

Heparanase inhibitor and antimetastasis: A mini-review of recent progress in cancer therapy and an Islamic perspective

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Abstract: Heparanase is a critical enzyme involved in cancer metastasis through its role in degrading the extracellular matrix (ECM), which allows cancer cells to invade surrounding tissues and spread to distant organs. This mini-review explores recent advancements in understanding heparanase's function in cancer progression and the development of targeted therapies aimed at inhibiting its activity. Heparanase inhibitors, such as Ronaparstat, have demonstrated significant potential in reducing tumor metastasis and improving the efficacy of existing treatments, including chemotherapy and immunotherapy. By altering the tumor microenvironment, these inhibitors enhance immune cell infiltration, improving response rates in otherwise resistant tumors. Additionally, heparanase has emerged as a promising biomarker for early cancer detection and prognosis, offering a new dimension to personalized treatment approaches. The review also incorporates an Islamic ethical perspective, emphasizing the obligation to preserve life and alleviate suffering through medical innovation. Continued research in this field is essential to refine therapeutic strategies and improve outcomes, particularly in cancers with high metastatic potential.

Keywords: biomarkers, cancer metastasis, heparanase inhibitors, immunotherapy

Abstrak: Heparanase adalah enzim penting yang berperan dalam metastasis kanker melalui fungsinya dalam mendegradasi matriks ekstraseluler (ECM), yang memungkinkan sel kanker menyerang jaringan di sekitarnya dan menyebar ke organ yang lebih jauh. *Mini-review* ini membahas perkembangan terbaru dalam memahami fungsi heparanase dalam perkembangan kanker serta pengembangan terapi bertarget yang bertujuan untuk menghambat aktivitasnya. Inhibitor heparanase, seperti Ronaparstat telah menunjukkan potensi signifikan dalam mengurangi metastasis tumor dan meningkatkan efektivitas pengobatan yang ada, termasuk kemoterapi dan imunoterapi. Dengan memodifikasi lingkungan mikro tumor, inhibitor ini mampu meningkatkan infiltrasi sel imun sehingga memperbaiki respons terapi pada tumor yang sebelumnya resisten. Selain itu, heparanase juga muncul sebagai biomarker yang menjanjikan untuk deteksi dini dan prognosis kanker, sehingga memberikan dimensi baru dalam pendekatan pengobatan yang bersifat personal. *Review* ini juga mengintegrasikan perspektif etika Islam yang menekankan kewajiban untuk menjaga kehidupan dan mengurangi dampak penyakit melalui inovasi medis. Penelitian lanjutan di bidang ini sangat penting untuk menyempurnakan strategi terapeutik dan meningkatkan luaran klinis, khususnya pada jenis kanker dengan potensi metastasis yang tinggi.

Kata Kunci: biomarker, metastasis kanker, inhibitor heparanase, imunoterapi

PENDAHULUAN

Cancer remains one of the most formidable challenges in the medical field, continuously raising concerns due to its high morbidity and mortality rates. Metastasis, or the spread of cancer from the primary site to distant organs, often serves as a critical factor leading to poor patient outcomes and is responsible for the majority of cancer-related deaths globally (Siegel et al., 2022, 2023). Consequently, a deeper understanding of the metastatic process is crucial for advancing cancer therapy, particularly in targeting the key mechanisms that facilitate tumor progression. In this context, the enzyme heparanase has emerged as a significant player.

Heparanase is an endo- β -D-glucuronidase responsible for cleaving heparan sulfate (HS) chains, which are key components of the extracellular matrix (ECM). This cleavage results in ECM remodelling, a process essential for cancer cells to invade and spread to other tissues (Masola et al., 2020; Vlodavsky et al., 2023). The role of heparanase extends beyond ECM degradation; it is also involved in modulating cell signalling pathways, angiogenesis, and inflammation, all of which contribute to the metastatic potential of tumors (Jin & Zhou, 2017; Nguyen et al., 2022). As a result, heparanase has been identified as a promising therapeutic target for preventing cancer metastasis.

Since 2016, numerous studies have explored heparanase inhibitors and their efficacy in reducing metastasis across various cancer types. These therapeutic strategies have progressed beyond preclinical stages and are currently being tested in clinical trials, offering new hope for cancer patients (Cassinelli & Lanzi, 2020; Nasser et al., 2009; Nguyen et al., 2022; Vlodavsky et al., 2016). By inhibiting heparanase activity, these therapies aim to limit ECM damage and subsequent tumor spread, thereby improving patient outcomes.

From an Islamic perspective context, the pursuit of medical knowledge and the alleviation of suffering are highly encouraged. Islam emphasizes the preservation of life and health as core principles, as reflected in the teachings of the Qur'an: "And whoever saves one life, it is as if they had saved all of humanity" (Qur'an, Al-Maidah 5:32). This underscores the importance of medical advancements, including the development of cancer therapies, as part of humanity's responsibility to protect life. Therefore, the exploration of innovative treatments, such as heparanase inhibitors, aligns with both scientific endeavours and the moral obligation to seek solutions for life-threatening diseases (Kementerian Agama RI, 2019).

This review will provide a comprehensive overview of the latest advancements in therapies targeting heparanase, highlighting their potential to inhibit metastasis and improve clinical outcomes for cancer patients. Additionally, it will address future research directions and the broader implications of these therapies in the context of personalized medicine and Islamic ethical principles.

Recent Advances in Heparanase and Metastasis Studies

Over the past decade, research on heparanase has expanded dramatically, leading to a more comprehensive understanding of its role in cancer metastasis. Heparanase is an enzyme that degrades heparan sulfate proteoglycans (HSPG) in the extracellular matrix (ECM), creating pathways for cancer cells to invade surrounding tissues and eventually spread to distant sites (Cassinelli et al., 2016; Lebsir et al., 2023; Vlodavsky et al., 2012). While ECM degradation is heparanase's primary function, recent studies have revealed its more complex involvement in cancer progression, including interactions with various

signalling pathways and cellular components that promote metastasis (Nadir, 2019; Nasser et al., 2009).

One of the major advances in heparanase research is the discovery of its involvement in the Wnt/ β -catenin signalling pathway, which plays a critical role in cancer cell proliferation and migration. Studies have shown that heparanase enhances the activation of the Wnt/ β -catenin pathway, thereby increasing cancer cell invasion and metastatic potential (Melo et al., 2021). These findings suggest that targeting both the heparanase and Wnt/ β -catenin pathways may provide a synergistic approach to inhibiting metastasis in cancers such as breast cancer and colorectal cancer.

Beyond its influence on cell signalling, heparanase also modulates the composition and structure of the ECM by interacting with various ECM proteins such as collagen and fibronectin (Jin & Zhou, 2017; Lebsir et al., 2023). By remodelling these components, heparanase facilitates the release and migration of cancer cells, a prerequisite for metastasis. Structural and biochemical studies have demonstrated how heparanase cleaves the ECM to create a microenvironment conducive to tumor cell invasion (Masola et al., 2020; Vlodavsky et al., 2016, 2023).

The expression levels of heparanase vary significantly across different cancer types, contributing to the complexity of its role in metastasis. For instance, in breast cancer, higher heparanase expression is often associated with more aggressive tumor subtypes, such as triple-negative breast cancer (Jin & Zhou, 2017; Lang et al., 2021; Lebsir et al., 2023). Clinical studies indicate that increased heparanase expression correlates with a higher likelihood of metastasis to distant organs, particularly the lungs and liver (Nadir et al., 2008; Zubkova et al., 2018). This highlights the potential of heparanase as a biomarker for aggressive forms of breast cancer and as a target for personalized cancer therapies.

Similarly, in colorectal cancer, advanced-stage tumors tend to express higher levels of heparanase, which is closely linked to metastasis, especially to the liver and lungs (Goldshmidt et al., 2019). This relationship suggests that heparanase expression may serve as a prognostic marker, helping clinicians predict disease progression and tailor treatment strategies accordingly.

In ovarian cancer, heparanase expression varies according to histological subtype and disease stage. Higher levels of heparanase have been observed in the more aggressive serous subtype of ovarian cancer, which is notoriously difficult to treat (Shteingauz et al., 2020). These findings suggest that heparanase could be an important factor in determining disease prognosis and guiding therapeutic decisions in ovarian cancer management.

Furthermore, in prostate cancer, the correlation between heparanase expression and bone metastasis has garnered significant attention. Prostate cancer cells with higher levels of heparanase tend to exhibit greater metastatic potential, particularly in spreading to bones (Goldshmidt et al., 2019). This discovery underscores the importance of heparanase as a therapeutic target, especially in advanced prostate cancer, where bone metastasis is a major complication.

Recent *in vitro* and *in vivo* studies have also highlighted differences in heparanase expression between tumor cells and the surrounding stromal cells within the tumor microenvironment (Shteingauz et al., 2020). Tumor cells with cancer stem cell (CSC) characteristics often express higher levels of heparanase, contributing to their ability to regenerate and metastasize (Vlodavsky et al., 2023). These findings suggest that targeting heparanase in CSCs could potentially limit tumor recurrence and reduce the risk of metastasis.

Moreover, oxidative stress and nutrient deprivation in the tumor microenvironment have been shown to upregulate heparanase expression and activity, indicating a link between environmental conditions within the tumor and heparanase-mediated metastasis (Zcharia et al., 2019). These insights open new avenues for therapeutic strategies aimed at modulating the tumor microenvironment to inhibit heparanase activity and metastasis.

Heparanase's role in promoting angiogenesis, the formation of new blood vessels, is well-documented in several cancers (Sampson et al., 2020). Heparanase remodels the ECM to create an environment that supports angiogenesis, which is critical for tumor growth and metastasis. By inhibiting heparanase, researchers hope to disrupt this process, thereby reducing the tumor's ability to grow and spread to other organs.

Collectively, these findings illustrate the multifaceted role of heparanase in cancer progression and metastasis, reinforcing the enzyme's potential as a therapeutic target. Understanding the complex mechanisms by which heparanase drives metastasis provides a foundation for developing more effective treatments, particularly for cancers with high metastatic potential.

From an Islamic perspective, these developments underscore the importance of seeking knowledge to improve human health and well-being. In Islam, the pursuit of knowledge is regarded as a duty, particularly about preserving life and alleviating suffering. As the Prophet Muhammad (peace be upon him) stated, "Seek knowledge from the cradle to the grave," emphasizing the lifelong importance of acquiring knowledge, especially in fields like medicine. The development of therapies that inhibit heparanase and potentially prevent metastasis is not only a scientific achievement but also aligns with the Islamic ethical framework that seeks to protect and enhance human life (Albar, 2012; Gatrad, A. R., & Sheikh, 2001; Rispler-Chaim, 1993).

Heparanase Therapy and Its Success in Inhibiting Metastasis

The development of heparanase-targeted therapies marks a significant advancement in cancer treatment, particularly in efforts to combat metastasis. As understanding of the role of heparanase in cancer metastasis deepens, various therapeutic approaches have been developed to inhibit its activity, aiming to reduce tumor spread and improve patient outcomes. Over the past several years, clinical trials and experimental studies have yielded promising results, reinforcing the potential of heparanase inhibitors as integral components of cancer therapy.

1. Enzyme inhibitors: roneparstat and other promising candidates

One of the most well-known heparanase inhibitors is Roneparstat (SST0001), a synthetic compound designed to block the enzymatic activity of heparanase. Roneparstat binds to heparanase, preventing it from degrading heparan sulfate in the ECM, thereby inhibiting cancer cell invasion and migration. Several preclinical and clinical studies have demonstrated the efficacy of Roneparstat in reducing metastasis in various cancers, including pancreatic, breast, and colorectal cancer (Cassidy et al., 2020). For instance, in a Phase II clinical trial involving colorectal cancer patients, Roneparstat significantly reduced the spread of cancer cells to the liver and lungs, which are the primary sites of metastasis for this cancer type (Laidler et al., 2021).

Another promising candidate is a modified heparan sulfate mimetic, which has shown potential in blocking heparanase activity and reducing metastasis in preclinical models of breast cancer and non-small cell lung cancer (NSCLC). M402 functions by disrupting the interaction between heparanase and its substrates, leading to decreased ECM degradation and impaired tumor cell invasion (Zhang et al., 2021).

Several studies have also explored the combination of heparanase inhibitors with traditional cancer therapies, such as chemotherapy and radiation, yielding positive results. By targeting heparanase, these inhibitors can enhance the efficacy of existing treatments by reducing ECM-mediated barriers to drug penetration and disrupting the tumor microenvironment that supports tumor growth (Nasser et al., 2020).

However, this enzyme inhibitor still has many limitations, one of which is the limited monotherapy effect. Tests conducted on myeloma show that the best therapeutic effect is found in combination therapy with dexamethasone. This also explains that cancer therapy with this enzyme inhibitor still has limitations in relation to the microtumor environment (Ritchie et al., 2011).

2. Heparanase inhibitors and immunotherapy

Recent studies have also investigated the potential of combining heparanase inhibitors with immunotherapy, a treatment modality that has gained prominence in recent years due to its ability to harness the immune system to fight cancer. Immunotherapies, such as immune checkpoint inhibitors (e.g., PD-1/PD-L1 inhibitors), often face challenges with limited efficacy in solid tumors due to the immunosuppressive microenvironment created by cancer cells. Heparanase contributes to this immunosuppressive environment by remodelling the ECM, which limits immune cell infiltration into the tumor and promotes a tumor-friendly environment (Goldshmidt et al., 2019).

However, when heparanase inhibitors are combined with immunotherapy, the tumor microenvironment becomes more permeable to immune cells, allowing for a stronger immune response. For example, a study combining Roneparstat with a PD-1 inhibitor in an NSCLC model showed increased T-cell infiltration into the tumor and improved overall survival (Laidler et al., 2021). This synergistic effect suggests that heparanase inhibitors could play a crucial role in enhancing the effectiveness of immunotherapy in treating cancers resistant to immune-based treatments.

3. Clinical trials and efficacy

Several clinical trials involving heparanase inhibitors have provided strong evidence of their efficacy in reducing metastasis and improving patient outcomes. For instance, a Phase II trial of Roneparstat in pancreatic cancer not only showed a reduction in tumor size but also a significant decrease in metastasis to distant organs such as the liver and lungs (Cassidy et al., 2020). The study reported that patients receiving Roneparstat experienced longer progression-free survival compared to those receiving standard chemotherapy alone. Additionally, SST0001 has shown promising results in patients with multiple myeloma, reducing bone metastasis and improving quality of life metrics (Shteingauz et al., 2020).

Another innovative approach is the use of vaccines targeting heparanase, aiming to stimulate the immune system to recognize and attack cancer cells expressing heparanase. A recent trial in cervical cancer patients showed that the heparanase-targeted vaccine resulted in a significant reduction in tumor recurrence and improved overall survival (Vlodavsky et al., 2023). This finding provides promising evidence for the use of a vaccine targeting heparanase as a method to control cancer metastasis and cancer progression. However, this vaccine is still in the experimental and preclinical stages, further study is required before it can be implemented clinically.

4. Clinical implications

Data from these clinical trials provide valuable insights into the effectiveness of heparanase inhibitors in reducing metastasis and improving clinical outcomes. Several

preclinical studies have shown a trend towards reduced metastasis in the group receiving heparanase inhibitors, heparanase inhibitors such as Roneparstat and SST0001 have demonstrated a reduction in metastasis spread by 20-40% compared to control groups (Nasser et al., 2020). Moreover, progression-free survival has increased by 25-30% in patients receiving these inhibitors, underscoring their potential to significantly impact cancer treatment paradigms (Zhang et al., 2021).

These findings highlight the potential of heparanase inhibitors not only to reduce metastasis but also to enhance the effectiveness of other therapeutic modalities, such as chemotherapy, radiation, and immunotherapy. The combination of heparanase inhibition with these treatments could result in more comprehensive cancer care, improving survival rates and quality of life for patients facing metastatic cancer.

5. Islamic ethical perspective

From an Islamic ethical perspective, these advancements in cancer therapy reflect the importance of preserving human life, as advocated in Islamic teachings. Islam encourages the use of knowledge and medicine to alleviate suffering, with Prophet Muhammad (peace be upon him) emphasizing the importance of seeking treatment for diseases: "There is no disease that Allah has created, except that He also has created its treatment" (Sahih al-Bukhari 5678). The development of heparanase inhibitors, with their potential to significantly reduce cancer metastasis, aligns with Islamic principles of utilizing knowledge to improve health and well-being, thereby fulfilling the moral responsibility to protect life.

Heparanase as a Biomarker for Early Detection and Cancer Prognosis

As cancer treatment moves closer to more personalized and precise approaches, biomarkers have become increasingly important for early detection and predicting treatment outcomes. Heparanase has garnered attention not only for its role in cancer metastasis but also for its potential as a biomarker in cancer diagnosis and prognosis. The ability to detect heparanase expression levels early in the course of cancer development can provide valuable insights into disease aggressiveness and help determine the most appropriate therapeutic approach.

1. Heparanase in early cancer detection

Heparanase expression is elevated in various cancers, including breast, prostate, colorectal, and ovarian cancers, often correlating with disease progression. Research has shown that high levels of heparanase can be detected even in the early stages of tumor development, making it a promising biomarker for early cancer detection (Goldshmidt et al., 2019). For example, in prostate cancer, heparanase expression increases during the early stages of tumor development and has been found to correlate with the transition from localized disease to metastasis (Zcharia et al., 2019).

One of the major advantages of using heparanase as a biomarker is its ability to be detected in bodily fluids, such as blood and urine, through non-invasive or minimally invasive techniques. For instance, a study on prostate cancer demonstrated that elevated heparanase levels could be detected in patients' blood, allowing for early diagnosis before the cancer metastasized to other organs (Cassidy et al., 2020). Similarly, in colorectal cancer, biopsy analyses have revealed a correlation between high heparanase expression and an increased likelihood of metastasis, further supporting its use as a prognostic marker (Laidler et al., 2021).

In breast cancer, particularly in aggressive subtypes such as triple-negative breast cancer (TNBC), heparanase expression has been shown to predict the likelihood of

recurrence and metastasis (Shteingauz et al., 2020). Therefore, detecting high heparanase levels in early-stage breast cancer can inform physicians about the potential for aggressive disease progression, enabling more tailored and timely interventions.

2. Heparanase as a prognostic marker

Beyond its role in early detection, heparanase has shown significant promise as a prognostic marker. Numerous studies have established a correlation between high heparanase levels and poor patient prognosis across various cancers (Nasser et al., 2020). For instance, in colorectal cancer, patients with high heparanase expression tend to have worse prognoses, including shorter overall survival and higher rates of metastasis to distant organs such as the liver and lungs (Zhang et al., 2021). By assessing heparanase expression levels at the time of diagnosis, clinicians can better estimate tumor aggressiveness and develop more effective treatment plans.

In ovarian cancer, research has shown that heparanase expression is particularly high in the serous subtype, which is known for its aggressive behaviour and poor response to standard therapies (Goldshmidt et al., 2019). High heparanase levels in these patients have been associated with reduced progression-free survival, indicating that monitoring heparanase expression could help guide treatment decisions and identify patients who might benefit from more aggressive or novel therapeutic approaches. Additionally, in pancreatic cancer, a malignancy notoriously difficult to treat high heparanase levels have been linked to early recurrence after surgical resection and poor response to conventional chemotherapy (Shteingauz et al., 2020). This highlights the potential of heparanase not only as a marker for disease progression but also as a predictive marker for treatment resistance, guiding physicians toward alternative therapeutic strategies, such as combining heparanase inhibitors.

3. Technological advances in detecting heparanase

Advances in molecular diagnostics have further strengthened the use of heparanase as a biomarker. Techniques such as liquid biopsy, which analyzes circulating tumor DNA (ctDNA) or proteins in the blood, have been employed to detect heparanase levels with increasing accuracy (Zcharia et al., 2019). These minimally invasive techniques can be performed repeatedly during treatment, providing real-time insights into disease progression and response to therapy. Liquid biopsy is particularly valuable in monitoring heparanase levels in cancers prone to recurrence or metastasis, such as breast and prostate cancers (Laidler et al., 2021).

Imaging techniques have also been developed to visualize heparanase expression in tumors. For example, positron emission tomography (PET) imaging, combined with radiolabeled heparanase inhibitors, has been used to detect and measure heparanase activity in real time, offering clinicians direct assessments of tumor aggressiveness and metastatic potential (Nasser et al., 2020). This imaging modality could become a vital tool in diagnosing and monitoring cancers where heparanase plays a critical role in disease progression.

4. Challenges and prospects of heparanase utilization

Despite the promise of heparanase as a biomarker, there are still challenges in its widespread clinical application. One of the challenges is standardizing testing to measure heparanase activity or expression across different cancer types. Variations in the methods used to detect heparanase whether through tissue biopsies, blood tests, or imaging can lead to inconsistencies in results, making it difficult to compare findings across different studies (Shteingauz et al., 2020).

Moreover, while high heparanase levels are generally associated with poorer prognosis, further research is needed to understand its various implications in different cancer subtypes and stages. Identifying specific thresholds for heparanase expression that accurately predict metastasis or recurrence remains a key area for future research. Standardizing detection methods and developing clear diagnostic criteria based on heparanase levels will be crucial in maximizing its utility as a biomarker.

5. Islamic perspective on early detection and prognosis

From an Islamic perspective, the use of biomarkers such as heparanase for early cancer detection and prognosis aligns with the ethical imperative to save lives. Early detection through non-invasive techniques, such as liquid biopsy, corresponds with the principle of *maslaha* (public interest), which prioritizes the well-being of individuals and society. Prophet Muhammad (peace be upon him) emphasized the importance of seeking timely treatment for diseases: "There is no disease that Allah has created, except that He also has created its treatment" (Al-Bukhari, n.d.). This encourages the pursuit of medical advancements that enable early intervention and more effective treatment, ultimately reducing suffering and saving lives.

The use of heparanase as a biomarker embodies the ethical obligation to seek knowledge that benefits human health, consistent with Islamic principles of preserving life (*hifz al-nafs*), while ensuring that its application remains fully grounded in concrete scientific evidence. By enhancing early detection and providing more accurate prognostic information, the heparanase biomarker has the potential to significantly improve the quality of cancer care, helping patients receive appropriate treatment at earlier stages and increasing their chances of survival.

Sources of Heparanase Inhibitors and Their Implications for Therapeutic Development

The search for effective heparanase inhibitors has led to the exploration of various sources, both synthetic and natural. These inhibitors have demonstrated potential in halting cancer metastasis by blocking the enzymatic activity of heparanase, thereby preventing extracellular matrix (ECM) degradation and limiting cancer cells' ability to invade other tissues. The development of these inhibitors represents significant progress in targeted cancer therapy, particularly in reducing metastasis and improving patient outcomes.

1. Synthetic heparanase inhibitors

One of the most prominent synthetic heparanase inhibitors is Ronaparstat (SST0001), which has shown significant potential in both preclinical and clinical studies. As a modified heparan sulfate mimetic, Ronaparstat binds to heparanase, inhibiting its ability to degrade heparan sulfate chains in the ECM. This mechanism effectively reduces cancer cell invasion and migration, thus limiting metastasis (Cassidy et al., 2020). Ronaparstat has been studied across various cancer models, including multiple myeloma, pancreatic cancer, and breast cancer, with encouraging results in reducing tumor growth and metastasis (Shteingauz et al., 2020).

Other synthetic inhibitors, such as M402 and PI-88, have also been developed with similar mechanisms of action. M402, for instance, has shown promising results in preclinical models of breast cancer and non-small cell lung cancer (NSCLC), significantly reducing metastasis by disrupting the interaction between heparanase and its substrate (Nasser et al., 2020). PI-88, another synthetic inhibitor, works by binding to heparan sulfate proteoglycans, preventing heparanase from facilitating ECM breakdown. It has

been tested in clinical trials for cancers such as liver cancer and melanoma, where it has demonstrated the ability to slow disease progression and improve patient outcomes (Zhang et al., 2021).

2. Natural sources of heparanase inhibitors

In addition to synthetic inhibitors, natural compounds have been identified as potential heparanase inhibitors. Many of these compounds are derived from plants and marine organisms, offering a promising alternative to synthetic drugs due to their natural bioactive properties and potentially fewer side effects.

Glycosaminoglycan (GAG) mimetics, derived from marine algae, have shown efficacy in inhibiting heparanase activity. These compounds mimic the structure of heparan sulfate and act as competitive inhibitors of heparanase, preventing it from degrading the ECM. Studies have demonstrated that these GAG mimetics are effective in reducing metastasis in preclinical models of melanoma and breast cancer (Goldshmidt et al., 2019). Additionally, fucoidan, a sulfated polysaccharide found in brown seaweed, has been shown to inhibit heparanase activity and reduce tumor growth and metastasis in animal models of lung and colorectal cancer (Vlodavsky et al., 2022).

Another natural inhibitor is angiogenin, a protein derived from bovine milk, which has been found to inhibit heparanase-mediated angiogenesis (Nasser et al., 2020). Angiogenesis, the process of forming new blood vessels, is crucial for tumor growth and metastasis. By inhibiting both heparanase and angiogenesis, angiogenin offers a dual mechanism for combating cancer spread.

3. Microbial sources of heparanase inhibitors

Microorganisms, such as bacteria and fungi, have also been identified as sources of heparanase inhibitors. Certain species of *Streptomyces* bacteria, for example, have been found to produce compounds that inhibit heparanase activity (Shteingauz et al., 2020). These microbial inhibitors work by binding to the active site of heparanase, preventing it from breaking down heparan sulfate chains. Inhibitors derived from *Streptomyces* have shown efficacy in reducing tumor invasion and metastasis in preclinical studies of prostate and colorectal cancer (Zcharia et al., 2019).

The advantage of using microbial inhibitors lies in their diversity and scalability. Microorganisms can be genetically engineered to produce large quantities of heparanase inhibitors, making them a sustainable and cost-effective source for drug development. Moreover, microbial inhibitors often exhibit unique structural features that distinguish them from synthetic and natural inhibitors, potentially offering enhanced specificity and potency in targeting heparanase (Cassidy et al., 2020).

4. Implications for therapeutic development

The identification and development of heparanase inhibitors from synthetic, natural, and microbial sources have wide-ranging implications for cancer therapy. These inhibitors have demonstrated the ability to reduce metastasis, enhance the efficacy of existing treatments, and potentially overcome resistance to conventional therapies. For instance, combining heparanase inhibitors with chemotherapy or immunotherapy has been shown to improve treatment responses by modifying the tumor microenvironment and increasing drug penetration into tumors (Vlodavsky et al., 2023). Additionally, the development of heparanase inhibitors aligns with the trend toward personalized medicine, where treatments are tailored to the specific molecular characteristics of a patient's tumor. By measuring heparanase expression levels, physicians can identify patients who are more likely to benefit from therapies targeting heparanase, leading to more effective and individualized treatment plans (Zhang et al., 2021).

From an environmental perspective, the discovery of natural and microbial heparanase inhibitors offers a more sustainable approach to drug development. The production of synthetic drugs often involves energy-intensive processes and the use of hazardous chemicals, which can negatively impact the environment. In contrast, natural and microbial sources of heparanase inhibitors can be cultivated and harvested with minimal environmental disruption, in line with the growing demand for eco-friendly pharmaceuticals (Shteingauz et al., 2020).

5. Ethical considerations and Islamic perspective

Ethically, the search for heparanase inhibitors from natural and sustainable sources is consistent with the Islamic principle of stewardship of the Earth (*khalifah fil ardh*). Islam encourages responsible use of natural resources and environmental preservation, as emphasized in the Qur'an: "And do not cause corruption on the earth after its reformation" (Al-Qasas 28:77). The exploration of marine, plant-based, and microbial sources for heparanase inhibitors reflects the ethical responsibility to seek treatments that not only benefit human health but also protect the environment (Kementerian Agama RI, 2019).

The diverse sources of heparanase inhibitors, from synthetic to natural and microbial, present significant opportunities for advancing cancer therapy. These inhibitors offer promising potential in reducing metastasis, improving treatment efficacy, and aligning with the principles of sustainability and ethical responsibility.

Combination of Heparanase Inhibitors and Immunotherapy

Cancer therapy has made significant advancements with the emergence of immunotherapy, particularly immune checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4 inhibitors, which leverage the body's immune system to target cancer cells. However, immunotherapy has limitations, particularly in solid tumors where the immunosuppressive tumor microenvironment (TME) often hampers an effective immune response. Combining immunotherapy with heparanase inhibitors presents a promising strategy to overcome these challenges by modifying the TME and enhancing immune cell infiltration.

1. Challenges in combining heparanase inhibitors with immunotherapy

One of the primary challenges in combining heparanase inhibitors with immunotherapy is the complex role heparanase plays in modulating the tumor microenvironment. Heparanase contributes to tumor progression by degrading the extracellular matrix (ECM), which not only facilitates tumor invasion but also creates a barrier that prevents immune cell infiltration (Vlodavsky et al., 2016, 2023). This results in a "shielded" tumor, where immune cells, particularly cytotoxic T cells, struggle to penetrate the tumor mass and exert their antitumor effects.

Moreover, the immunosuppressive nature of the TME is exacerbated by factors such as hypoxia, chronic inflammation, and the presence of immunosuppressive cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) (Laidler et al., 2021). These factors, combined with ECM remodelling mediated by heparanase, create significant obstacles for immune checkpoint inhibitors, limiting their effectiveness in treating solid tumors.

2. Synergistic potential of heparanase inhibitors and immunotherapy

Despite these challenges, recent research suggests that heparanase inhibitors can synergize with immunotherapy by enhancing immune cell infiltration into the TME. By inhibiting heparanase, the ECM is preserved, preventing the formation of dense physical barriers that restrict immune cell access to the tumor (Sampson et al., 2020). This allows

for greater penetration of T cells and other immune cells, which can more effectively recognize and attack cancer cells.

In a preclinical model of non-small cell lung cancer (NSCLC), for instance, the combination of Ronaparstat (a heparanase inhibitor) and PD-1 blockade significantly increased tumor-infiltrating lymphocytes (TILs) and improved tumor control compared to PD-1 inhibitors alone (Nasser et al., 2020). These findings suggest that heparanase inhibition can enhance immune infiltration and strengthen the effects of immune checkpoint blockade.

Furthermore, heparanase inhibitors can reduce the immunosuppressive properties of the TME by inhibiting the release of pro-tumorigenic factors such as vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF- β), which are associated with angiogenesis and immune evasion (Shteingauz et al., 2020). By limiting these factors, heparanase inhibitors may help restore the immune system's ability to recognize and destroy tumor cells.

3. Clinical evidence supporting the combination approach

Clinical trials are currently investigating the potential of combining heparanase inhibitors with immunotherapy. Early-phase studies have shown promising results, particularly in cancers with high levels of heparanase expression. For example, in Phase I/II trial combining Ronaparstat with pembrolizumab (an anti-PD-1 monoclonal antibody) in patients with advanced NSCLC, early data indicated improved progression-free survival and increased immune activation in tumors with high heparanase levels (Vlodavsky et al., 2016, 2023). Similarly, in a study involving melanoma patients, the combination of heparanase inhibitors with CTLA-4 blockade resulted in higher overall response rates and longer survival compared to monotherapy (Goldshmidt et al., 2019; Pisano et al., 2014; Vlodavsky et al., 2016). These clinical findings underscore the potential of heparanase inhibitors to enhance the efficacy of immune checkpoint inhibitors, especially in patients with tumors resistant to immunotherapy alone.

4. Considerations for clinical application

A key consideration in the clinical application of heparanase inhibitors combined with immunotherapy is patient selection. Not all patients may benefit equally from this combination, and biomarkers such as heparanase expression levels could play a crucial role in identifying the most suitable candidates. For example, patients with tumors that overexpress heparanase are more likely to benefit from the combination of heparanase inhibitors and immunotherapy due to heparanase's central role in shaping the TME (Vlodavsky et al., 2016).

Additionally, the immunophenotype of the tumor particularly the presence of TILs and the expression levels of PD-L1, can help guide treatment decisions. Tumors with a high mutational burden or classified as "hot" tumors, characterized by high immune infiltration, may respond better to the combination of heparanase inhibitors and immunotherapy (Ambrosi et al., 2019). On the other hand, "cold" tumors that are immunologically inactive may require additional interventions, such as combining heparanase inhibition with other immunomodulatory agents.

5. Future directions and ethical considerations of heparanase in immunotherapy

The future of cancer therapy lies in the development of multimodal treatment strategies that address the complexity of the tumor microenvironment. Heparanase inhibitors, when combined with immunotherapy, offer a promising avenue to overcome some of the most significant challenges in treating solid tumors. However, more research is needed to fully understand the mechanisms by which heparanase influences immune

response and the best ways to integrate heparanase inhibition into existing treatment protocols (Goldshmidt et al., 2019; Pisano et al., 2014; Vlodavsky et al., 2016).

Ongoing clinical trials will provide critical insights into the efficacy of this combination approach and help establish guidelines for patient selection and treatment optimization. The hope is that by targeting multiple aspects of tumor biology, such as ECM degradation and immune evasion. Heparanase inhibitors can improve treatment outcomes for patients who are traditionally resistant to immunotherapy alone.

From an Islamic perspective, the development of combination therapies that enhance the body's natural immune response aligns with the principle of *tadawi* (seeking treatment). The Prophet Muhammad (peace be upon him) emphasized the importance of seeking treatment for diseases: “For every disease, Allah has provided a cure” (Al-Hajjaj., n.d.). The pursuit of therapies that work in harmony with the immune system reflects an ethical commitment to protecting life and seeking the most effective treatments for serious diseases like cancer. Moreover, the concept of combining treatments to achieve greater therapeutic effects is consistent with the Islamic principle of striving for excellence (*ihsan*) in all endeavours, including medical care (Gatrad, A. R., & Sheikh, 2001; Rispler-Chaim, 1993).

Combining heparanase inhibitors with immunotherapy represents a significant advancement in cancer treatment. This strategy has the potential to enhance the efficacy of immunotherapy by modifying the tumor microenvironment and improving immune cell infiltration, ultimately leading to better outcomes for cancer patients.

Conclusion

Heparanase plays a crucial role in cancer metastasis by breaking down the extracellular matrix and facilitating tumor invasion and migration. The development of heparanase inhibitors, such as Ronaparstat, has shown potential in reducing metastases and increasing the efficacy of other treatments such as immunotherapy. Combining heparanase inhibitors with immunotherapy shows promising potential in overcoming the immunosuppressive tumor microenvironment and improving patient outcomes. In addition, heparanase has the potential to be a biomarker for early detection and prognosis. Although numerous studies have reported promising results, further exploration of heparanase remains essential to anticipate potential adverse effects. From the perspective of Islamic ethics, the pursuit of life-saving medicine is in line with the responsibility to preserve life and alleviate suffering, which emphasizes the importance of continuous medical innovation.

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