

P 175 ACTIVIN A AS AN INHIBITOR OF LYMPH VESSEL FORMATION IN MELANOMA

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Activin A proteins are homodimers of inhibin β A subunits and potentially inhibit blood vessel angiogenesis in part via induction of p21. Follistatin serves as an antagonist, it binds activin with high affinity and neutralizes most but not all of its biological actions. To investigate the role of activin A and follistatin in lymph vessel angiogenesis in melanoma, we selected human A375 melanoma cells which express high levels of the inhibin β A subunit. We stably over-expressed control vectors, inhibin β A subunit or follistatin and injected them intradermally into SCID mice. The arising primary tumours were excised at a size of 400mm³ and animals were monitored for metastasis to sentinel lymph nodes (SLN). Blood and lymph vessel formation was quantified by immunohistochemistry and real time PCR. We found growth rates of primary tumors to be equal in controls, inhibin β A subunit and follistatin over-expressing melanoma, whereas inhibin β A over-expressing tumors grew faster and more aggressive. Inhibin β A over-expressing tumors show a significant decrease in peritumoural lymph vessels but interestingly an increase of metastasis in the SLN. In conclusion, our results point to a dual role of activin A as an inhibitor of tumour lymph angiogenesis and a promoter of tumour invasiveness.

P 176 POSSIBLE CAUSES AND CONSEQUENCES OF THE OVEREXPRESSION OF THE VITAMIN D CATABOLIZING ENZYME CYP24A1 IN COLORECTAL CANCER

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Vitamin D insufficiency increases risk of colorectal cancer. Vitamin D is produced photochemically in the skin, thus low sunlight exposure results in vitamin D insufficiency. Vitamin D is further processed in the liver to its storage form calcidiol [25-OH vitamin D₃]. Calcidiol can be activated by 1α -hydroxylation to the secosteroid hormone calcitriol [$1\alpha,25$ -OH vitamin D₃]. Although systemic levels of bioactive calcitriol are regulated by the kidneys, almost every tissue can synthesize and degrade calcitriol. Tissue calcitriol acts in an autocrine/paracrine manner and controls proliferation, apoptosis, and differentiation. In colorectal cancer, the calcidiol and calcitriol-degrading enzyme CYP24A1 is substantially overexpressed both on mRNA and protein level. High CYP24A1 levels markedly reduce the half-life of vitamin D metabolites, likely reducing the anti-tumorigenic effects of calcitriol in the tumor. The causes and consequences of this overexpression are not fully understood. Here, we investigated gene amplification of the CYP24A1 locus [20q13.2] as a possible cause of CYP24A1 overexpression and increased proliferation as a consequence thereof. Quantitative real time PCR assays showed that approximately 60% of colorectal tumors carry CYP24A1 gene amplification (n=127). This gene amplification correlated with increased mRNA expression ($p=0.38$, $p<0.001$). Aberrantly high CYP24A1 expression may reduce the anti-proliferative actions of calcitriol and lead to increased proliferation. In our colorectal cancer cohort, CYP24A1 mRNA expression correlated with expression of several proliferation markers (e.g. CDC6 $p=0.60$, $p<0.001$). In conclusion, our data suggest that CYP24A1 gene amplification results in increased mRNA expression in colorectal tumors. Further, high CYP24A1 expression correlates with increased proliferation, possibly caused by an inhibition of the anti-proliferative effects of calcitriol. Tumor specific inhibition of CYP24A1 may provide a future strategy to restore local vitamin D levels and its anti-tumorigenic activities. This work is funded by the FWF grant #P22200-B11