ABSTRACT FORM

to be sent by e-mail to the Organising Secretariat (elena.delboca@achelois.eu)
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ABSTRACT TITLE

Castration-induced SPARC down-regulation in stromal cells drives neuroendocrine differentiation of prostate cancer

ABSTRACT TEXT (max 2500 characters – including spaces)

Background

Neuroendocrine differentiation (NED) often occurs in a relevant subset of prostate cancer patients as a mechanism of resistance to androgen deprivation therapy (ADT). Tumor cell plasticity toward NED can be sustained by tumor microenvironment. The matricellular protein SPARC is a crucial modulator of cancer progression, exerting different functions depending on its tumor or stromal expression. Here, we elucidated the role of stromal SPARC in NED.

Methods

We modeled human disease using TRAMP mice, which spontaneously develop prostate cancer following the onset of puberty. H&E staining and IHC for SPARC, CK8, SYP and GRP78 and ISH for *miR29b* and IL-6 were performed on prostates isolated from 30-week old TRAMP, castrated TRAMP and *Sparc*$^{-/-}$ TRAMP mice. TRAMP–derived adenocarcinoma cell lines were cultured in transwell with *Sparc*-deficient or proficient fibroblasts, the latter condition treated or not with enzalutamide. Tumor samples from prostate cancer patients undergoing ADT were evaluated for SPARC, GRP78 and NE markers.

Results

Crossing TRAMP mice with *Sparc*-/- mice, we observed the appearance of focal areas of NED. The same percentage of NED was observed in TRAMP mice after castration, but not in untreated counterparts, suggesting that SPARC deficiency and castration converge to the same disease outcome. Accordingly, we found that SPARC expression in stromal cells was strongly reduced in castrated TRAMP mice. Moreover, prostate adenocarcinoma cell lines acquired NE features when cultured in presence of *Sparc*-deficient fibroblasts or when injected in *Sparc*-/- mice. This transition occurs through IL-6 release by *Sparc*-deficient fibroblasts. Indeed, IL-6R targeting limited NED *in vitro* and *in vivo*. We further detailed a tumor-stroma crosstalk triggered by castration in TRAMP mice and mimicked *in vitro* by culturing tumor cells and fibroblasts with enzalutamide. We identified the heat shock protein GRP78 as primer of this crosstalk leading to NED through stromal-SPARC down-regulation induced by miR29b released by tumor. Accordingly, GRP78 targeting strongly reduced NED *in vitro* and *in vivo*. Notably, GRP78 is amplified in human NEPC, correlated with pathways related to NED. Finally, we confirmed GRP78 and SPARC modulation and the focal up regulation of NE markers in paired prostate cancer samples collected before and after ADT in a small cohort of patients.

Conclusions

Our results highlight the pivotal role of stromal components in NED, indicating possible diagnostic and therapeutic targets.

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