PGE-2 induces the angiogenic switch in advanced prostate tumors targeting miR-186

E. Terzuoli[1], F. Finetti[1], A. Giachetti[1], S. Donnini[1] and M. Ziche[1]
[1]Department of Life Sciences, University of Siena, Via Aldo Moro, 2, 53100 Siena, Italy; [2]Istituto Toscano Tumori (ITT), 50136 Florence, Italy

PGE-2 promotes tumor angiogenesis via secretion of proangiogenic growth factors. miRNAs have emerged as key regulators of several cellular processes including angiogenesis; whether miRNAs influence the PGE-2-mediated angiogenesis is unknown. In this work, we investigated whether PGE-2 induces the angiogenic switch in prostate tumors modulating miR-186 expression.

We demonstrated that in prostate cancer cells bearing mPGES-1, mPGES-$1^{+/+}$ cells, PGE-2 signaling modulates miRNAs biogenesis, downregulating miRNAs upstream to angiogenic growth factor expression. Among the miRNAs, miR186 and miR15a, regulator of VEGF and HIF-1Î± expression was repressed. As a consequence, VEGF and HIF-1Î± expression was significantly increased in mPGES-$1^{+/+}$ cells, and in vivo, in nude mice, mPGES-$1^{+/+}$ promoted highly vascularized tumors.

In human prostate tumors, mPGES-1 expression correlates with high Gleason score, VEGF and HIF-1Î± expression, and microvessel density, evaluated by immunohistochemical analysis.

We also observed a weak but negative association among miR-15a or miR-186 and mPGES-1 expression in In human prostate tumors was noted. These miRNAs therefore appear to be elevated in samples with lower levels of mPGES-1 and VEGF, suggesting miR-15a and miR-186 as potential prognostic biomarkers in advanced prostate cancer linking high mPGES-1 levels with enhanced VEGF/angiogenic features.

These results present evidence for a new regulatory mechanism in which PGE-2, by modulating miRNA processing pathway, promotes angiogenesis in prostate tumors.

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