Testosterone and dihydrotestosterone synthesized from DHEA in stromal cells of prostate cancer affect androgen receptor activity

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Background: One of the mechanisms by which advanced prostate cancer (PCa) usually relapses after androgen deprivation therapy (ADT) is the adaptation to residual androgens in PCa tissue. It has been observed that androgen biosynthesis in PCa tissue, the so-called 'intracrine' androgen formation, plays an important role in this adaptation. Aim: To investigate how stromal cells derived from normal prostate and prostate cancer affect adrenal androgen DHEA and to explore its metabolism in androgen-sensitive PCa LNCaP cells. Methods: We cocultured the LNCaP cells transfected with a luciferase reporter (pGL3PSAp-5.8) driven by PSA promoter and commercially available normal prostatic stromal cells (PrSC) or stromal cells from prostate cancer obtained at prostatic needle biopsy (PCaSC). Subsequently, we added DHEA and examined the PSA promoter activity 24 h later by a luciferase assay. Also, we cocultured them using Boyden chamber to examine the effect of DHEA under the coculture on LNCaP growth 4 days after DHEA addition (Fig. 1B). For knockdown of AR in PrSC, we transfected AR siRNA; for knockdown of the AR in LNCaP cells, we transfected shRNA-hAR plasmid. We measured the concentration of androgens (T, DHT, androstenedione, and androstenediol) in culture medium by LC-MS/MS. Results: DHEA alone had little effect on PSA promoter activity and the proliferation of LNCaP cells. However, when LNCaP cells were treated with DHEA in the presence of prostate-derived stromal cells, especially PCa-derived stromal cells (PCaSC), stromal cells accelerated DHEA-induced PSA promoter activity via androgen receptor activation. Moreover, PCaSC stimulated the proliferation of LNCaP cells under physiological concentrations of DHEA. Biosynthesis of testosterone or DHT from DHEA in stromal cells was involved in this acceleration of LNCaP cell proliferation. Androgen biosynthesis from DHEA depended upon the activity of various steroidogenic enzymes present in stromal cells. Conclusions: this coculture assay system provides new insights into 'paracrine' and 'intracrine' androgen biosynthesis under the microenvironment of PCa cells before and after ADT, and offers a model system for the identification of important steroidogenic enzymes involved in PCa progression and for the development of the corresponding inhibitors of androgen biosynthesis.