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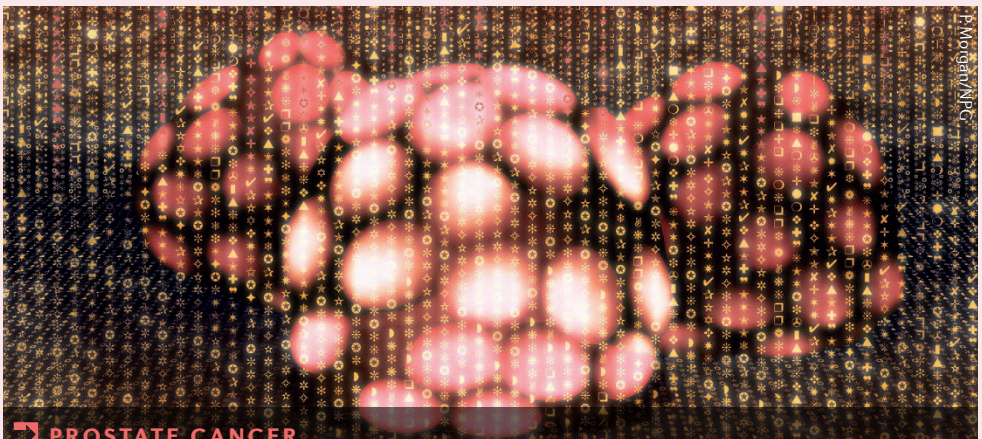

PROSTATE CANCER

A glitch in the extracellular matrix

> collagen 1 fibres in normal and normal adjacent tissue had a more random orientation

Characterization of the structure and function of the extracellular matrix microenvironment that facilitates prostate cancer metastasis has been performed. The differences observed between the extracellular matrix that surrounds poorly metastatic tumours and tumours that readily metastasize could be used as a prognostic tool for patients with this disease.

Zaver M. Bhujwalla, corresponding author, told *Nature Reviews Urology* "Metastatic prostate cancer continues to present a major challenge in prostate cancer treatment. A compelling need exists to understand the metastatic cascade in prostate cancer so we can design effective interventions to prevent metastasis."

In order to gain understanding into the metastatic cascade, Penet and colleagues developed xenografts from the same prostate cancer cell line grown subcutaneously in mice and implanted them either subcutaneously or orthotopically for investigation. Mice with orthotopically implanted tumours frequently developed metastases, but subcutaneously implanted tumours did not metastasize as readily.

Ex vivo analysis of collagen 1 fibres on tumour slices showed differences in overall and normoxic region fibre volume, with orthotopic tumours having significantly more collagen 1 than subcutaneous tumours. Collagen 1 gene expression was also increased by fivefold to sevenfold in orthotopic xenografts compared with subcutaneous xenografts, according to microarray data.

In vivo, MRI showed that orthotopic tumours had significantly higher vascular volume, percentage of pooling voxels and total pooling voxels and significantly lower efflux and influx rates than subcutaneous tumours.

Cancer-associated fibroblasts (CAFs) are the main source of collagen 1 in tumours, and immunohistochemical and immunoblot analyses of actin, aortic smooth muscle (also known as α smooth muscle actin) expression — a marker of CAFs — showed that orthotopically implanted tumours had more CAFs than subcutaneously implanted tumours. Expression of transforming growth factor β, which is known to increase collagen 1 production, was also increased in orthotopic tumours.

Second-harmonic-generation microscopy of human prostate cancer tissue microarray samples confirmed that they contained collagen 1 fibres. The volume of collagen 1 fibres was similar in biopsy samples from normal, normal adjacent, and malignant tissues from prostate cancer that had not metastasized and cancer that had metastasized. However, microscopic imaging revealed the pattern of the fibres was notably different between malignant and nonmalignant tissue, which was confirmed by the difference in aspect ratios on Fourier analysis.

The aspect ratios of malignant tissue from disease with or without metastasis were significantly different from those of normal and normal adjacent tissue. Furthermore, significant differences in aspect ratios were obtained between malignant tissues with metastasis and malignant tissues without metastasis. Collagen 1 fibres in biopsy samples from malignant tissue with metastasis had preferential alignment compared with malignant tissue without metastasis, normal tissue and normal adjacent tissue — collagen 1 fibres in normal and normal adjacent tissue had a more random orientation.

Bhujwalla concluded: "For the first time, we have identified significant differences in collagen 1 fibre patterns in a tissue microarray of human prostate cancers. These results highlight the role of CAFs in supporting or creating aggressive cancers, and the importance of developing strategies to deplete CAFs in prostate cancer. Significant differences in macromolecular transport, collagen 1 fibre patterns and CAF infiltration were observed. These factors all merit further development as biomarkers for prostate cancer prognosis."

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ORIGINAL ARTICLE Penet, M.-F. *et al.* Structure and function of a prostate cancer dissemination permissive extracellular matrix . *Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.CCR-16-1516 (2016)