

# Racial disparity in prostate cancer: Biomarkers for prognosis and therapy



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## ABSTRACT

**Background.** African-American (AA) men have higher incidence and mortality from prostate cancer compared to Caucasian-American (CA) men. Despite these recognitions, precise causes underlying such prevalent racial disparities remain poorly understood. The stromal microenvironment has emerged as a key player in the development and progression of cancer regulating the inflammatory signaling pathways. In our recently published study (Clin. Cancer Res. 26:1915-1923, 2020) we have demonstrated the role of stroma in driving aggressiveness in AA prostate cancer patients prognostic of tumor recurrence. Here we investigate an association between CXCR4 expression and prognosis related to racial disparity and prostate cancer.

**Methods.** Fresh frozen and paraffin-embedded sections were obtained post-surgery and expression of CXCR4 and its associated molecules were determined in both AA and CA specimens. Western blotting was performed for CXCR4, IL-6 and MMP9 and CK18 as epithelial loading control in prostate cancer AA men and matched Gleason score from CA men of Gleason score 6-8.

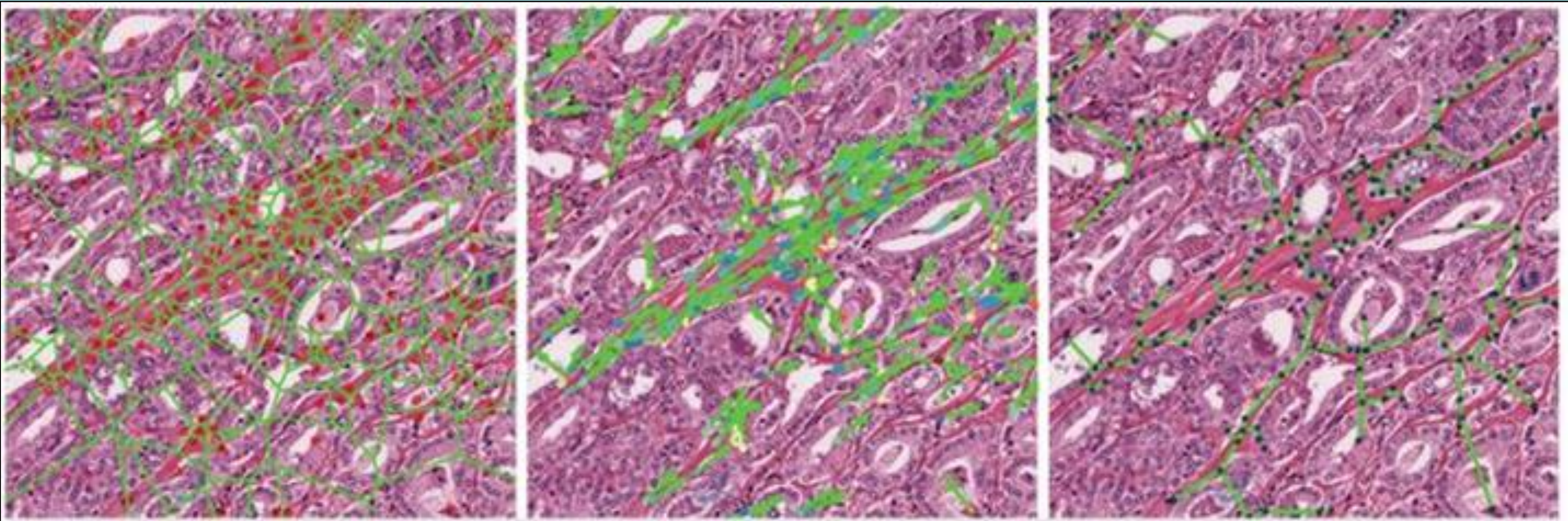
**Results.** A marked increase in the expression of CXCR4, IL6 and MMP9 were noted in AA-prostate cancer specimens compared to CA tumors. We also evaluated the pathological grade, metastasis, and patient prognosis. CXCR4 staining was moderate to strong in the prostate cancer from AA men compared to CA men with moderate to weak expression which positively associated with tumor progression. These observations are consistent with the evidence that the tumor-adjacent stroma heavily influences prostate cancer aggressiveness in AA patients which is different from the CA men.

**Conclusions.** CXCR4 expression appears to be distinctly different in prostate cancers from AA and CA men. We suggest CXCR4 as a useful prognostic marker and therapeutic target for racial disparities of prostate cancer.

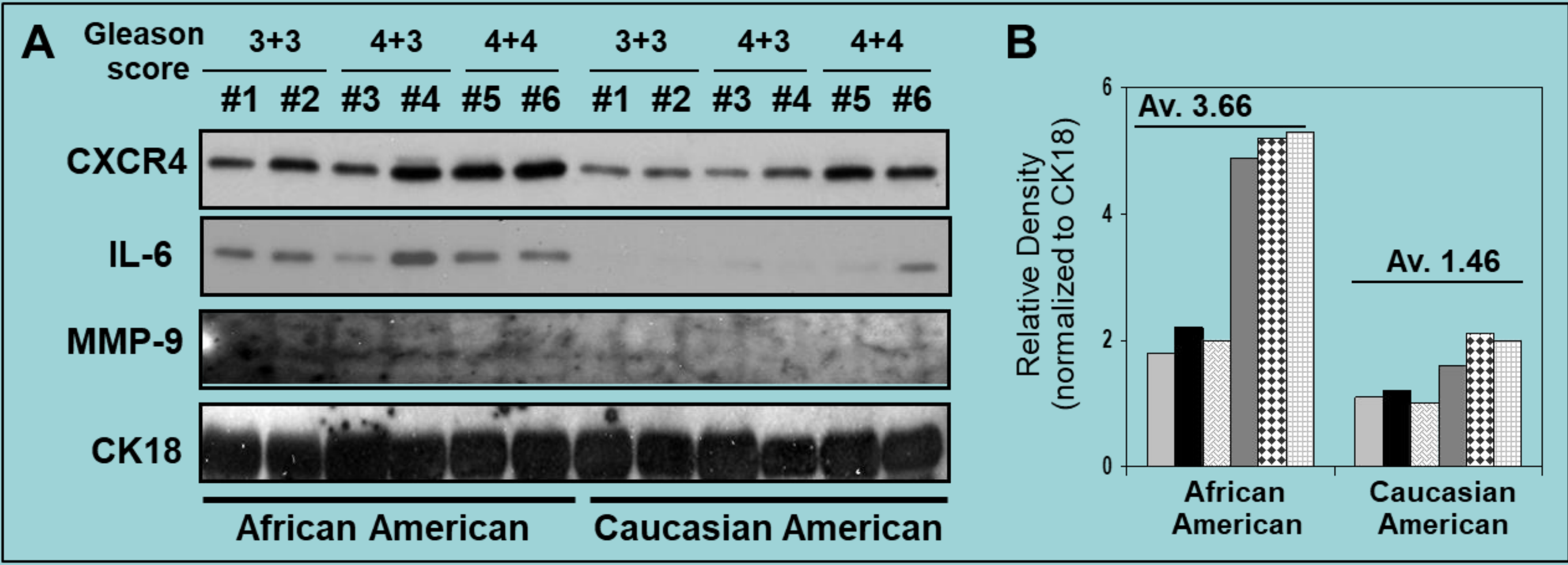
## ACKNOWLEDGEMENTS

The research work is supported by the Department of Defense grant W81XWH-18-1-0618 and W81XWH-19-1-0720 to SG.

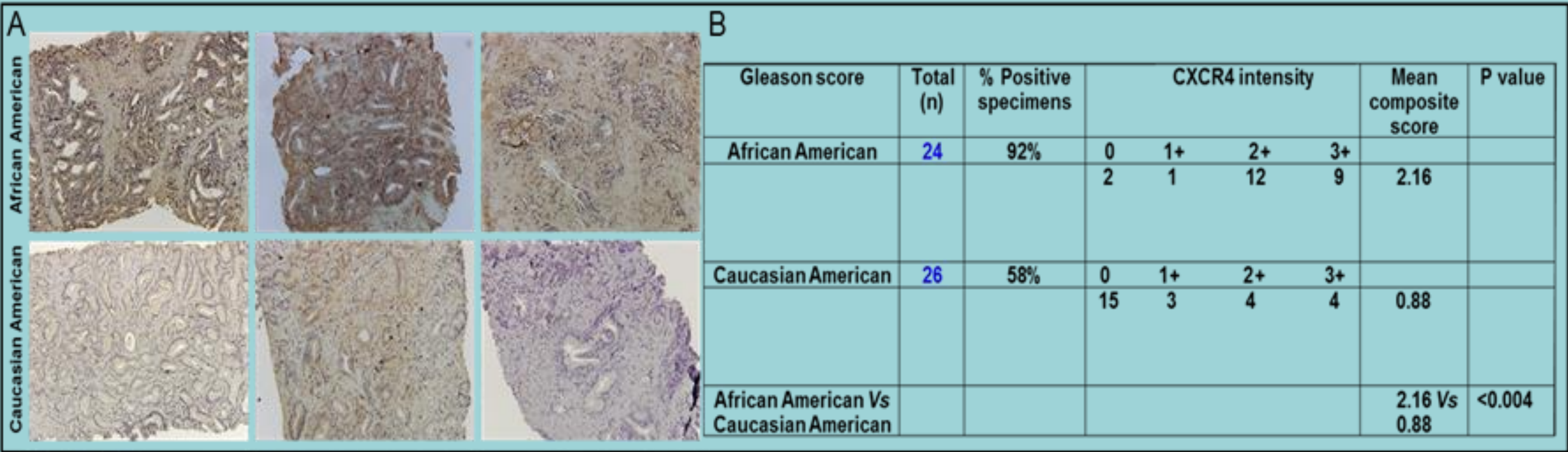
## RESULTS



**Figure 1.** Quantitative histomorphometry of stromal morphology. Automatic analysis of stromal texture, stromal nuclear shape, arrangement and orientation. (Adapted from Bhargava et al. Clin Cancer Res 2020;26:1915-1923).



**Figure 2.** Expression of CXCR4, p-Akt, total Akt, p-S6K and MMP9 in representative PCa specimens from AA and CA men. (A) Protein expression in PCa specimens was analyzed by Western blotting, and (B) Densitometric analysis for CXCR4.



**Figure 3.** Expression of CXCR4 in prostate tumor specimens from AA and CA human subjects. (A) paraffin-embedded sections of prostate cancer from AA and CA men were used for CXCR4 expression by immunohistochemistry. A strong staining pattern was observed in AA tumor specimens compared to CA specimens. (B) CXCR4 expression was highly significant after adjusting for race ( $P < 0.004$ ) – with strong the CXCR4 expression in AA men. Expression scale 0-not expressed, 1-weak, 2-moderate, and 3-strong.

## MATERIALS AND METHODS

**Stromal detection and segmentation.** Stroma were segmented using a previously developed deep learning method based on convolutional neural networks.

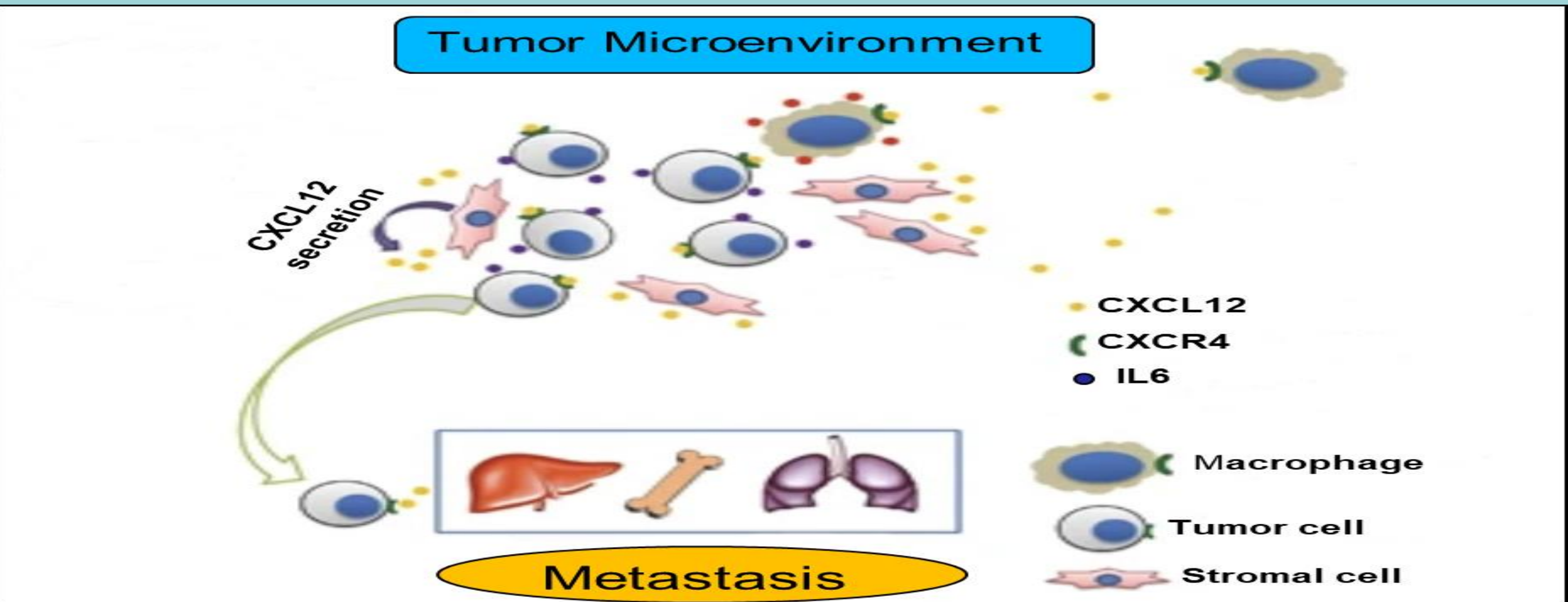
**Western blotting.** Sample underwent protein denaturation, followed by gel electrophoresis.

**Immunohistochemistry.** IHC was performed according to standard protocol.

## CONCLUSIONS

❖ CXCR4 is differentially expressed in higher levels in the prostate tumors of African-Americans (AA) compared to Caucasian-Americans (CA).

❖ High immunoreactivity of CXCR4 in prostate cancer of AA patients suggests that CXCL12 binds to its unique receptor CXCR4 at the membrane, translocates to the nucleus and then becomes more invasive, and thus can be considered a prognostic factor.



**Figure 4.** CXCL12 can induce CXCR4-positive (CXCR4 (+)) cancer cells and CXCR4 (+) stromal cells to secrete growth factors and cytokines and recruit CXCR4 (+) cancer cells to initiate distant metastasis. CXCL12 can induce CXCR4 (+) cancer cells to secrete IL-6, and many other growth factors and cytokines. CXCL12 is physiologically expressed mainly by mesenchymal stromal cells in various organs, such as the liver, lungs and BM. CXCR4 (+) cancer cells can be recruited to these CXCL12-rich mesenchymal stroma niches to initiate metastasis.