MMP2 Small Immuno Protein Antibody Uptake is Associated With αvβ3 Expression in Xenograft Tumors in Mice

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Keyword(s): MMP2, Gelatinase, Imaging, Integrin

Abstract

INTRODUCTION AND AIM:
MMP2 plays a vital role in tumorigenesis, angiogenesis and tumor invasion. We have recently developed a human monoclonal antibody specific to MMP2 in a small immuno protein (SIP) format specifically optimized for imaging purposes. The aim of this study is to determine the potential use of the MMP2-SIP Antibody (aMMP2) as an imaging tool for tumor invasion.

METHODS:
To provide evidence of aMMP2 specificity in vivo, we generated a panel of MMP2 knockdown (KD) cell lines in HT1080, U373 and U87 using MMP2 lentiviral shRNA constructs. HCT116 having very low MMP2 expression was taken as an additional negative control. Cells were injected subcutaneously in the lateral flank of NMRI-nu mice. Near InfraRed Fluorescence imaging was performed, at an average tumor volume of 300mm³, using the Optix MX2 at 0.5, 2, 4, 8, 24 and 48 hour post injection of tracer (hpi) to understand the biodistribution of the tracer. A blank scan is performed before the tracer injection to correct for auto-fluorescence. Tumor to background ratios (TBR) were calculated by using ART Optix Optiview software. MMP2, αvβ3 levels and tumor microenvironmental parameters are characterized by immunohistochemistry.

RESULTS:
HCT116 had a very low uptake as expected. Surprisingly, also for U373 control (EV) tumors, TBR was found to be very low. While, KD had significantly lower TBR at 48 hpi than EV in U87; HT1080 and U373 tumors showed no difference (Figure 1).
In all the three models, MMP2 levels were significantly lower in the KD tumors compared to EV. Interestingly, the uptake of aMMP2 correlated with αβ3 levels. Both HT1080 EV and KD tumors had high levels of αβ3 contrarily; U373 had low/no αβ3 levels even though there are high levels of MMP2 present. U87 KD tumors also had significantly lower αβ3 than the EV tumors correlative to aMMP2 uptake (Figure 2). We have observed no differences between EV and KD in tumor microenvironmental parameters such as hypoxic fraction, vessel density and perfusion in all three models.
CONCLUSIONS:
48hpi is the optimal time point for imaging with aMMP2. aMMP2 uptake in the tumors is only partially MMP2 dependent and was correlative to the $\alpha_v\beta_3$ levels. The amount of $\alpha_v\beta_3$ which activates MMP2 might be equally important when considering MMP2 antibody targeting. Future investigations are required for the further understanding of the mechanism and firm conclusions.
References:


Acknowledgements:

Financial support by Quic-Concept