

Heparins in Thrombosis and Cancer

Citation for published version (APA):

Vignoli, A. V. (2018). *Heparins in Thrombosis and Cancer: Effects on the Vascular Endothelium*. Maastricht University. <https://doi.org/10.26481/dis.20181116av>

Document status and date:

Published: 01/01/2018

DOI:

[10.26481/dis.20181116av](https://doi.org/10.26481/dis.20181116av)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Valorisation

Cancer patients are at high risk of developing venous thromboembolism (VTE), including deep venous thrombosis and pulmonary embolism.

Indeed, in cancer patients VTE represents the second cause of death after the tumor itself, and significantly worsens their morbidity and the quality of life.

It is now well established that while the presence of a tumor predisposes the onset of VTE in the host, the activation of the hemostatic system in cancer may have a role not only in thrombosis but also in tumor growth and dissemination.

The effort of the current research aims to find valuable tools able to break down this mutual, vicious relationship.

In this respect, heparins, particularly the low molecular weight (LMWH) subcategory, are good candidates in that not only they are the drug of choice for the prophylaxis and treatment of VTE in a wide spectrum of pathological settings, including cancer, but they also appear to be endowed with direct and indirect anti-tumor features.

This has led to the development of a number of prospective randomized clinical trials to test LMWH to improve cancer survival as a primary end-point in cancer patients. Although the results are controversial, the interest in this research area remains high. Given the potential benefit of increased survival in oftentimes still fatal disease, any benefit, even small effects, may be clinically relevant. Therefore, it makes sense to dig deeper into the biology of cancer cells and to

better establish the effects of different types of heparins, on growth and proliferation of tumor cells.

We choose to study the impact of heparins on the vascular endothelium, this because endothelial cells play multiple roles in several patho-physiological processes, including hemostatic activation and cancer progression, so they appear an ideal target when you aim to impair the cancer/thrombosis association.

We could demonstrate that heparins may prevent the pro-thrombotic switch of the endothelial cells when exposed to tumor-derived products, as well as standard cytokines. This is relevant because the inhibition of fibrin formation has been considered a possible tool against the progression of malignant disease.

Endothelial cells take also part in tumor-driven angiogenesis. We could observe that heparins are able to impair the tumor-induced formation of capillary-like tubules (a key step in the neo-angiogenesis process) by endothelial cells in the well-known matrigel-based model. By counteracting the formation of new blood vessels, one could limit the tumor growth.

Then, we showed that heparins are able to counteract the direct adhesion of tumor cells to the vascular endothelium monolayer, by employing leukemic cells (but data are ongoing also with cells from solid tumor). This has important implications in that this effect may prevent tumor dissemination. We also showed that heparins counteract the

migration of cells from pancreatic cancer, a very aggressive subtype of cancer.

It has to be noted that we employed only cells of human origin, with regard to both endothelium and tumor. In particular, we used in all studies endothelial cells of the microcirculation, the most involved type in the pathological conditions, while the majority of published studies with the vascular endothelium have utilized cells from the macrocirculation.

Moreover, in our studies, we used not only the classical unfractionated heparin (UFH) and various types of LMWH, but also one representative of the very new ultra-low molecular weight heparin (ULMWH) subclass, i.e. RO-14. These newest heparins are characterized by a lower mean MW, and a more defined composition of polysaccharidic chain content. They are also characterized with a high anti-FXa activity and only residual anti-FIIa activity, thus the ratio anti-FXa/anti-FIIa is much greater compared to classical LMWH [1], that means that they should be endowed with a better efficacy/risk ratio compared to LWMH. Some ultra-LMWH are in clinical development [1-2]. However, little is known about their anti-cancer effects. Indeed, we first describe here that one of these ultra-LMWH i.e. RO-14 possess an anti-angiogenic activity similar to those shown by LMWH [3]. RO-14 also possesses a direct inhibitory effect on the migration of the pancreatic cancer cells.

With all the limitations coming from being *in vitro* studies, taken together these data further contribute to support the evidence of a possible *in vivo* anti-tumor effect of LMWH.

They also provide ground for future extensive studies, both in animal models and in clinical trials, about a possible role for LMWH and ULMWH in the cancer/thrombosis setting.

In summary, the potential therapeutic benefit of heparin derivatives for patients with malignant disease, is still out of reach. This does not mean that the promising findings from *in vitro* and animal studies could not translate into effective therapies. The use of specific fractions, such as non-anticoagulant heparins with reduced bleeding potential, and the application of better experimental models of disease, should be able to advance our knowledge. This gain in knowledge should translate into feasible focused clinical trials in highly selected patients with cancer, as to obtain proof of principle data on efficacy and mechanisms of action. The use of biomarkers, both for cancer cell death, as well as for vascular damage, hypercoagulability and other markers of vascular disease related to cancer, should help to explore the underlying mechanisms further.

References

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