PGE2 induces the angiogenic switch in metastatic castration resistant prostate tumor cells targeting angiogenic miRNA

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In previous works we reported that inflammatory conditions like the ones mimicked by PGE2, modulate the angiogenic switch in several tumors favoring transactivation of EGF and FGF2 receptors and inducing VEGF release (2009, 2010). As a consequence of this cascade of events epithelial tumors become more aggressive and do not respond to target therapy. Angiogenesis is known to play a central role in the progression of prostate cancer. Despite this evidence, inhibition of various angiogenesis pathways and of vascular endothelial growth factor (VEGF) signaling, failed to improve survival in clinical trials. Based on the above we hypothesize that in metastatic castration resistant prostate tumors inflammatory conditions and PGE2 could contribute to modulate angiogenesis and elude treatments.
To contribute to the understanding of the molecular mechanism of PGE-2-regulating angiogenesis in metastatic prostate cancer, we evaluated the effect of PGE-2 on angiogenic and antiangiogenic factors and on the expression of miRNAs relevant for angiogenesis. In prostate cancer cells overexpressing or silenced for the enzyme producing PGE-2, the microsomal PGE synthase-1 (mPGES-1) gene (DU145-SC and DU145-KO, respectively), we showed that tumor PGE-2 increased VEGF release and reduced endostatin levels. Furthermore, genome-wide sequencing of small RNAs revealed angiogenic and anti-angiogenic miRNA associated with DU145-SC, including miR-15a, miR-186, miR-103 and miR-125b, respectively. In vivo, DU145-KD xenograft tumors, showed reduced growth and vascularization when compared to DU145-SC tumors. Together these results demonstrate that PGE-2 mediates angiogenesis in prostate cancer by modulating miRNA expression.

References
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