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The molecular function of heparanase-1 in malignant melanoma

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Heparanase-1 (HPSE) is able to degrade heparan sulfate, thus playing a pivotal role in structural remodeling of the ECM and the glycocalyx. The protumorigenic, proangiogenic and prometastatic properties of HPSE have been identified in many human cancer entities. In this study, we investigated the function of HPSE in human malignant melanoma *in vitro*. Moreover, melanoma tumor xenografts were also examined to investigate the role of HPSE *in vivo*. HPSE-deficient cells showed a reduced shedding of the glycocalyx accompanied with retainment of VEGF at the cellular surface and an impaired tumor cell invasion. *In vivo* experiments further confirmed that HPSE deficiency attenuated tumor growth as well as tumor vascularization. In contrast, we measured an increased nuclear translocalization of NF-κB followed by a strongly elevated expression of the protumorigenic factors pentraxin-3, tissue factor, TNF-α and most prominently, MMP-9, upon HPSE knock-down. Inhibitory assays showed that the regulatory effect of HPSE on MMP-9 expression was independent of HPSE enzymatic activity. The regulatory effect of HPSE on gene expression was also confirmed *in vivo*. Immunofluorescence staining revealed a counter-staining of HPSE and NF-κB in the nucleus. Accordingly, activation of NF-κB with recombinant TNF-α reduced not only the expression of HPSE but also its nuclear localization suggesting a close relationship between NF-κB and HPSE. Finally, we visualized a direct charge-driven molecular interaction between HPSE and DNA by using AFM and a co-precipitation approach, indicating a novel role of HPSE in the nucleus of human malignant melanoma cells. These findings are novel and contribute to a more comprehensive understanding of the dual function of HPSE in the course of protein expression and tumor cell progression in malignant melanoma, thus providing new insights in the therapeutic strategies against this life-threatening disease.