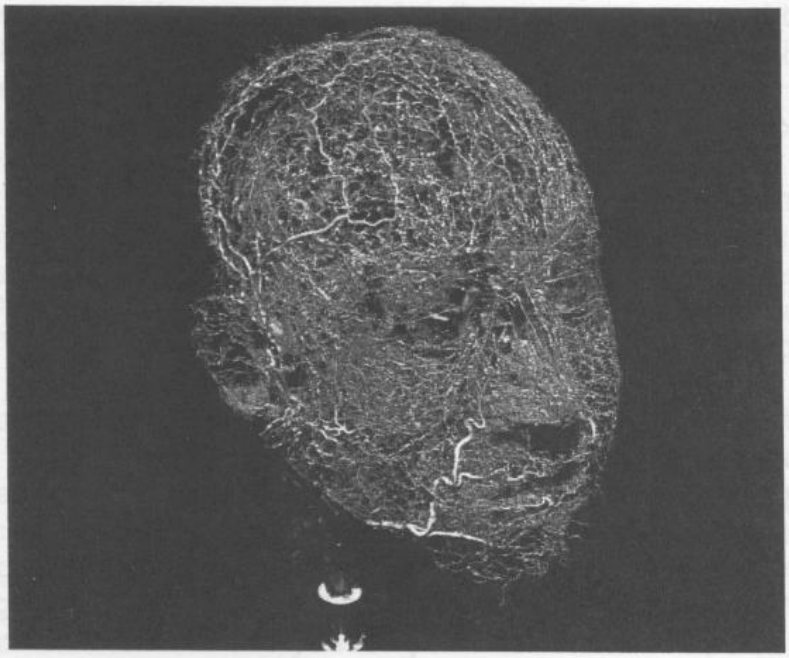
FEBS WORKSHOP

MOLECULAR AND CELLULAR MECHANISMS IN ANGIOGENESIS

Capri, Italy, October 14-17, 2012



Body Worlds Exhibition - Gunther Von Hagens

PROGRAMME & BOOK OF ABSTRACTS

1962 - 2012 IGB CNR

The pattern recognition receptor PTX3 as an angiostatic epithelial/stromal FGF-targeting inhibitor in hormonal cancers

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Fibroblast growth factors (FGFs) exert non-redundant autocrine/paracrine functions in prostate cancer by stimulating angiogenesis and tumor growth. Here dihydrotestosterone (DHT) upregulates FGF2 and FGF8b production in androgen-dependent murine cancer cells, activating a FGF/FGF receptor-dependent autocrine loop of stimulation. The soluble pattern recognition receptor long pentraxin-3 (PTX3) acts as a natural FGF antagonist that binds FGF2 and FGF8b *via* its *N*-terminal domain. Accordingly, recombinant PTX3 protein and the PTX3 *N*-terminus-derived pentapeptide Ac-ARPCA-NH_2 abolished the mitogenic response of prostate TRAMP-C2 and breast S115 tumor cells to DHT, FGF2 and/or FGF8b. Also, PTX3 hampers the angiogenic activity of DHT-activated cells grafted on the chick embryo chorioallantoic membrane (CAM). In keeping with these observations, human PTX3 overexpression inhibits the mitogenic activity exerted by DHT or FGFs on tumor cell transfectants and their angiogenic activity in the CAM assay. Also, hPTX3-overexpressing cells show a dramatic decrease of their angiogenic and tumorigenic potential when grafted in syngeneic or immunodeficient athymic male mice. In keeping with the anti-tumor activity of PTX3 in prostate cancer, immunohistochemical analysis of prostate needle biopsies from primary prostate adenocarcinoma patients showed that parenchymal PTX3 expression, abundant in basal cells of normal prostatic glands, is lost in high-grade prostatic intraepithelial neoplasia and in invasive tumor areas where PTX3 immunoreactivity is confined to the perivascular and intra-peripheral nerve tumor stromal component. These results identify PTX3 as a potent FGF antagonist endowed with antiangiogenic and antineoplastic activity in androgen-dependent tumors, including prostate cancer.

References

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3. *Leali, D., et al. Long pentraxin-3 inhibits FGF8b-dependent angiogenesis and growth of steroid hormone-regulated tumors. Mol Cancer Ther, 10: 1600-1610, 2011.*