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Abstract

New Approaches Targeting the Invasive Phenotype of Prostate Cancer-Associated Fibroblasts †

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Abstract: Prostate cancer (PC) is one of the most widespread malignancies among males worldwide. The androgen receptor (AR) drives its development and progression and still represents the main target of PC therapy. Second-generation antiandrogens have, indeed, improved the patient's management. Nonetheless, hormone resistance and tumour progression frequently develop. While the majority of drugs currently used in PC target the AR functions in epithelial PC cells, the role of the receptor in PC-associated fibroblasts (CAFs) and PC progression remains unresolved, and only a few therapeutics affecting the stromal AR functions have been developed so far. By combining several approaches, we have shown that AR associates with Filamin A (FLNa), thus promoting migration and invasion of androgen-challenged CAFs from PC patient's specimens at different Gleason's scores. By using 2D and 3D cultures, we have demonstrated that CAFs move towards epithelial PC cells and promote the increase in PC organoid size. The stapled peptide Rh-2025u disrupts the androgen-triggered AR/FLNa complex assembly and impairs these responses in monolayer cells as well as 3D models. Furthermore, it reduces the overall tumour area in androgen-treated 3D co-culture. Mechanistically, our findings posit that AR/FLNa complex recruits β1 integrin and the membrane type-matrix metalloproteinase 1 upon the androgen challenging of CAFs. The activation of a protease cascade leading to extracellular matrix (ECM) remodelling then follows. Rh-2025u peptide interferes in the assembly of this multimolecular complex and impairs ECM remodelling. As such, CAFs can no longer navigate through ECM. In summary, we propose the Rh-2025u peptide as a new drug, which alone or in combination with other emerging therapies may allow a more rational treatment of PC. Pharmacological blockade of AR functions in CAFs is indeed neglected and the approach we propose would improve the treatment's outcome in PC patients.

Keywords: prostate cancer; carcinoma-associated fibroblasts; invasion; 3D models

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