in the invasion of lymphatic vessels by cancer cells is another significant feature of uPA's function in cancer metastasis. By regulating the activity of proteases and other molecules involved in cell migration and invasion, as well as by encouraging the creation of pre-metastatic niches in the lymphatic channels, uPA has been discovered to enhance cancer cell invasion of the lymphatic vessels [29]. uPA also contributes to the survival of cancer cells in lymphatic arteries and lymph nodes. Cancer cells must be able to endure long enough to spread to distant organs through lymphatic arteries and lymph nodes. uPA has been discovered to influence the activity of molecules that are both pro- and anti-apoptotic, as well as through supporting the development of protective microenvironments, to enhance cancer cell survival in lymphatic arteries and lymph nodes [29].

uPA also contributes to the immune system's evasion of cancer cells in lymphatic arteries and lymph nodes. Cancer cells must be able to elude the immune system in order to live and proliferate as metastases in the lymphatic arteries and lymph nodes. By altering the activity of molecules involved in immune cell recruitment and activation as well as by encouraging the development of immunosuppressive microenvironments, uPA has been discovered to improve cancer cells' ability to evade the immune system in lymphatic arteries and lymph nodes [30]. The participation of uPA in the process of cancer cell dormancy is a crucial component of its function in cancer spread. Cancer cells that metastasize to other organs may go into a dormant condition, where they are not actively multiplying but are still alive and have the

capacity to become active again and expand. By modifying the action of molecules involved in cell proliferation, survival, and death, uPA has been reported to induce the dormancy of cancer cells [31]. It has been discovered that uPA contributes to the spread of cancer cells. To create numerous metastases, cancer cells must be able to disseminate, or spread, to a number of organs. By regulating the activity of proteases and other molecules involved in cell migration and invasion, as well as by encouraging the development of pre-metastatic niches in various organs, uPA has been discovered to enhance the dispersion of cancer cells.

It has also been discovered that uPA is involved in the recurrence of cancer cell metastasis. After first therapy, cancer cells that metastasize might return. By altering the function of molecules involved in cancer cell dormancy and by encouraging the development of pre-metastatic niches in several organs, uPA has been discovered to increase the recurrence of cancer cells [32]. The participation of uPA in the development of cancer cell chemoresistance is a crucial component of its function in cancer spread. Cancer is frequently treated with chemotherapy, however cancer cells might become resistant to the treatments. By regulating the activity of molecules involved in cell survival and apoptosis, as well as by encouraging the development of protective microenvironments, uPA has been discovered to enhance cancer cell chemoresistance [33]. uPA also contributes to the control of cancer cells' epigenetic processes. The expression of genes involved in the initiation and progression of cancer can be affected by epigenetic alterations such as DNA methylation and histone modifications. By modifying the activity of enzymes involved in DNA methylation and histone modifications, uPA has been discovered to support cancer cell epigenetic control [34].

Aside from this, uPA has also been found to play a role in autophagy, a process during which cancer cells are digested. Degradation of cellular components occurs during the cellular process known as autophagy, which can affect cancer cell survival and resistance to treatment. By controlling the activity of molecules involved in the autophagic process, uPA has been discovered to encourage autophagy in cancer cells. uPA's participation in the process of cancer cell immune evasion is a crucial feature of its function in cancer spread. Cancer cells must be able to avoid detection by the immune system in order to spread and thrive. By modifying the function of molecules involved in immune cell recruitment and activation as well as by encouraging the development of immunosuppressive microenvironments, uPA has been demonstrated to increase cancer cell immune evasion. It has been revealed that uPA contributes to the immune editing of cancer cells. Cancer cells change through a mechanism called immunological editing that makes them immune-resistant. By regulating the function of molecules important in cancer cell survival, proliferation, and apoptosis, uPA has been demonstrated to increase immune editing in cancer cells [35].

Moreover, uPA has been found to be involved in the process of cancer cells evading immune detection. Cancer cells that have been identified by the immune system are able to avoid immunological assault through a mechanism known as immune escape. By altering the activity of molecules important in cancer cell survival, proliferation, and apoptosis as well as by encouraging the development of immunosuppressive microenvironments, uPA has been reported to increase cancer cell immune escape.

Role of Urokinase in the Regulation of Extracellular Matrix Protein Degradation

Extracellular matrix (ECM) protein breakdown is tightly controlled by uPA. A complex network of proteins and carbohydrates called the extracellular matrix (ECM) gives cells and tissues structural support. Plasminogen, a precursor of plasmin, a crucial enzyme in ECM degradation, is activated by uPA, which then participates in the breakdown of ECM proteins. Plasminogen activation is a vital step in the ECM remodelling process during physiological processes including wound healing and tissue repair. Nevertheless, severe ECM deterioration may be a factor in the emergence of pathological situations including cancer metastasis and persistent inflammation [36]. Additionally, by cleaving ECM proteins including laminin and collagen, uPA directly contributes to the breakdown of ECM proteins [37].

By cleaving certain peptide links, a procedure known as proteolysis, uPA can break down these proteins. uPA-mediated proteolysis can help create a favourable environment for the invasion and migration of cancer cells [38]. According to recent research, uPA also controls the activity of matrix metalloproteinases (MMPs), which are enzymes that break down ECM proteins. MMP-2 and MMP-9, which are involved in ECM breakdown and cancer cell invasion, have been discovered to be activated by uPA [39]. Tissue inhibitors of metalloproteinases (TIMPs), which are inhibitory regulators of MMP activity, have also been discovered to be inhibited by uPA. Targeting uPA, however, could also stop the growth and spread of the underlying tumour in addition to the metastatic process.

Additionally, the tumour microenvironment, the development of therapeutic resistance, genetic and epigenetic variables, and uPA's participation in ECM degradation may all have an impact. To overcome resistance and improve the effectiveness of therapy, it is crucial to devise combination medicines that take these aspects into account and focus on numerous routes. The involvement of uPA in the movement and invasion of cancer cells is another significant component of this compound's function in the breakdown of the ECM. By altering the activity of molecules involved in cell-matrix interactions, such as integrins and other ECM receptors, uPA has been reported to facilitate cancer cell motility and invasion [40]. Focal adhesions, which are structures that facilitate cell-matrix interactions and are implicated in cancer cell migration and invasion, have been revealed to be regulated by uPA [41]. The activity of cytoskeletal proteins like actin and myosin, which are involved in cell invasion and migration, has also been discovered to be modulated by uPA [42]. Furthermore, uPA has the ability to activate downstream signalling pathways, including the PI3K/Akt and RhoA/ROCK pathways, which are necessary for the invasion and migration of cancer cells [43].

The prsence of uPA in cancer cells contributes to angiogenesis. Blood vessel creation, or angiogenesis, is an essential mechanism for the growth and spread of cancer cells. By regulating the activity of molecules involved in blood vessel creation, such as VEGF and other angiogenic growth factors, uPA has been discovered to stimulate angiogenesis [23][24]. uPA also contributes to the multiplication of cancer cells. Cancer cell development and metastasis depend heavily on the process of cancer cell proliferation, which is cell division. uPA has been reported to increase the proliferation of cancer cells by altering the activity of molecules that control the cell cycle, such Cyclin D1 and CDK4 [44]. The participation of uPA in the fibrosis process is a crucial component of its role in the breakdown of the ECM. Organ dysfunction can result from fibrosis, which is the abnormal buildup of ECM proteins in tissues. In addition to controlling the activity of ECM-degrading enzymes like MMPs and encouraging the recruitment and activation of fibroblasts, which are cells that create ECM proteins, uPA has been discovered to have a role in fibrosis. Numerous clinical disorders, including chronic renal disease,

lung fibrosis, and liver fibrosis, have been linked to uPA, according to studies [45].

uPA also participates in bone remodeling, according to research. An essential physiological process for preserving bone strength and avoiding fractures, bone remodelling includes the ongoing turnover of the bone matrix. By controlling the activity of ECM-degrading enzymes such MMPs and by encouraging the recruitment and activation of osteoclasts, cells that resorb bone matrix, uPA has been discovered to have a function in bone remodelling [46]. The involvement of uPA in tissue repair and regeneration is a crucial feature of its function in ECM breakdown. By encouraging the breakdown of ECM proteins and the activation of cells involved in tissue repair, such as fibroblasts, endothelial cells, and immune cells, uPA has been revealed to play a crucial role in tissue repair and regeneration [47]. The activation of angiogenesis and the promotion of the migration and proliferation of cells involved in tissue repair are two mechanisms through which uPA has been identified to speed up wound healing [48]. uPA also contributes to tissue regeneration by encouraging stem cells to differentiate into other cell types, such as endothelial cells, and by encouraging the growth of new blood vessels. uPA's participation in the autophagic process is a crucial feature of its function in the breakdown of the ECM. Lysosomal destruction of cellular components, such as ECM proteins, is a part of the cellular process known as autophagy. By encouraging the breakdown of ECM proteins and controlling the activity of autophagy-related proteins including LC3 and Beclin 1, uPA has been discovered to have a function in autophagy [49].

The autophagic breakdown of ECM proteins by uPA could also contribute to the spread of cancer. Additionally, it has been discovered that uPA contributes to the control of immunity and inflammation. TNF-alpha and IL-1beta, which are important in the control of ECM breakdown and cancer cell invasion, have been discovered to be affected by uPA [50]. uPA modifies the activity of immune cells including macrophages and T cells, which control the breakdown of the extracellular matrix and the invasion of cancer cells. The involvement of uPA in cancer cell survival and treatment resistance is a crucial feature of its function in ECM breakdown. By altering the activity of molecules important in cell survival and drug resistance, such as Bcl-2 and P-glycoprotein, uPA has been reported to enhance cancer cell survival and drug resistance. By controlling the activation of signalling pathways such the PI3K/Akt and MAPK pathways, which are crucial for cancer cell survival and drug resistance, uPA has also been reported to enhance cancer cell survival and drug resistance [51].

A role for uPA also has been found in cancer cell stemness and medication resistance. The ability of cancer cells to self-renew and differentiate, which is essential for cancer cell proliferation and metastasis, is known as cancer cell stemness. By modifying the activity of molecules implicated in cancer cell stemness and drug resistance, such as Oct4, Sox2, and ABCB1, uPA has been reported to enhance cancer cell stemness and drug resistance [52]. The participation of uPA in the process of cancer cell immune evasion is a crucial component of its function in ECM breakdown. By altering the activity of molecules implicated in cancer cell immune evasion, such as PD-L1 and IDO, uPA has been discovered to facilitate this process [53]. uPA also aids in the immune evasion of cancer cells by controlling the activation of signalling pathways such the PI3K/Akt and MAPK pathways [54]. uPA also encourages cancer cell immune evasion by altering the activity of immune cells necessary for controlling cancer cell immune evasion, such as T cells and macrophages. Additionally, it has been discovered that uPA contributes to the chemoresistance of cancer cells. Chemotherapy, which is essential for

cancer cell proliferation and spread, can be overcome by cancer cells by developing chemoresistance. By modifying the function of molecules that contribute to cancer cell chemoresistance, such as Bcl-2 and P-glycoprotein, uPA has been reported to induce chemoresistance in cancer cells [55].

The urokinase plasminogen activator receptor (uPAR) and integrins are also shown to be modified by uPA. uPAR is a cell surface receptor that binds uPA and encourages the breakdown of the ECM and the invasion of cancer cells. Integrins are transmembrane receptors that mediate interactions between cells and their environments. They also help cancer cells invade healthy tissues and degrade ECM. By controlling the development of focal adhesions, which are structures that facilitate cell-matrix interactions and are implicated in ECM breakdown and cancer cell invasion, uPA has been reported to affect the activity of integrins [56]. Studies have revealed that uPA can encourage the activation of integrins that are involved in the invasion of cancer cells, such as alpha-5 beta-1 and alpha-v beta-3 [57]. uPA interacts with other ECM-degrading enzymes, such MMPs, to regulate the breakdown of ECM proteins. According to studies, uPA can control the expression and activation of MMPs, including MMP-9, to control their activity [58].

Role of uPA in Cancer Cell Invasion and Migration

Modulation of integrin activity is one of the main ways that uPA enhances cancer cell invasion and migration. Integrins are transmembrane receptors that play a crucial part in the invasion of cancer cells by mediating interactions between cells and the matrix. Studies have revealed that uPA can encourage the activation of integrins that are involved in the invasion of cancer cells, such as alpha-5 beta-1 and alpha-v beta-3 [57]. For instance, uPA can activate the alpha-5 beta-1 integrin in breast cancer cells, resulting in enhanced cell motility and invasion, according to a research by Liu et al., 2009 [59]. In a similar vein, Zhou et al., 2018 [60] discovered that uPA may activate the alpha-v beta-3 integrin in ovarian cancer cells, increasing cell migration and invasion. The actin cytoskeleton is regulated by uPA, which also promotes the invasion and migration of cancer cells. A network of proteins called the actin cytoskeleton aids in cell mobility and offers structural support to cells. According to studies, uPA might encourage the development of actin stress fibres, which are crucial for cell migration [61]. Additionally, RhoA, a small GTPase that is essential for cytoskeleton structure, cell migration, and tumour growth, can be activated by uPA. The activation of signalling pathways such the PI3K/Akt and RhoA/ROCK pathways, which are necessary for cancer cell invasion and migration, has also been discovered to be controlled by uPA, which has been proven to enhance cancer cell invasion and migration [62]. For instance, a research by Ghasemi et al., 2019 [63] discovered that the RhoA/ROCK pathway may be activated by uPA in breast cancer cells, increasing cell migration and invasion. Additionally, it has been discovered that uPA stimulates the invasion and migration of cancer cells via controlling the activity of growth factors including VEGF and FGF. Growth factors such as VEGF and FGF, which support angiogenesis, have been discovered to be overexpressed in a variety of cancers. According to studies, uPA can stimulate the production of VEGF and FGF, which increases cell migration and invasion [64]. For instance, uPA can activate VEGF in lung cancer cells and encourage cell migration and invasion, according to a research by Liu et al., 2016 [65].

By interacting with other ECM-degrading enzymes such matrix metalloproteinases, uPA promotes cancer cell invasion and

migration through a different mechanism (MMPs). MMPs are a class of enzymes that break down ECM proteins and are essential for the invasion and migration of cancer cells. According to research, uPA can control the expression and activation of MMPs like MMP-2 and MMP-9 to control their activity. For instance, Wu et al., 2009 [66] discovered that uPA may activate MMP-2 in lung cancer cells, increasing cell invasion and migration. Similar to this, Zou et al., 2016 [67] discovered that uPA can influence MMP-9 expression in ovarian cancer cells, which promotes enhanced cell migration and invasion. Additionally, it has been shown that uPA increases the invasion and migration of cancer cells by altering the activity of molecules that aid in cell adhesion, such as the uPA receptor (uPAR) and the vitronectin receptor (VNR). While the VNR is a transmembrane protein that binds vitronectin and controls cell adhesion, the uPAR is a transmembrane protein that binds uPA and controls its activity. The creation of a complex between uPAR and VNR, which is facilitated by uPA, has been linked to enhanced cell migration and invasion, according to studies.

The modulation of the epithelial to mesenchymal transition (EMT) programme by uPA is another way it encourages cancer cell invasion and migration. Epithelial cells undergo the EMT programme, which results in the loss of their polarity and adhesion abilities and the acquisition of mesenchymal traits, including enhanced motility, invasiveness, and resistance to apoptosis, which are linked to the migration and invasion of cancer cells. According to studies, uPA can cause EMT in cancer cells by turning on signalling channels including the TGF- and Wnt pathways [68]. For instance, Zhang et al., 2013 [69] found that uPA may activate the Wnt pathway in breast cancer cells, induce EMT, and accelerate cell invasion. Furthermore, it has been discovered that uPA stimulates the invasion and migration of cancer cells by altering the activity of cytoskeleton-related proteins such vimentin, N-cadherin, and E-cadherin. A mesenchymal cell-associated cytoskeleton protein called vimentin is increased during EMT. The adhesion molecules N- and E-cadherin, which are connected to epithelial cells, are downregulated during EMT. According to studies, uPA can encourage the overexpression of vimentin and the downregulation of N- and E-cadherin, which enhances cell invasion and migration [70].

By controlling the action of proteases such plasminogen activator inhibitor type-1, uPA also encourages the invasion and migration of cancer cells (PAI-1). Studies have revealed that uPA can control the activity of PAI-1, which increases cell migration and invasion. PAI-1 is an inhibitor of uPA. For instance, Li et al., 2015 [71] discovered that uPA can downregulate PAI-1 expression in breast cancer cells, increasing cell motility and invasion. By altering the activity of signalling molecules including phosphatidylinositol 3-kinase (PI3K) and extracellular signal-regulated kinase, uPA has also been shown to support cancer cell invasion and migration (ERK). Important signalling molecules like PI3K and ERK control cell motility, proliferation, and survival. Studies have demonstrated that uPA can activate the PI3K and ERK pathways, increasing cell invasion and migration [72]. For instance, uPA can activate the PI3K pathway in breast cancer cells and encourage cell migration and invasion, according to a research by Wang et al., 2019 [73]. uPA has been found to promote cancer cell invasion and migration by modulating the activity of cell survival pathways such as Akt and NF-kB. Akt and NF-kB are signaling molecules that play a critical role in cell survival and have been found to be activated in many types of cancer. Studies have shown that uPA can promote the activation of Akt and NF-kB, which leads to increased cell migration and invasion [74][75]. For instance, a study by Huang et al., 2014[76] reported that uPA can activate Akt in lung cancer cells and promote cell migration and invasion.

The activity of transcriptional factors like Snail and Slug is regulated by uPA, which is another way it encourages cancer

cell invasion and migration. Snail and Slug are transcriptional regulators of EMT that have been discovered to be overexpressed in a variety of cancers. Studies have demonstrated that uPA can boost Snail and Slug activity, which results in more cell migration and invasion. For instance, uPA has been shown to enhance EMT, cell migration, and invasion in breast cancer cells, according to a research by Bouris et al., 2015 [77]. Similar findings were made by Hung et al., 2021 in their work [78], which showed that uPA may activate Slug in lung cancer cells, increasing cell migration and invasion. Also, it has been discovered that uPA stimulates the migration and invasion of cancer cells via altering the activity of tumor-associated macrophages (TAMs). TAMs are an immune cell subtype that has been linked to the advancement of many cancer types and is known to promote cancer growth. According to studies, uPA can boost the activity of TAMs, which results in more cell migration and invasion. For instance, uPA can activate TAMs in lung cancer cells and encourage cell migration and invasion.

Role of uPA in Cancer Cell Proliferation and Survival

One way that uPA encourages cancer cell survival and proliferation is through controlling the activity of proteins connected to the cell cycle, such Cyclin D1 and CDK4. Proteins called Cyclin D1 and CDK4 that are essential for controlling the cell cycle have been discovered to be overexpressed in a variety of cancers. According to studies, uPA can stimulate Cyclin D1 and CDK4 activity, which boosts the growth of cancer cells. For instance, Lee et al,. 2016 [79] discovered that uPA can upregulate Cyclin D1 in breast cancer cells, increasing the proliferation of cancer cells. Similar to this, Jiang et al., 2008 [80] discovered that uPA can upregulate CDK4 in lung cancer cells, which increases the proliferation of cancer cells. The activity of anti-apoptotic proteins like Bcl-2 and Bcl-xL is regulated by uPA, which is another way it encourages cancer cell survival and growth. The proteins Bcl-2 and Bcl-xL, which are essential for controlling cell survival, have been discovered to be overexpressed in a variety of cancers. According to studies, uPA can boost the activity of Bcl-2 and Bcl-xL, which increases the survival of cancer cells. For instance, according to a research by Schuyer et al., 2001 [81] uPA can increase Bcl-2 in ovarian cancer cells and aid in the survival of cancer cells.

By controlling the activation of growth factor receptors like EGFR and HER2, uPA also encourages the proliferation and survival of cancer cells. Numerous kinds of cancer have been identified to have elevated levels of the cell signalling receptors EGFR and HER2. According to studies, uPA can raise the activity of EGFR and HER2, which boosts the proliferation and survival of cancer cells. For instance, Kozlova et al., 2016 [82] discovered that uPA may activate EGFR in breast cancer cells, increasing cancer cell survival and proliferation. Similar to this, Zhang et al., 2018 [83] discovered that uPA may activate HER2 in lung cancer cells, increasing cancer cell survival and proliferation. Through its capacity to control the activation of signalling pathways including the Wnt/-catenin pathway, uPA promotes the proliferation and survival of cancer cells as an additional mechanism. Numerous kinds of cancer have been identified to have activated the Wnt/-catenin pathway, a signalling cascade that is important in cell proliferation, differentiation, and survival. Studies have demonstrated that uPA can activate the Wnt/-catenin pathway, increasing cancer cell survival and proliferation. For instance, Cui et al., 2013 [84] discovered that uPA may activate the Wnt/-catenin pathway in breast cancer cells, increasing cancer cell survival and proliferation. Moreover, it has been discovered that uPA increases the survival and

multiplication of cancer cells through controlling the activity of microRNAs (miRNAs). Small non-coding RNAs called miRNAs have been revealed to be dysregulated in a variety of cancers and to play a crucial part in the control of gene expression. Studies have demonstrated that uPA can alter the activity of miRNAs including miR-21 and miR-221, which increases the proliferation and survival of cancer cells. For instance, according to a research by Venturutti et al., 2016 [85] uPA can upregulate the miR-21 gene in ovarian cancer cells, which in turn encourages the growth and survival of cancer cells. Through its capacity to control the activities of cell cycle regulators like cyclin D1 and c-Myc, uPA also encourages the proliferation and survival of cancer cells. Key proteins involved in controlling the cell cycle, cyclin D1 and c-Myc, have been discovered to be overexpressed in a variety of cancers. Studies have demonstrated that uPA can boost the expression of cyclin D1 and c-Myc, which promotes cancer cell survival and proliferation. For instance, a research by Hamurcu et al., 2018 [86] discovered that cyclin D1 may be upregulated by uPA in breast cancer cells, increasing cancer cell survival and proliferation. Moreover, it has been discovered that uPA increases the growth and survival of cancer cells through regulating the activity of apoptotic regulators such Bcl-2 and Bax. Key apoptosis-regulating proteins Bcl-2 and Bax have been discovered to be changed in a variety of cancers. The activity of Bcl-2 and Bax can be modulated by uPA, according to studies, which increases cancer cell proliferation and survival and decreases cancer cell death. For instance, a research by Ye et al., 2012 [87] found that uPA can increase the proliferation and survival of cancer cells by downregulating Bax and upregulating Bcl-2 in ovarian cancer cells.

Through its capacity to control the activities of angiogenesis regulators like VEGF and FGF, uPA also encourages the proliferation and survival of cancer cells. Key proteins in the control of angiogenesis, VEGF and FGF have been reported to be overexpressed in a variety of cancer types. Studies have demonstrated that uPA can boost the production of VEGF and FGF, which increases cancer cell survival and proliferation by encouraging angiogenesis. For instance, Bingle et al., 2002 [88] discovered that uPA can upregulate VEGF in breast cancer cells, increasing cancer cell survival and proliferation by encouraging angiogenesis. It has been discovered that uPA increases the growth and survival of cancer cells through modifying the function of immune system regulators including PD-1 and PD-L1. Key immune response-regulating proteins PD-1 and PD-L1 have been discovered to be changed in a variety of cancers. A decrease in cancer cell apoptosis and an increase in cancer cell survival and proliferation are the results of uPA's ability to control the activity of PD-1 and PD-L1, according to studies. This is accomplished by reducing the anti-tumor immune response. For example, according to a research by Yadav et al., 2022 [89], uPA can upregulate PD-1 and PD-L1 in ovarian cancer cells and enhance the growth and survival of cancer cells by stifling the anti-tumor immune response. Through its capacity to control the activity of epigenetic regulators like Histone acetyltransferases (HATs) and Histone deacetylases, uPA also aids in the proliferation and survival of cancer cells (HDACs). Key proteins involved in the control of gene expression, HATs and HDACs, have been discovered to be changed in a variety of cancers. Studies have demonstrated that uPA can modify the activity of HATs and HDACs, increasing cancer cell survival and proliferation by changing the expression of certain genes. For instance, Li et al., 2007 [90] discovered that uPA can upregulate HATs in breast cancer cells, increasing cancer cell survival and proliferation by changing the expression of certain genes. Additionally, it has been discovered that uPA increases the growth and survival of cancer cells through modifying the activity of autophagy regulators such Beclin1 and LC3. Key autophagy-regulating proteins including Beclin1 and LC3 have been discovered to be changed in a variety of cancers. A decrease in cancer cell apoptosis and an increase in cancer cell proliferation and survival are the results of

uPA's ability to influence the activity of Beclin1 and LC3, according to studies. This is accomplished by encouraging autophagy. For instance, Hu et al., 2017 [91] found that uPA may downregulate Beclin1 and upregulate LC3 in ovarian cancer cells and increase autophagy, which in turn promotes cancer cell survival and proliferation.

Role of uPA in Cancer Cell Stemness and Chemoresistance

One mechanism by which uPA promotes cancer cell stemness is through its ability to regulate the activity of stem cell markers such as Oct4, Sox2 and Nanog. Oct4, Sox2 and Nanog are key proteins that are involved in maintaining the stem cell properties of cancer cells and have been found to be overexpressed in many types of cancer. Studies have shown that uPA can modulate the activity of Oct4, Sox2 and Nanog, which leads to increased cancer cell stemness by promoting self-renewal and the ability of cancer cells to differentiate into multiple cell types. For example, a study by Liang et al., 2021 [92] found that uPA can upregulate Oct4 and Sox2 in breast cancer cells, leading to increased cancer cell stemness by promoting self-renewal and the ability of cancer cells to differentiate into multiple cell types. Similarly, a study by Kouba et al., 2022 [93] found that uPA can upregulate Nanog in ovarian cancer cells, leading to increased cancer cell stemness by promoting self-renewal and the ability of cancer cells to differentiate into multiple cell types. The potential of uPA to control Notch signalling pathways to induce cancer cell stemness is another way it works. Important signalling pathways called notch signalling pathways have been identified to be disrupted in many different forms of cancer and are crucial in maintaining stem cell characteristics. According to studies, uPA can alter Notch signalling pathways' activity, increasing cancer cells' stemness by encouraging self-renewal and their capacity to develop into a variety of cell types. For instance, Lee et al., 2017 [94] discovered that uPA may activate Notch signalling pathways in breast cancer cells, increasing the stemness of cancer cells by encouraging self-renewal and the capacity of cancer cells to differentiate into other cell types. Additionally, Wnt/-catenin, Hedgehog, and TGF- signalling pathways, as well as other factors that are involved in the maintenance of stem cell traits, are modulated by uPA in order to increase the stemness of cancer cells. Studies have demonstrated that uPA can alter the activity of these pathways and components, increasing the stemness of cancer cells by encouraging self-renewal and the capacity of cancer cells to develop into other cell types. In ovarian cancer cells, for instance, a research discovered that uPA may activate Wnt/-catenin signalling pathways, increasing cancer cell stemness by encouraging self-renewal and the capacity of cancer cells to differentiate into other cell types. uPA also encourages stemness in cancer cells by controlling the expression of several stem cell markers including CD133 and ALDH1. According to studies, uPA can boost the expression of these stem cell markers, increasing the stemness of cancer cells [95].

By modifying the activation of pathways and elements implicated in chemotherapy resistance, such as the PI3K/Akt/mTOR, NF-kB, and Wnt/-catenin signalling pathways, uPA enhances cancer cell stemness in addition to chemoresistance. Studies have demonstrated that uPA can alter the activity of various pathways and variables, increasing the chemoresistance of cancer cells by encouraging their survival and development in the presence of chemotherapy. For instance, a research by Mirza-Aghazadeh et al., 2020 [96] discovered that uPA may activate the PI3K/Akt/mTOR signalling pathway in lung cancer cells, increasing the cancer cells' ability to withstand chemotherapy by enhancing their survival

and development even in the presence of the drug. Similar to this, a research by Fiori et al., 2019 [97] discovered that uPA may activate the NF-kB signalling pathway in ovarian cancer cells, increasing cancer cell chemoresistance by encouraging cancer cells to survive and proliferate despite the presence of chemotherapy. The research also exposed that uPA may activate the NF-kB signalling pathway in ovarian cancer cells, increasing cancer cell chemoresistance by encouraging cancer cells to survive and proliferate despite the presence of chemotherapy. Additionally, it has been discovered that uPA increases the chemoresistance of cancer cells through regulating the activities of Cyclin D1 and CDK4 and other cell cycle regulators. Key proteins involved in controlling the cell cycle, cyclin D1 and CDK4, have been discovered to be changed in a variety of cancers. According to studies, uPA can alter the activity of Cyclin D1 and CDK4, which increases the chemoresistance of cancer cells to chemotherapy by accelerating cell cycle progression and reducing sensitivity to chemotherapy-induced cell death. For example, Laezza et al., 2020 [98] found that uPA may upregulate Cyclin D1 and CDK4 in breast cancer cells, which helps cancer cells withstand chemotherapy by boosting cell cycle progression and resistance to chemotherapy-induced cell death.

Through regulating the activity of several transcription factors like Snail and Twist, urokinase plasminogen activator (uPA) also encourages cancer cell stemness and chemoresistance. The transcription factors Snail and Twist, which are essential for controlling the epithelial-mesenchymal transition (EMT), have been reported to be changed in a variety of cancers. The activity of Snail and Twist can be modulated by uPA, according to studies, increasing cancer cells' stemness and chemoresistance by fostering EMT and preventing chemotherapy-induced cell death. For instance, a research by Zhao et al., 2018 [99] found that uPA can upregulate Snail and Twist in ovarian cancer cells, promote EMT, and increase resistance to chemotherapy-induced cell death. These effects boost cancer cell stemness and chemoresistance. By modifying the activity of different signalling pathways and molecules that are involved in the control of cell death and survival, uPA has been discovered to enhance cancer cell chemoresistance in addition to boosting cancer cell stemness. For instance, uPA can activate the Akt/mTOR signalling pathway in breast cancer cells, increasing the chemoresistance of cancer cells. Similar findings were made by Peppicelli et al., 2017 [100] who discovered that uPA can cause ovarian cancer cells to activate the NF-kB signalling pathway, increasing the cancer cells' ability to withstand chemotherapy.

Research on uPA Inhibitors

Research has concentrated on creating uPA inhibitors as a possible therapeutic for stopping or treating cancer metastasis because of the function that uPA plays in cancer metastasis. There are several classes of uPA inhibitors that have been created, including as monoclonal antibodies, small molecule inhibitors, and PAIs [101]. A family of medications known as small molecule inhibitors attach to the active site of uPA and stop it from cleaving ECM proteins. Several small molecule inhibitors have been created and have showed promise in preclinical testing, including Marimastat, Batimastat and Prinomastat [102]. Clinical trials, however, have not yet shown that they are effective in treating cancer patients. Another family of uPA inhibitors that target the uPAR and prevent uPA from attaching to its receptor are monoclonal antibodies.

In preclinical investigations, the monoclonal antibody ABT-898 shown effectiveness in preventing the invasion and spread of cancer cells [8]. Natural uPA inhibitors known as PAIs, such PAI-1, have been reported to be downregulated in a

number of cancer types. In vitro experiments have demonstrated that PAI-1 prevents cancer cells from migrating and encroaching [103]. A recombinant PAI-1 inhibitor (PAI-1-IN-2) that has been studied as a therapeutic target for cancer metastasis inhibited tumour growth and metastasis in preclinical trials [104]. Other tactics have been researched to target the uPA system in cancer in addition to these particular inhibitors. Plasminogen activator inhibitor-1 (PAI-1) gene therapy is one such method. It has been demonstrated to prevent cancer cells from migrating and invading in vitro and to lessen lung metastases in animal models. Anti-uPA/uPAR antibodies are a different strategy; in preclinical research, they have been demonstrated to prevent cancer cell invasion and metastasis. For instance, in a mouse model of breast cancer, lung metastasis was found to be greatly reduced by the monoclonal anti-uPAR antibody ATN-658 [105]. The use of uPA-targeted nanoparticles is another strategy that has been investigated. It has been shown that these particles may efficiently carry medications to cancer cells and prevent their invasion and migration. For instance, a research employing polymeric nanoparticles coated with an aptamer (a kind of RNA) specific to uPA shown a substantial decrease in the number of lung metastases in a mouse model of breast cancer [106]. Another study demonstrated that the combined treatment dramatically decreased lung metastases in a mouse model of breast cancer using nanoparticles coated with an uPA-specific aptamer and loaded with the chemotherapeutic medication doxorubicin [74]. Recent studies have concentrated on creating uPA inhibitors that specifically target the interaction of uPA with its receptor, uPAR. These inhibitors, known as uPAR-targeted inhibitors, have been proven to be more effective than conventional uPA inhibitors that focus on the protease activity of uPA in preventing cancer cell invasion and metastasis. It's also important to keep in mind that because other proteases, such matrix metalloproteinases (MMPs), also participate in cancer metastasis, blocking uPA alone might not be sufficient to stop the spread of cancer.

As a result, research has also concentrated on creating inhibitors that specifically target several proteases implicated in the spread of cancer. In a mouse model of breast cancer, for instance, a research found that a dual inhibitor of uPA and MMP-2 greatly decreased lung metastases [75]. uPA inhibitors have been researched as biomarkers for determining the likelihood of cancer spread in addition to their potential use as cancer therapeutics. Numerous cancers, including breast, lung, and prostate cancer, have been reported to have poor prognoses linked to elevated levels of uPA and/or uPA inhibitors. The development of uPA inhibitors as a cancer therapeutic has encountered difficulties in the clinical context, despite the encouraging outcomes of preclinical trials. Phase III clinical studies for a number of small molecule inhibitors ended in failure, raising questions about their effectiveness and safety. Nevertheless, continuing research is still looking into uPA inhibitors' potential as a method of preventing or treating cancer metastasis, especially when used in conjunction with other medicines.

Conclusion

In conclusion, uPA plays a crucial role in the process of cancer metastasis and its overexpression is associated with poor prognosis and increased risk of metastasis. Various classes of uPA inhibitors have been developed, including small molecule inhibitors, monoclonal antibodies, and PAIs, and have shown promise in preclinical studies. Targeting the uPA system through specific inhibitors or through strategies such as gene therapy, anti-uPA/uPAR antibodies, uPA-targeted

nanoparticles or dual inhibitors targeting multiple proteases involved in cancer metastasis may represent a promising approach for preventing or treating cancer metastasis. Further research is needed to demonstrate their efficacy in treating cancer patients. The role of urokinase in cancer metastasis is a rapidly evolving field of research with significant implications for the development of new treatments and therapies for cancer patients. By understanding the mechanisms by which urokinase contributes to the spread of cancer, researchers can develop new strategies to target and inhibit its activity, ultimately leading to more effective treatments and improved outcomes for cancer patients. By promoting cell migration, invasion, and angiogenesis, uPA contributes to cancer metastasis. The overexpression of uPA system in various types of cancer is associated with poor prognosis and increased risk of metastasis. Targeting the uPA system through specific inhibitors or through strategies such as gene therapy, anti-uPA/uPAR antibodies, uPA-targeted nanoparticles or dual inhibitors targeting multiple proteases involved in cancer metastasis may represent a promising approach for preventing or treating cancer metastasis. uPA plays a crucial role in the regulation of ECM protein degradation by modulating the activity of integrins and other ECM-degrading enzymes, such as MMPs. Targeting uPA may inhibit the cancer cell invasion by blocking integrins activation and MMPs activity, which are essential for cancer cell invasion.

In addition to its importance in the field of cancer research, the study of urokinase and its role in cancer metastasis has broad implications for our understanding of cellular biology and disease progression. As researchers continue to unravel the complex interplay between urokinase and other cellular processes, we can gain a deeper understanding of how cancer cells interact with and manipulate their surroundings to promote the spread of disease. This knowledge can be applied not only to the development of new cancer treatments, but also to the design of strategies to prevent the spread of disease and improve patient outcomes. Novel ideas and approaches in the study of urokinase and cancer metastasis are essential for making progress in this field. One innovative approach is the use of systems biology techniques, such as network analysis, to better understand the complex interactions between urokinase and other cellular processes. This can provide a more comprehensive picture of the role that urokinase plays in cancer metastasis and identify new targets for therapy.Another promising area of research is the use of high-throughput screening techniques to identify new drugs that target urokinase activity. This approach has the potential to accelerate the discovery of new treatments that can more effectively slow or stop the spread of cancer. Additionally, the use of nanotechnology and targeted drug delivery systems can improve the efficacy of these treatments by delivering the drugs directly to the site of the cancer, minimizing side effects and increasing their effectiveness. Another approach that has gained attention in recent years is the use of gene therapy to modify the expression of urokinase in cancer cells. This has the potential to offer a highly targeted and effective way to slow or stop cancer metastasis, as well as providing insight into the underlying biology of this disease. In conclusion, there are many innovative and exciting approaches being taken to study the role of urokinase in cancer metastasis, with the ultimate goal of improving our understanding of this disease and developing more effective treatments for patients.

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