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AUTHOR'S VIEW

Functional evidence that progenitor cells near sites of inflammation are precursors for aggressive prostate cancer

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ABSTRACT

While chronic inflammation has been causally associated with several epithelial malignancies, whether it causally contributes to the development of prostate cancer has remained unclear. We recently reported that progenitor-like inflammation-associated luminal cells marked by low expression of Cluster of Differentiation 38 (CD38) can initiate human prostate cancer and predict poor outcome.

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In 2016, an estimated 180,890 new cases of prostate cancer will be diagnosed, and approximately 26,120 men will die of the disease.[1] Despite extensive research efforts, the prevalence of prostate cancer remains a mystery. Chronic inflammation has been causally associated with the development of epithelial malignancies such as stomach, large intestine, liver, and urinary bladder cancers. Recent studies have identified an association between inflammation and the development of prostate cancer.[2]

De Marzo, Nelson, and colleagues have reported changes in the morphology of epithelial cells associated with chronic inflammation in the human prostate known as proliferative inflammatory atrophy (PIA).[3] Luminal cells in PIA have an atrophic appearance, exhibit an imbalance between proliferation and apoptosis, and show signs of oxidative stress. Additionally, these cells show an increase in the anti-apoptotic factor B-cell lymphoma 2 (BCL2) and a decrease in androgen receptor (AR) signaling. PIA is commonly observed in close spatial proximity to premalignant and malignant tissue, suggesting that PIA may represent a precursor to prostate cancer.[3] However, the functional role of these cells in prostate cancer had not been investigated due to an inability to isolate PIA-like and non-PIA epithelial cells from viable human prostate tissue.

We identified a unique population of luminal cells marked by low expression of Cluster of Differentiation 38 (CD38lo) that exhibit many hallmarks of cells associated with PIA, including increased BCL2 expression and reduced androgen signaling.[4] Gene expression analysis of CD38lo cells revealed enrichment of many inflammatory-related genes, and immunohistochemical staining of human prostate tissue confirmed that CD38lo luminal cells are predominantly localized in glands adjacent to inflammation.

Having established that CD38lo luminal cells represent an inflammation-associated cell population with hallmarks of PIA, we sought to assess their proliferative potential in three progenitor assays (colony-forming, sphere-forming, organoid-forming). CD38lo luminal cells isolated from freshly dissociated primary human prostate tissue exhibited a level of progenitor activity in between the stem-like basal cells and the differentiated CD38hi luminal cells. Importantly, the inflammation-associated CD38lo luminal cells represent an enriched luminal progenitor subset.

In previous studies, we have shown that basal cells from human prostate tissue can generate tumors following oncogenic transformation.[5] In contrast, *ex vivo*-expanded luminal cells only give rise to indolent-like tumors with limited proliferative potential.[6] In our recent study, CD38lo luminal progenitor cells were lentivirally transduced with oncogenes (Myc, AKT1, and AR), expanded in organoid culture, and transplanted subcutaneously with Matrigel and urogenital sinus mesenchyme cells into immune-deficient mice. Transplanted oncogene-expressing CD38lo luminal cells developed features of highly proliferative prostate adenocarcinoma, suggesting that they can initiate aggressive human prostate cancer *in vivo*.[4]

Our development of an approach to isolate PIA-like luminal cells based on low expression of CD38 allowed us to functionally test their capacity. Our demonstration that PIA-like luminal cells isolated from human prostate tissue can initiate prostate cancer[3] provides functional evidence to support the model that PIA may represent a precursor to prostate cancer (Fig. 1). Furthermore, our ability to isolate PIA-like luminal cells allowed us to profile and characterize them in a deeper way than in previous studies. We can now show that PIA-like cells exhibit elevated nuclear factor kappa B (NF-kB) signaling,[4], which has been associated with aggressive prostate cancer.[7] Moreover, since CD38lo cells display decreased androgen signaling and elevated BCL2 expression, they would be predicted to respond poorly to hormonal therapy.

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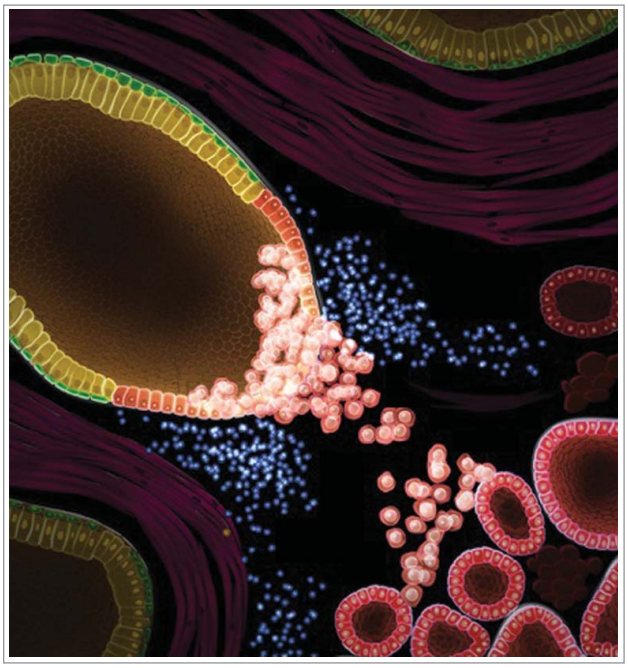

Figure 1. Initiation of aggressive prostate cancer by oncogene-expressing Proliferative Inflammatory Atrophy (PIA)-like luminal cells. PIA-like luminal cells (red) are associated with regions that contain inflammation (blue). When lentivirally transduced with oncogenes (Myc, AKT1, and androgen receptor), these cells expand and can initiate aggressive prostate cancer (bottom right corner). Visualization by Kandeo Studios.

Previous studies in mouse models have demonstrated that acute inflammation promotes an expansion of progenitor-like cells,[8] and an increase in basal-to-luminal differentiation.[9] While we show that PIA-like luminal cells are enriched in regions of inflammation, an inability to study kinetic processes in human tissue prevents us from uncovering the sequence of events that links inflammation and PIA-like luminal progenitor cells. Serial biopsies of benign human prostate tissue containing chronic inflammation may help uncover the precise order of events involved in PIA. Interestingly, our gene expression analysis revealed that PIA-like cells upregulate several pro-inflammatory cytokines and chemokines,[4] suggesting that PIA-like cells may actively recruit inflammation. The assays used to measure progenitor activity require that epithelial cells be removed from their native environment, dissociated into single cells, and grown in a culture system lacking several of the key cell types found in the prostate microenvironment including inflammatory cells. We hope that future studies will be able to incorporate more of these microenvironmental cell types and may enable us to study the influence of inflammation on human prostate epithelial development and malignant transformation in culture.

A key goal of prostate cancer research is to uncover the biology that drives aggressive prostate cancer to allow us to distinguish indolent from aggressive disease and develop therapeutic targets to treat advanced stage disease. In this study, we illustrate that low *CD38* mRNA levels in prostatectomy specimens from two separate cohorts are prognostic for biochemical recurrence, suggesting that CD38lo aggressive cancers may arise from PIA-like CD38lo luminal cells. Given that CD38lo luminal cells and CD38lo tumors exhibit progenitor-like features, we hypothesize that CD38 loss may be functionally significant. CD38 consumes cellular nicotinamide adenine dinucleotide (NAD),[10] suggesting that loss of CD38 may increase the pool of NAD available for cellular metabolism in CD38lo luminal cells and CD38lo prostate cancer. Future studies should investigate if an increased pool of NAD provides CD38lo luminal cells with a proliferative advantage. Finally, NF-kB signaling and other signaling pathways found to be important in CD38lo luminal cells should be investigated as therapeutic targets to prevent the initiation and progression of CD38lo luminal cell-derived aggressive prostate cancer.

Disclosure of potential conflicts of Interest

No potential conflicts of interest were disclosed.

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