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The antineoplastic role of heparins

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Abstract

Heparins are sulfated glycosaminoglycans that have been used for decades for the prevention and treatment of venous thromboembolism (VTE). The close relationship between coagulation, inflammation, tumor progression, angiogenesis and metastasis has stimulated extensive investigation into whether heparins possess clinically relevant antineoplastic properties independent of their anticoagulant effects. Experimental studies have demonstrated that unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs) and structurally modified non-anticoagulant heparins can interfere with several stages of tumor progression. Proposed mechanisms include inhibition of heparanase, interference with P- and L-selectin-mediated tumor-platelet and tumor-endothelial cell interactions, modulation of angiogenic growth factors, inhibition of lymphangiogenesis, disruption of the CXCL12–CXCR4 axis, interference with integrin-mediated adhesion, alteration of tumor-stromal interactions and effects on cancer stem-cell biology. Heparins may also modify thrombin- and fibrin-dependent mechanisms that protect circulating tumor cells and facilitate metastatic dissemination.Clinical evidence, however, is considerably less consistent than the preclinical literature. Several randomized trials have reported improved survival in selected cancer populations receiving LMWH, whereas other well-designed studies have failed to demonstrate a significant survival advantage. Meta-analyses have generally shown that LMWH reduces thromboembolic events but have not established a universal survival benefit attributable to direct antitumor activity. The distinction between anticoagulant and antineoplastic effects is particularly important because therapeutic heparins carry clinically relevant bleeding risks. Consequently, heparins should not currently be regarded as conventional anticancer drugs, although their molecular interactions with tumor cells, platelets, endothelium, extracellular matrix and the tumor microenvironment provide a rationale for developing next-generation non-anticoagulant heparin derivatives. This review summarizes the molecular basis, experimental evidence, clinical data, limitations and future therapeutic perspectives concerning the antineoplastic role of heparins.

Keywords: heparin, antineoplastic role, cancer, tumor growth, metastasis.

Introduction

Cancer and thrombosis are biologically interconnected conditions. Malignant cells can activate coagulation, platelets, endothelial cells and inflammatory pathways, while coagulation proteases and fibrin can in turn facilitate tumor growth and dissemination. This reciprocal relationship is particularly relevant in advanced malignancy, in which venous thromboembolism is a frequent complication and an important contributor to morbidity and mortality.Heparin is a heterogeneous, highly sulfated glycosaminoglycan composed principally of uronic acid and glucosamine residues. Unfractionated heparin (UFH) has a broad molecular-weight distribution, whereas low molecular weight heparins (LMWHs) are produced by controlled depolymerization and have lower and more homogeneous molecular weights. Their principal pharmacological action is anticoagulation through potentiation of antithrombin-mediated inhibition of activated coagulation factors, particularly factor Xa and thrombin. [1-5]

The observation that cancer patients treated with heparins sometimes experienced outcomes that appeared to exceed the expected benefits of thrombosis prevention generated interest in a possible direct antineoplastic effect. [6-9]

Subsequent experimental work demonstrated that heparins can inhibit tumor-cell adhesion, platelet-tumor cell aggregation, extracellular-matrix degradation, angiogenesis, lymphangiogenesis and metastatic colonization. The concept is biologically plausible because many proteins involved in malignant progression -including growth factors, chemokines, selectins, integrins and extracellular-matrix enzymes- interact with heparan sulfate or other sulfated glycosaminoglycans. Heparin can therefore influence tumor biology without necessarily acting through its anticoagulant activity. [8–12]

Nevertheless, enthusiasm for heparin as an anticancer agent must be tempered by the clinical evidence. Although selected trials have demonstrated improved survival, others have shown no significant benefit and subsequent systematic reviews have reached differing conclusions. The most important unresolved question is whether the survival differences observed in some studies represent a reproducible direct antitumor effect or are secondary to prevention of fatal thromboembolism, differences in patient selection, tumor biology, treatment duration, or other confounding factors. [6]

This review evaluates the current evidence for the antineoplastic role of heparins, focusing on molecular mechanisms, experimental models, clinical trials, safety considerations, and prospects for the development of non-anticoagulant heparin-based therapeutics.

Heparins and their structural characteristics

Heparin is a naturally occurring sulfated glycosaminoglycan characterized by substantial structural heterogeneity [1]. UFH generally contains longer polysaccharide chains, whereas LMWHs consist of shorter fragments generated by chemical or enzymatic depolymerization. Common LMWHs include dalteparin, enoxaparin, nadroparin, tinzaparin and bemiparin.The biological effects of heparins depend not only on molecular weight but also on sulfation pattern, chain length, iduronic-acid content, conformational flexibility and the distribution of functional binding domains. These structural features are important because anticoagulant and non-

anticoagulant activities do not necessarily require identical molecular determinants. The antithrombin -binding pentasaccharide sequence is essential for the anticoagulant effect. By contrast, inhibition of selectins, heparanase, chemokines, growth factors or integrins may require longer oligosaccharide sequences or different sulfation patterns. This provides a conceptual basis for designing modified heparins that retain selected antineoplastic properties while minimizing anticoagulation and bleeding. [2,3,10]

Cancer-associated coagulation and the biological rationale for heparin therapy

The coagulation system participates actively in cancer biology. Tumor cells can express tissue factor and other procoagulant molecules, activate platelets, generate thrombin and promote fibrin deposition. Thrombin can activate protease-activated receptors and stimulate signaling pathways associated with proliferation, migration, inflammation, and angiogenesis.Fibrin may provide a provisional matrix around tumor cells and contribute to the formation of platelet-rich microthrombi. These structures can protect circulating tumor cells from mechanical stress and immune-mediated elimination while facilitating interactions with the vascular endothelium. [13-18]

Platelets are particularly important in hematogenous metastasis. Tumor cells can induce platelet activation and aggregation, generating tumor cell-platelet complexes that interact with endothelial cells and leukocytes. Experimental studies have shown that inhibition of platelet function or P-selectin-mediated interactions can reduce metastatic dissemination. [13,19,20]

Heparin may therefore influence cancer progression at two levels: first, by suppressing thrombin and coagulation-dependent processes; and second, by exerting non-anticoagulant effects on molecular interactions involved in metastasis, such as selectin inhibition, heparanase inhibition, inhibition of angiogenesis and lymphangiogenesis, modulation of CXCL12-CXCR4 axis, modulation of integrin-mediated adhesion, effect on tumor growth and cellular signaling, effect on cancer stem cells and tumor microenvironment. [11,21,22]

A. Selectin inhibition

Metastasis requires a series of coordinated events, including local invasion, intravasation, survival in the circulation, endothelial adhesion, extravasation and colonization of distant organs. Cell-adhesion molecules, particularly selectins and integrins, participate in several of these steps.P-selectin is expressed on activated platelets and endothelial cells, whereas E-selectin is expressed primarily by activated endothelium and L-selectin is expressed on leukocytes. These receptors recognize specific carbohydrate structures on tumor cells (e.g. death receptor-3, PSGL-1 and other selectin-ligand mucins), thus facilitating adhesive interactions during metastatic dissemination. [23-31]

Experimental studies demonstrated that P-selectin deficiency attenuates tumor growth and metastasis, supporting a causal role for selectin-dependent interactions. Heparin can interfere with P-selectin-mediated adhesion and thereby inhibit formation of platelet-tumor cell complexes, which shield cancer cells from immune clearance. [28,29,32,33]

A particularly important observation was that heparin could inhibit experimental metastasis even when its anticoagulant activity was markedly reduced. This finding suggested that the antimetastat-

ic effect could not be attributed entirely to inhibition of thrombin. [34,35]

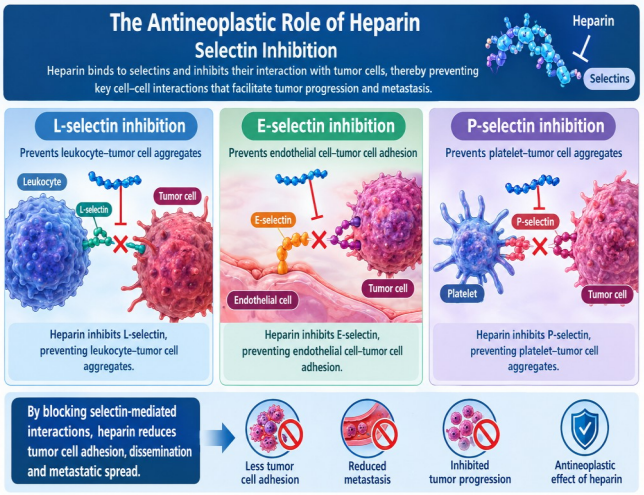
Heparin has also been shown to inhibit L-selectin-dependent interactions, impairing leukocyte-tumor cell aggregates and potentially interfering with leukocyte recruitment and establishment of a metastatic microenvironment. [23]

In addition, endothelial activation triggers the release of chemokines, such as CCL5, providing another mechanism through which selectins contribute to metastatic colonization. Heparin can inhibit E-selectin, thus blocking endothelial activation and inhibiting adhesion of cancer cells to endothelial cells. [24,25]

Tumor cell-induced platelet aggregation is a well-described phenomenon, particularly in aggressive carcinomas. Pancreatic and other carcinoma cells can induce platelet aggregation in vitro, while platelet-tumor cell interactions promote endothelial adhesion and metastatic dissemination. Heparin may interfere with this process by inhibiting P-selectin and other adhesion pathways. Modified heparins that retain selectin-binding activity but have minimal anticoagulant properties have therefore been investigated as potential antimetastatic agents.These findings support the concept that the metastatic effects of heparin are not simply consequences of anticoagulation but can involve direct interference with tumor-host cell recognition. [19,20,23,28,29,32,33]

The effect of heparin on selectin inhibition is illustrated in figure 1.

Figure 1: Heparin binds and inhibits P-, E- and L-selectin, inhibiting Tumor cell aggregates with Platelets, Endothelial cells and Leukocytes respectively



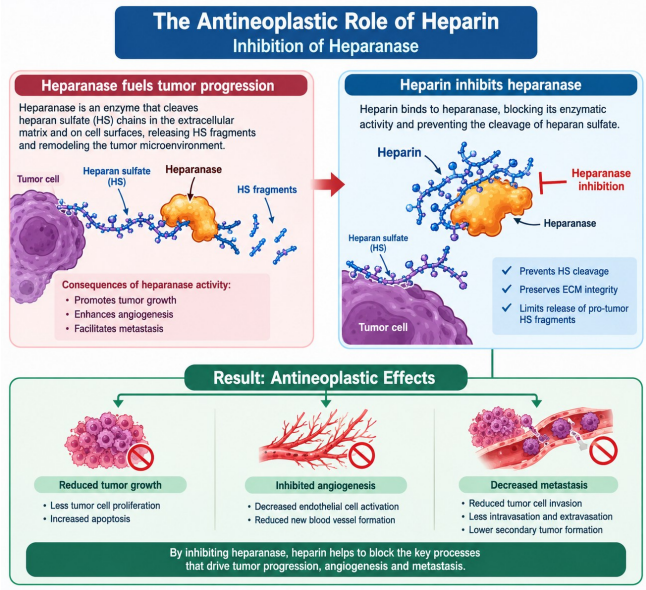
B. Heparanase inhibition

Heparanase is an endoglycosidase that cleaves heparan sulfate proteoglycans within the extracellular matrix and basement membrane. It has become one of the most intensively studied molecular targets connecting heparin biology with cancer progression.Heparanase is overexpressed in numerous human malignancies and increased expression has been associated experimentally with tumor invasion, angiogenesis, metastatic dissemination and unfavorable outcomes. By degrading heparan sulfate, heparanase facilitates remodeling of the extracellular matrix and releases heparin-binding growth factors, including fibroblast growth factors and vascular endothelial growth factor, therefore promoting both invasion and angiogenesis, as illustrated in figure 2. [18,36]

Native heparin can inhibit heparanase activity, while selected non-anticoagulant heparin derivatives may inhibit the enzyme with greater therapeutic selectivity. Experimental studies have demonstrated suppression of metastasis using chemically modified heparins with reduced anticoagulant ac-

tivity.This mechanism is particularly attractive because heparanase inhibition could theoretically provide antineoplastic effects without requiring systemic anticoagulation. Several heparanase-directed molecules, including heparin mimetics, have subsequently been developed and evaluated experimentally. [37-40]

Figure 2: Heparin inhibits heparanase, thus inhibiting its enzymatic activity on heparan sulfate, blocking tumor growth, angiogenesis and metastatic potential

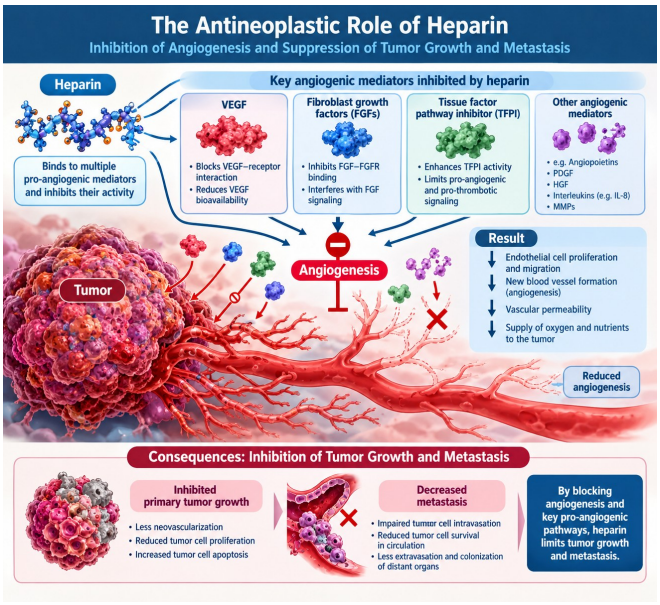


C. Angiogenesis and lymphangiogenesis

Tumor progression beyond a microscopic size requires vascular support. Angiogenesis supplies oxygen and nutrients and also creates routes for tu--cell dissemination. Heparin can influence angiogenesis through interactions with VEGF, fibroblast growth factors, tissue factor pathway inhibitor and other angiogenic mediators, as described in figure 3. [21,22,41]

The relationship between heparin and angiogenesis is complex. Heparin can bind heparin-binding growth factors and alter their availability, receptor interactions, or extracellular localization. Certain LMWHs have been shown experimentally to inhibit endothelial-cell proliferation, migration and tube formation. [14]

Figure 3: Heparin inhibits angiogenesis via VEGF, FGF, TFPI and other angiogenic mediators, resulting in tumor cell growth and metastasis inhibition



Tinzaparin, for example, has demonstrated anti-angiogenic activity in experimental systems, with some of these effects attributed to tissue factor pathway inhibitor [42]. Other chemically modified heparin conjugates have been designed specifically to increase binding to VEGF and inhibit angiogenic signaling. [37,39,40]

Heparin derivatives such as PG545 have provided additional proof of principle. PG545 combines heparanase-inhibitory and anti-angiogenic properties and has demonstrated inhibition of tumor growth and metastasis in several experimental models. [43]

However, these findings should not be interpreted as evidence that conventional clinical anticoagulant doses of LMWH function as anti-angiogenic drugs in patients. The concentrations and experimental exposure conditions used in preclinical studies may differ substantially from clinically achievable systemic concentrations.

In parallel, the lymphatic system is an important route of metastatic dissemination. VEGF-C and VEGF-D signaling through VEGFR-3 is a major pathway driving lymphangiogenesis. Experimental studies indicate that heparin derivatives can interfere with this pathway. LHbisD4, a modified LMWH conjugate, has been shown to inhibit VEGF-C-induced VEGFR-3 signaling and lymphatic vessel formation in experimental models. Such findings extend the proposed antineoplastic role of heparins beyond hematogenous metastasis. Nevertheless, most evidence remains preclinical, and it is unknown whether conventional LMWH therapy can produce a clinically meaningful inhibition of lymphangiogenesis in humans. [44-49]

D. Modulation of the CXCL12–CXCR4 axis

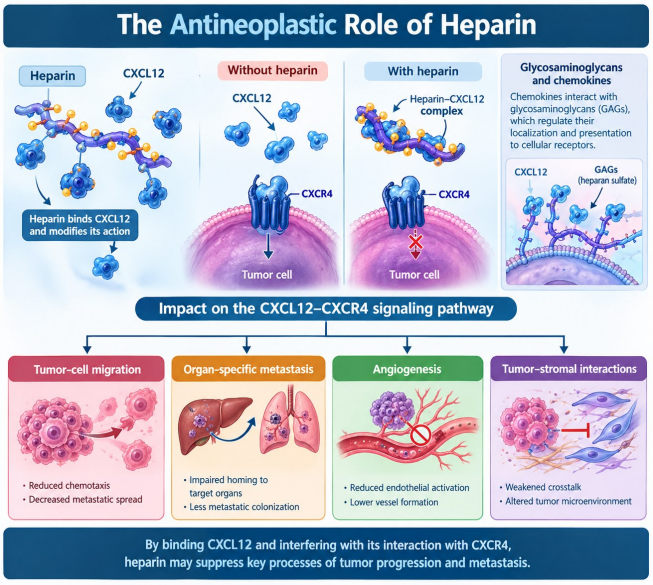
The CXCL12–CXCR4 signaling pathway has an important role in tumor-cell migration, organ-specific metastasis, angiogenesis and interactions between malignant cells and stromal cells. [16,50-52]

Chemokines interact with glycosaminoglycans, which regulate their localization and presentation to cellular receptors. Heparin can bind CXCL12 and modify its oligomerization and receptor interactions. [15,16,50-52]

Experimental work has shown that tinzaparin can interfere with CXCL12–CXCR4-mediated breast cancer metastasis. Enoxaparin has also been reported to inhibit CXCL12-dependent proliferation, adhesion, and hepatic metastasis of colon cancer cells. [53-60]

These observations suggest that heparins may disrupt chemokine-mediated communication between tumor cells and the metastatic niche. Importantly, this mechanism is distinct from anticoagulation and may represent a useful target for future non-anticoagulant derivatives (see figure 4).

Figure 4: Heparin inhibits CXCL12-CXCR4 signaling pathway, thus inhibiting tumor cell-stromal cell interactions, angiogenesis, tumor cell migration and metastasis



E. Integrin-mediated adhesion

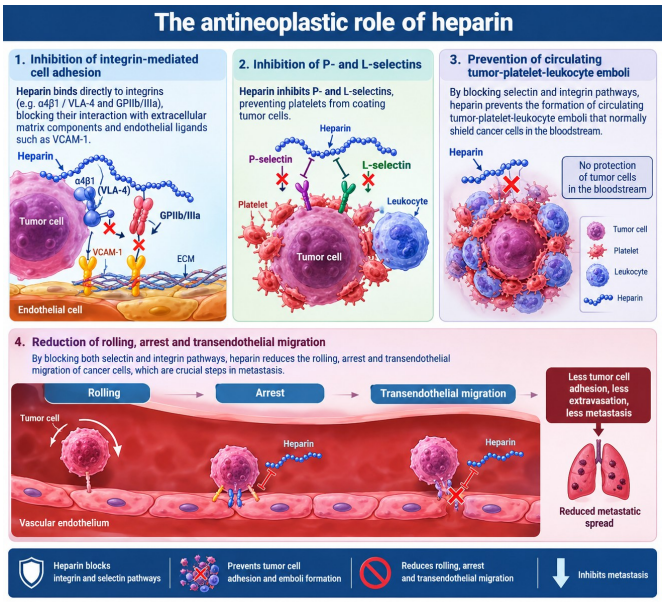
Integrins regulate tumor-cell adhesion to extracellular-matrix proteins, platelets, leukocytes and endothelial cells. Heparin can interact with several integrins and may interfere with their ligand-binding functions. [61-63]

The VLA-4/VCAM-1 pathway is particularly relevant to tumor-cell adhesion to vascular endothelium. Experimental studies have demonstrated binding between heparin and VLA-4, while modified heparins can inhibit melanoma-cell adhesion. [61,63]

Similarly, αIIbβ3-mediated interactions contribute to platelet–tumor cell adhesion. Modified heparins have demonstrated inhibitory effects on melanoma-cell attachment to platelets through this mechanism. [19,38]

These findings support a model in which heparin can interfere with several independent adhesion pathways simultaneously, potentially explaining why relatively transient exposure may produce longer-lasting effects on experimental metastatic colonization (figure 5).

Figure 5: Heparin inhibits integrin-mediated cell adhesion, preventing tumor cell aggregates with leukocytes, platelets and endothelial cells and thus blocking tumor cell adhesion, extravasation and metastasis



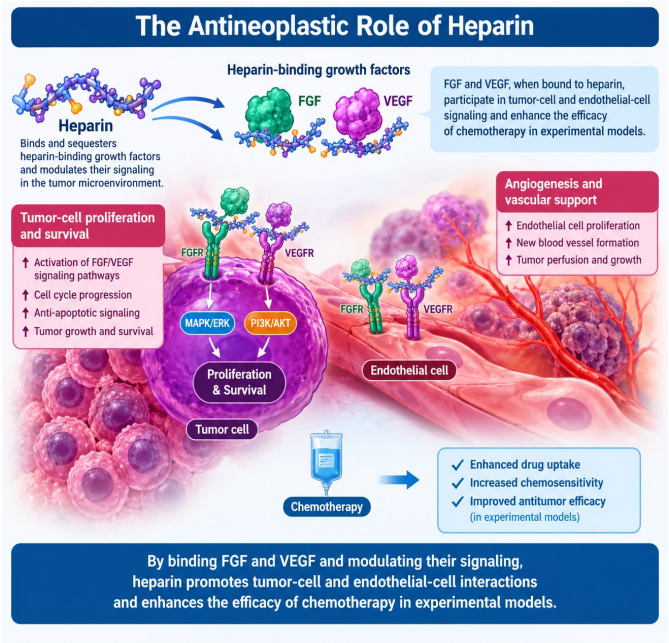
F. Effects on tumor growth and cellular signaling

Although the strongest experimental evidence concerns metastasis, heparins may also affect tumor-cell proliferation and survival.Heparin-binding growth factors such as FGF and VEGF participate in tumor-cell and endothelial-cell signaling. By competing for these ligands or altering their interactions with receptors and extracellular-matrix components, heparin can modify proliferative signaling. [11,21,22,64,65]

Some LMWHs have also been reported to enhance the efficacy of chemotherapy in experimental models. Combination of LMWH with doxorubicin reduced breast cancer metastasis in mice, while other studies have reported enhanced effects of chemotherapy in pancreatic cancer. [8,9]

These observations raise the possibility that heparins could act as adjuvant agents rather than as conventional cytotoxic drugs. Nevertheless, the clinical evidence for improved chemotherapy efficacy remains limited and heterogeneous (figure 6).

Figure 6: Heparin inhibits tumor cell proliferation and survival, inhibiting angiogenesis and enhancing chemosensitivity to antineoplastic drugs



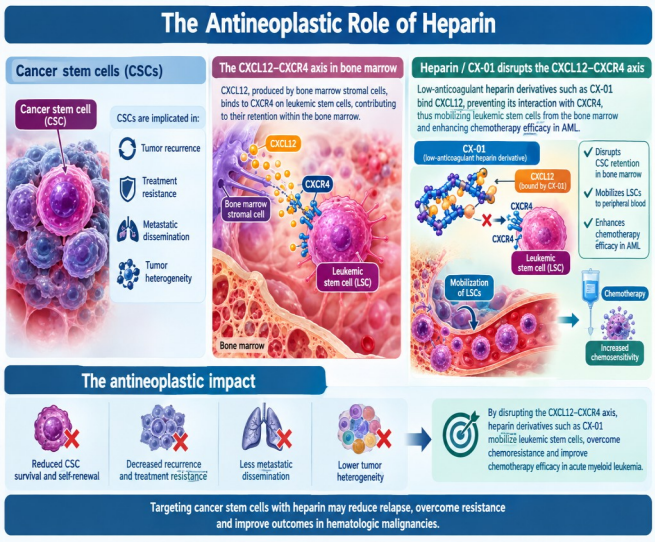
G. Cancer stem cells

Cancer stem cells are implicated in tumor recurrence, treatment resistance, metastatic dissemination and tumor heterogeneity. Glycosaminoglycans participate in stem-cell niche interactions and heparin-sensitive chemokine pathways are involved in the retention of hematopoietic and leukemic stem cells. The CXCL12–CXCR4 axis contributes to retention of leukemic stem cells within the bone marrow. Low-anticoagulant heparin derivatives such as CX-01 have been investigated for their ability to disrupt this interaction and improve chemotherapy efficacy in acute myeloid leukemia.

A related approach involves G2.2, a nonsaccharide heparin mimetic capable of inhibiting colon cancer stem-cell populations through p38 MAPK activation. [16,50-52,54-60]

These studies suggest that heparin-like compounds could potentially target tumor-cell populations that are relatively resistant to conventional chemotherapy (figure 7). However, this remains an emerging field, and clinical validation is required.

Figure 7: Heparin effects on cancer stem cells by disrupting the CXCL12-CXCR4 axis

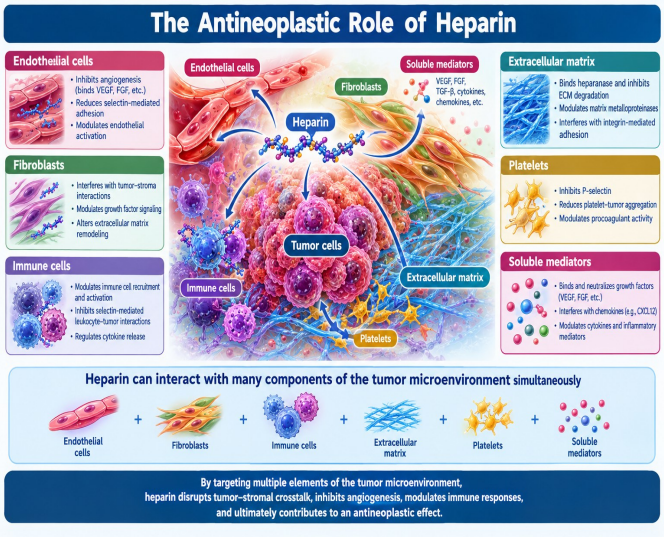


H. Heparin and the tumor microenvironment

The tumor microenvironment contains endothelial cells, fibroblasts, immune cells, extracellular matrix, platelets and soluble mediators. Heparin can interact with many of these components simultaneously. Heparan sulfate proteoglycans regulate the localization and activity of growth factors and chemokines. Consequently, pharmacological modulation of glycosaminoglycan-dependent signaling could affect multiple components of the tumor microenvironment rather than a single oncogenic pathway. [11,15,21,22,37-39]

This multimolecular activity may be advantageous in tumors characterized by extensive biological redundancy. Conversely, it complicates pharmacological development because the precise molecular target responsible for an observed clinical effect may be difficult to identify (figure 8).

Figure 8: Heparin effects on tumor cell microenvironment: endothelial cells, fibroblasts, immune cells, Platelets, extracellular matrix and soluble mediators



Clinical evidence for an antineoplastic effect of heparin

The clinical literature is substantially more controversial than the experimental literature. One of the earliest observations came from studies of patients with cancer-associated thrombosis in which LMWH appeared to be associated with lower mortality than conventional anticoagulation [11]. Subsequent randomized studies investigated whether LMWH could improve survival in cancer patients without an established indication for anticoagulation. The MALT study randomized patients with advanced malignancy without VTE to nadroparin or placebo. The study reported improved overall survival with nadroparin, particularly among patients with a life expectancy of at least six months. However, the trial was relatively small, and subsequent studies have not consistently reproduced this magnitude of benefit [6]. The FAMOUS trial in-

vestigated dalteparin in patients with advanced cancer and did not demonstrate a statistically significant overall survival benefit in the primary analysis, although survival differences were observed in selected subgroups [12].

Small-cell lung cancer has generated particular interest. A randomized clinical trial reported improved outcomes with LMWH combined with chemotherapy [8], while an earlier multicenter study reported increased survival following subcutaneous heparin treatment [66]. These findings suggest that tumor type may modify the potential effect of heparins. Similarly, selected studies in pancreatic cancer have reported favorable outcomes with LMWH [9], although differences in trial design, concomitant treatment, thrombosis risk, and patient selection limit generalization. In a recent review [67] authors conclude that although benefit of LMWH on cancer patients' survival is controversial, it appears to be associated with a reduction in VTE, while an increased bleeding risk is minor and controllable. Based on the above controversial results, it seems imperative that randomized controlled trials targeting the survival benefit of heparin use in cancer patients are needed and justified. [6,11,12,68-71]

Meta-analyses and the interpretation of survival data

Several meta-analyses have examined whether anticoagulation produces an antineoplastic survival benefit. An early pooled analysis of patients receiving long-term LMWH for VTE did not demonstrate a significant reduction in cancer mortality, while a subsequent meta-analysis of anticoagulants as cancer treatment suggested that survival effects might vary according to tumor type and stage. [7]

Importantly, an updated systematic review and meta-analysis of randomized trials including nearly 6,000 patients with advanced cancer found no discernible mortality effect from LMWH compared with placebo or no anticoagulant therapy. These findings substantially weaken the hypothesis that LMWH should routinely be prescribed solely to prolong survival. Individual-participant-data analyses have likewise emphasized that prophylactic heparin can reduce symptomatic VTE but have not established a universal survival advantage. [72]

The discrepancy between experimental and clinical evidence may have several explanations. First, experimental studies frequently administer heparin at concentrations or schedules that may not correspond to routine clinical exposure. Second, different heparin preparations possess different molecular characteristics. Third, tumors vary considerably in their dependence on coagulation, selectin signaling, heparanase, angiogenesis and chemokine pathways. Finally, the clinical effects of anticoagulation may be dominated by prevention of VTE rather than direct inhibition of tumor progression.

Anticoagulant versus antineoplastic effects of heparin

A central issue is distinguishing direct antineoplastic activity from secondary effects of thrombosis prevention. Reduction of fatal pulmonary embolism can improve survival without modifying the tumor itself. Similarly, prevention of microvascular thrombosis may improve organ function and reduce morbidity without producing a direct cytostatic or antimetastatic effect. Evidence supporting an anticoagulant-independent mechanism includes experimental studies using non-anticoagulant heparins that retain antimetastatic activity.Inhibition of selectins and heparanase provides particularly strong

mechanistic evidence. [10,39,40]

However, translating these mechanisms into clinical practice requires compounds that retain the relevant molecular interactions while eliminating or substantially reducing anticoagulant activity. Conventional UFH and LMWH are limited by bleeding risk when used solely for an unproven anticancer indication.

Non-anticoagulant heparins and heparin mimetics

The development of non-anticoagulant heparins represents one of the most promising directions in this field.Chemically modified heparins have been designed to reduce antithrombin binding while preserving selectin or heparanase inhibition. Other derivatives have been engineered to increase affinity for VEGF, VEGF-C, or other heparin-binding proteins. [10,37-40]

PG545 is an example of a heparanase-inhibiting heparin mimetic with anti-angiogenic and antitumor properties [73]. Roneparstat is another non-anticoagulant heparin derivative developed primarily as a heparanase inhibitor [74].

The advantage of these compounds is conceptual: if tumor-promoting pathways can be targeted without producing clinically significant anticoagulation, the therapeutic window could be substantially improved.

Heparins as drug-delivery platforms

Heparin's high negative charge and ability to bind numerous proteins have also stimulated investigation into its use in nanomedicine and drug delivery.Heparin-containing nanoparticles have been developed to enhance tumor accumulation and facilitate chemotherapy delivery. Such approaches exploit the biochemical properties of heparin while potentially minimizing systemic anticoagulant exposure. Experimental LMWH-based nanoparticles have demonstrated antitumor and antimetastatic activity in breast cancer models [75]. Non-anticoagulant LMWH derivatives have also been reported to increase intratumoral uptake of chemotherapeutic agents. [10,37-40]

These approaches may ultimately prove more clinically feasible than systemic administration of conventional heparin as a direct anticancer drug.

Safety considerations

The principal limitation of conventional heparins is bleeding. This is particularly relevant in patients with cancer, who may have thrombocytopenia, mucosal tumors, recent surgery, brain metastases, renal dysfunction, or concurrent anticancer therapies that increase bleeding risk. Heparin-induced thrombocytopenia represents another clinically important complication, although it is considerably less frequent with LMWH than with UFH. Modern cancer-associated thrombosis guidelines recognize LMWH as an established option for treatment and prevention of VTE, but they do not recommend heparin solely as a general anticancer treatment. The 2023 ASCO guideline continues to support LMWH in appropriate settings, particularly for postoperative prophylaxis and selected treatment scenarios, while direct oral anticoagulants are also recognized options. [76-80]

Thus, the clinical indication for conventional heparin in oncology remains primarily prevention or treatment of VTE rather than direct tumor control.

Future research priorities

Several areas require further investigation.

First, future clinical trials should stratify patients according to tumor biology rather than treating all malignancies as a single population. Tumors with high heparanase expression, strong P-selectin-dependent biology, pronounced tissue-factor activity, or high metastatic potential may be more responsive to heparin-derived antineoplastic interventions.

Second, biomarker-driven trials are needed. Potential biomarkers include tumor heparanase expression, circulating selectin ligands, tissue factor activity, coagulation activation markers, CXCL12/CXCR4 expression, and molecular characteristics of the tumor microenvironment.

Third, clinical development should prioritize non-anticoagulant derivatives. Such compounds could allow evaluation of direct antitumor mechanisms without the confounding effects of anticoagulation and without exposing patients unnecessarily to bleeding risk.

Fourth, future studies should distinguish endpoints. Overall survival alone cannot reliably determine whether a drug has a direct antineoplastic mechanism. Metastasis-free survival, circulating tumor-cell burden, thromboembolic events, radiographic response, molecular biomarkers, and disease-specific progression should be evaluated simultaneously.

Finally, combination strategies deserve attention. Heparin-derived compounds could potentially be combined with chemotherapy, anti-angiogenic agents, immune checkpoint inhibitors, or targeted therapies. The most compelling rationale may be for compounds that simultaneously disrupt coagulation-dependent metastasis, tumor cell-platelet adhesion, extracellular-matrix remodeling and tumor angiogenesis.

Conclusions

The biological evidence supporting an antineoplastic role for heparins is substantial. Heparins can influence several processes central to cancer progression, including tumor-cell adhesion, platelet–tumor cell interactions, extracellular-matrix degradation, heparanase activity, angiogenesis, lymphangiogenesis, chemokine signaling, integrin-mediated adhesion and tumor–stromal communication.

Among these mechanisms, inhibition of P-selectin-mediated interactions and heparanase appears particularly well supported experimentally. Modulation of the CXCL12–CXCR4 pathway and angiogenic signaling provides additional mechanisms that may contribute to the antimetastatic properties of LMWHs and modified heparins.

The clinical evidence, however, does not justify considering conventional heparins established anticancer agents. Randomized trials have produced heterogeneous results and contemporary systematic reviews have not demonstrated a consistent survival benefit across unselected cancer populations. The clearest established clinical role of heparins in oncology remains prevention and treatment of cancer-associated thrombosis.

The future of the field therefore lies less in repurposing conventional anticoagulant doses of UFH or LMWH as universal cancer therapy and more in identifying the specific molecular activities responsible for antitumor effects. Non-anticoagulant hep-

arins and heparin mimetics capable of selectively inhibiting heparanase, selectins, angiogenesis, chemokine signaling, or tumor cell-platelet interactions may ultimately provide a safer and more rational therapeutic strategy.

In conclusion, heparins should currently be regarded as multifunctional modulators of tumor biology with established antithrombotic utility but incompletely validated direct antineoplastic efficacy. Continued translational research integrating tumor biology, coagulation biology and biomarker-driven clinical trials is warranted.

Acknowledgements:

The figures included are AI-generated via ChatGPT.

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