Role of prostaglandin E2 in EGFR mediated DU145 prostate cancer growth and epithelial mesenchymal transition

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Treatment of patients with metastatic castrate-resistant prostate cancer remains a significant clinical challenge. In prostate cancer, overexpression and over-activity of epidermal growth factor receptor (EGFR) contributes to metastatic progression and correlate with disease relapse, high Gleason score, and advanced stage disease, suggesting that this receptor may be a potential molecular target for prostate cancer treatment (Di Lorenzo et al., 2002, Hammarsten et al., 2007). Nevertheless in several trials, prostate cancer did not respond to EGFR inhibitors.

The pro-inflammatory prostaglandin E-2 (PGE-2) has been shown to modulate the oncogenic EGFR pathways including tumor growth and epithelial mesenchymal transition (EMT) (Donnini et al., 2012, Finetti et al., 2012). In this work, we investigated whether, in prostate cancer, overexpression of microsomal PGE synthase-1 (mPGES-1), the enzyme responsible for PGE-2 production, might be involved in the mechanism of EGFR-mediated tumor progression. By using the DU145 cell line, a model of metastatic castrate-resistant prostate cancer overexpressing EGFR and transfected or silenced for the mPGES-1, we investigated: 1) the involvement of mPGES-1/EGFR signaling cascade on tumor cell progression in terms of EMT and growth, in *in vivo* and *in vitro* studies, and 2) the contribution of mPGES-1 expression to tumor cell responsiveness to the EGFR inhibitor, erlotinib.

Our results show that in DU145 cells overexpression of mPGES-1 correlates with the EMT markers vimentin and fibronectin, increased growth and lack of responsiveness to erlotinib. Consistently, genetic deletion of mPGES-1 resulted in reduced growth of tumors and increased the responsiveness to the EGFR inhibitor erlotinib. These data indicate that mPGES-1 might be a novel marker of progression in prostate cancer.

References

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