The role of the microenvironment in therapeutic response to anti-prostate cancer treatment

Damien A Leach[1], Gilberto Serrano de Almeida[1], Saiful Miah[2], Mathias Winkler[2], Hashim Ahmed[1, 2], Charlotte Bevan[1]

1.Department of Surgery & Cancer, Imperial College London, London W120NN, UK

2.Department of Urology, Imperial Healthcare NHS Trust, Fulham Palace Road, London, W6 8RF, UK

Background:

Cancers do not exist in isolation - surrounding any tumour are supportive cells, which create the microenvironment in which cancer cells reside. Cancer and microenvironment cells interact and communicate with each other, physically and via aparacrine signalling. In the prostate, androgen receptor (AR) signalling in the surrounding fibroblasts is strikingly distinct from that within cancer cells, and has specific functions to produce, maintain, and modulate the extracellular matrix (ECM) which surrounds and interacts with cancer cells. The supportive cells of metastatic sites differ from those in the primary site and produce different types of cellular microenvironments.

Methods:

Bioinformatic analysis was performed to assess expression of AR and its coregulators in primary and metastatic cancer at different sites (bone, lymph node, liver). Explant models were constructed using patient prostate tissue samples from biopsy and transurethral resection, and treated with clinically relevant treatments. Explant models were also created using mouse tissue to assess AR activity and treatment response in the different organs that are associated with prostate metastases. *In vitro* 3D-cultures were created to represent the microenvironments of prostate and metastatic sites. Samples from the in vitro and explant models were assessed for mRNA and protein levels.

Results:

Dichotomising microdissected patient material of matched cancer and stromal tissue, based on stromal AR level shows distinct transcriptional profiles in the matched cancer cells. Bioinformatics analysis of prostate cancer and metastases at different sites, and cells of the different metastatic sites, identified differential expression of AR, nuclear receptor coregulators, and integrin and cell surface receptors associated with internalising extracellular signals. In mouse tissue, the liver, bone and lung showed differences in AR signalling and treatment response compared to prostate. Using *in vitro* 3D-models, LNCaP and C4-2B cells showed differences in gene transcription and androgen regulation, as well as differences in proliferation and apoptotic markers, dependent on which organ the microenvironment components they were cultured in was derived from.

Conclusions:

Different microenvironment cells and components are associated with different responses and behaviours, notably altered AR signalling, in the prostate cancer cells they contact. This suggests that treatments will have different effects in different metastatic sites, and in metastatic compared to primary sites, which may be of particular importance for patients with visceral disease where prognosis is worse.

Conflict of Interest:

No conflict of interest to declare

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