O23 Effects of systemic glucocorticoid administration on stromal and epithelial GR signaling with consequences for prostate cancer progression.

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Introduction & Objectives: The major obstacle in management of advanced prostate cancer (PCa) is the occurrence of resistance to endocrine-therapy. Although the androgen receptor (AR) has been linked to therapy failure, the underlying escape mechanisms have not been fully clarified. Being closely related to the AR, the glucocorticoid receptor (GR) has been suggested to play an essential role in therapy resistance. Given that glucocorticoids (GCs) are frequently applied to PCa patients, it is important to unravel the exact role of stromal and epithelial GR signaling for PCa progression and therapy resistance.

Materials & Methods: Global GR expression was assessed in 177 primary prostate tumors as well as in metastatic lesions by immunohistochemistry (IHC). Stromal and epithelial GR target genes were identified in immortalized and primary cancer associated fibroblasts (CAFs) as well as in epithelial PCa cell lines after dexamethasone treatment by microarray analysis. Expression and localization of selected regulated target genes/proteins was confirmed by qRT-PCR, Western-blot, and by IHC in used cell lines and in primary tumor samples cultivated in tissue slice cultures (TSC) in the presence or absences of GCs.

Results: Epithelial GR expression is reduced compared to stromal expression in primary PCa, however, is restored and elevated in metastatic lesions. Microarray analysis revealed a unique stromal and epithelial GR target gene signature, respectively. Interestingly, only a small set of genes was regulated similarly in both compartments. Of note, dexamethasone treatment resulted in GR mediated activation of GR/AR signature genes/proteins in primary hormone naive tumor TSC specimens. Importantly, elevated expression of identified GR down-stream targets could be confirmed in material of neo-adjuvant docetaxel and GC treated patients in comparison to control patients, proofing induced stromal and epithelial GR signaling also in a clinical setting.

Conclusions: Systemic GC administration results in an elevated global GR activation. Identified stromal and epithelial GR mediated target genes might be the underlying source for accelerated PCa progression. Future studies however are needed to further assess the clinical relevance of identified GR targets.