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Prostatic proliferative inflammatory atrophy: welcome to the club†

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Abstract

Single cell RNA sequencing studies in the human prostate have defined a population of epithelial cells with transcriptional similarities to club cells in the lung. However, the localization of club-like cells in the human prostate, and their relationship to prostate cancer, is poorly understood. In a new article in the Journal of Pathology, RNA *in situ* hybridization was used to demonstrate that club cell markers are expressed in luminal cells adjacent to inflammation in the peripheral zone of the human prostate, where prostate cancer tends to arise. These club-like cells are commonly found in Proliferative Inflammatory Atrophy (PIA) lesions and express markers consistent with an intermediate epithelial cell-type. Future studies will be needed to understand the functional role of club-like cells in human prostate inflammation, regeneration and disease.

Keywords

Prostate; inflammation; cancer

Chronic inflammation is a potential risk factor for prostate cancer [1]. In the benign human prostate, glands adjacent to areas of chronic inflammation exhibit increased proliferation despite an atrophic morphology, termed Proliferative Inflammatory Atrophy (PIA). These inflammation-adjacent glands are hypothesized to be precursor lesions for prostate cancer

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[2]. The phenotype of the cells that reside in these PIA lesions and their role in prostate cancer initiation is of considerable interest.

The prostate epithelium is comprised primarily of luminal cells, which line the interior of the secretory ducts, and basal cells, which contact the extracellular matrix. Single cell RNA sequencing (scRNAseq) studies of normal human prostate tissues have defined greater complexity of cell-types [3], including the identification of a population of epithelial cells that transcriptionally resemble lung club cells. Huang and colleagues [4] set out to identify the localization of prostate club cells and assess their relationship to prostate adenocarcinoma using chromogenic RNA *in situ* hybridization (RISH) in both healthy and diseased prostate.

To define the precise location of club cells in human prostate tissue, Huang *et al.* assessed five marker genes (polymeric immunoglobulin receptor (*PIGR*), lactoferrin (*LTF*), matrix metallopeptidase 7 (*MMP7*), Ceruloplasmin (*CP*), and secretoglobin Family 1A Member 1 (*SCGB1A1*)) commonly associated with lung club cells. Although these markers were present in multiple regions of the prostate, there was considerable heterogeneity in their expression patterns. The authors identified uniform expression of *CP* and *PIGR* along the prostatic urothelium, with co-expression of the other markers (*LTF*, *MMP7*, *SGCB1A1*) in only a subset of urothelial cells and periurethral prostatic glands. Importantly, in the peripheral zone of the prostate (where most prostate cancers arise), expression of the club cell genes was limited to luminal epithelial cells in focal atrophy/PIA both in benign regions and admixed with prostate cancer, as well as in post atrophic hyperplasia (a distinct subset of focal atrophy). Here, *PIGR* and *LTF* were uniformly expressed in atrophy lesions, with variable co-expression of *CP*, *MMP7*, and *SCGB1A1*.

The most frequent genomic event in localized prostate cancer is the fusion of the androgen-regulated promoter of Transmembrane Protease Serine 2 (*TMPRSS2*) with the transcription factor ETS Related Gene (*ERG*) [5], resulting in overexpression of ERG. Sfanos and colleagues previously identified bacterial infection-associated ERG^+ PIA lesions transitioning into early invasive adenocarcinoma [2]. Here the authors found two club cell markers, PIGR and LTF, in PIA regions adjacent to ERG^+ PIA and early invasive adenocarcinoma, but only PIGR was expressed in cancer lesions. Additionally, through analysis of young organ donor tissue and radical prostatectomy samples, the authors found $PIGR^+$ cells to be largely absent in non-cancerous tissue, aside from regions of PIA. Accordingly, cancer-adjacent benign tissue (where PIA is most prevalent) exhibited a higher proportion of $PIGR^+$ cells than cancer regions and benign glands from healthy donors, which was consistent across multiple genetic ancestries.

The authors also found that $PIGR^+$ cells in PIA lesions shared characteristics of previously reported intermediate epithelial cells [6]. Importantly, these $PIGR^+$ cells displayed low androgen receptor (AR) and CD38 (consistent with CD38-low progenitor-like luminal cells [7]), and high expression of both basal and luminal lineage markers (Figure 1). Finally, the authors generated epithelial organoids from radical prostatectomy tissue samples taken from patients of distinct ancestries. Through scRNA-seq of these patient derived organoids, the authors identified a subset of cells expressing club cell markers. Interestingly, both the

club-like and other epithelial cell populations appeared responsive to androgen deprivation and AR inhibition.

Club cells serve a protective and regenerative role in the lung through the secretion of anti-microbial and anti-bacterial proteins [8]. While prostate club cells share several markers with lung club cells, future studies will be needed to clarify the functional similarities or differences between these groups. Prostate tumors are generally considered immunogenically “cold” with minimal infiltration of immune cells, likely due to an immunosuppressive tumor microenvironment [9]. Given that prostate club cells are more abundant in PIA lesions than in adenocarcinoma, determining how club cells modulate the immune environment in normal and diseased prostate will be crucial. As prostate cancers are often driven by aberrant AR signaling, it will also be important to clarify the extent to which club cells rely on AR for their proliferation and function.

Previous work has indicated that cells with intermediate luminal epithelial characteristics are capable of serving as tumor-initiating cells for prostate adenocarcinoma [7]. Further investigation into the tumorigenic capacity of PIA-associated prostate club cells is essential for understanding their role in facilitating human prostate cancer initiation. While the authors report that cells with intermediate epithelial expression patterns also express club cell markers, as evidenced by RISH and scRNA seq, there is still considerable heterogeneity in the club cell and other epithelial lineage markers.

Further, we have demonstrated an age-related increase in the proportion of progenitor-like luminal cells in the prostate [10]. It is possible that the abundance of $PIGR^{+}$ club cells in the diseased prostate is associated with this expansion. Identifying the progenitor cell populations that give rise to prostate club cells may help elucidate the mechanisms driving the abundance of club cells in older, diseased prostates.

In summary, Huang *et al.* have defined the spatial localization of club cells in young, healthy prostate and in older, diseased prostate [4] (Figure 1). Future work should functionally characterize the role of prostate club cells to better understand (1) how they regulate prostatic immune cell infiltration, (2) whether they contribute to tumor initiation and progression, and (3) what mechanisms underlie their increased frequency in older patients and adjacent to prostate tumors.

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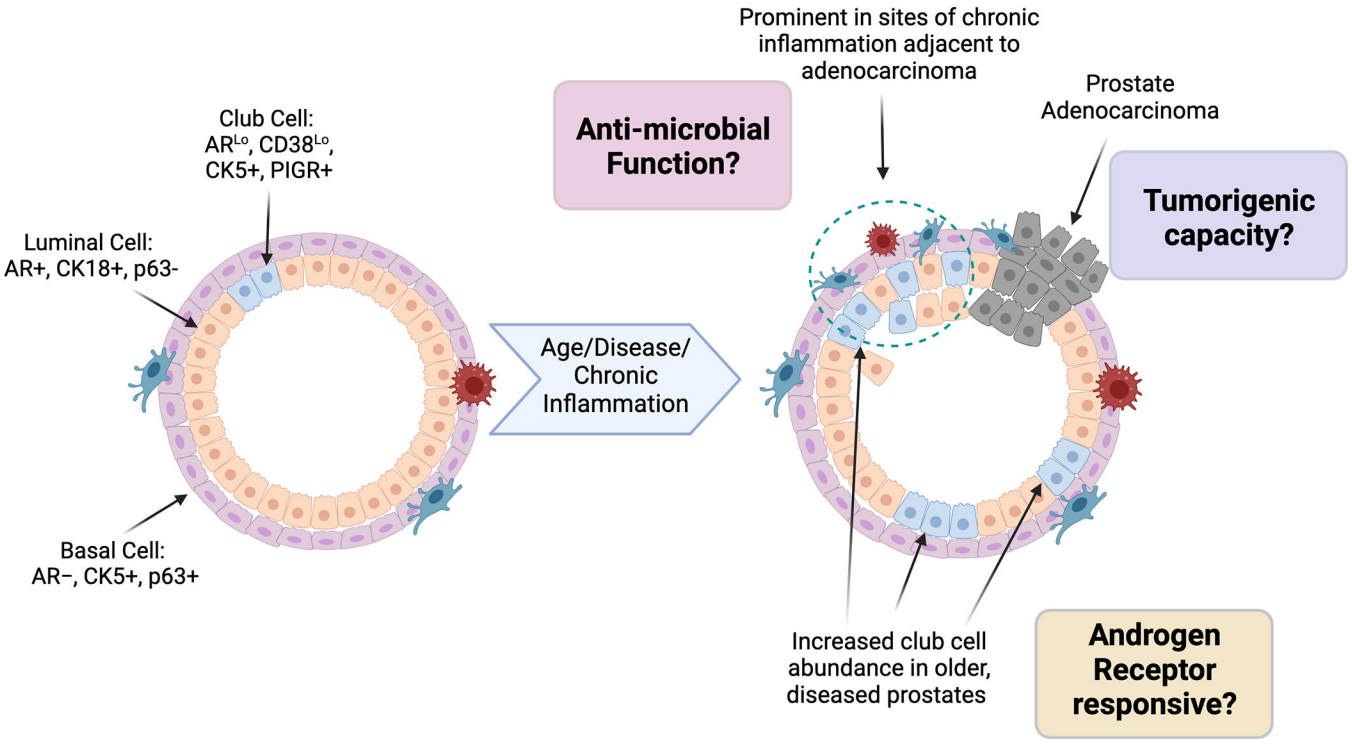

Figure 1.

Schematic representing the increase in PIGR^{+} club-like cells associated with age, disease and inflammation in the human prostate. Basal cells are shown in purple. Luminal cells are shown in orange. Club-like cells are shown in light blue. Immune/inflammatory cell-types are shown in red and teal around the outside of glands. Tumor cells are shown in grey. Dotted line on the right represents regions of Proliferative Inflammatory Atrophy (PIA) with a high proportion of club-like cells. Questions for future research about the function, tumorigenic capacity, and reliance on androgen receptor signaling are indicated. This figure was generated in BioRender.