Editorial

Periprostatic adipose tissue interacts with prostate cancer to promote aggressive disease

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Prostate cancer is now the most commonly diagnosed cancer among men in the developed world and is responsible for a significant number of cancer deaths each year (1). It has become increasingly clear that the epithelial component of the tumour itself is not the only aspect of the disease that determines clinical outcomes. It is now known that many different aspects of the tumour microenvironment are contributing to prostate cancer development and severity. Alterations in the number and/or phenotype of fibroblasts, adipocytes and many types of leukocytes have each been linked to the tumour microenvironment as well as disease outcomes in several cancer types, often in both oncogenic and tumour suppressing roles. For instance, fibroblasts can be reprogrammed by cancers to contribute to proliferation and invasion while tumour-associated macrophages have been demonstrated to suppress T-cells and promote angiogenesis and tumour cell dissemination (2,3). Macrophage infiltration is associated with poor prognosis in breast, gastric, cervix and prostate cancers (4,5), whilst infiltration of cancer by cytotoxic T-cells and natural killer cells is often associated with better cancer outcomes.

Against the broader backdrop of the tumour microenvironment, body weight, adipocytes, and the periprostatic adipose compartment have recently been gaining increasing attention in prostate cancer studies. Obesity is a known risk-factor for developing at least 9 different cancers and approximately 20% incidence of these particular cancers across Europe and North America are directly attributable to obesity (6). While not associated with incidence, obesity has long been positively linked to the aggressiveness of prostate cancer (7). A pooled analysis of 11 prospective and case-control studies found that obesity is correlated with a 25% increased risk of developing high-grade cancer as well as a 25% increased risk of prostate cancer mortality (8). Obesity-driven inflammation and upregulation of inflammatory-cytokines have also been associated with prostate cancer progression (9). However, there remains controversy surrounding whether obesity affects prostate cancer by making it harder to detect, thus presenting at a more advanced stage, or whether the metabolic phenotype and chronic inflammation of obesity has a direct impact on prostate cancer progression. A recent study by Chow *et al.* which compared the expected PSA, based on tumour characteristics, of obese prostate cancer patients with their observed PSA levels found that obesity-related suppression of PSA secretion accounted for a threefold reduction in expected serum PSA levels, and the resulting diagnostic bias was responsible for the poorer cancer outcomes in obese patients(10). This observation is consistent with reports that obese men have a lower risk of being diagnosed with low-grade prostate cancer (8).

Beyond obesity, a number of studies have found that increased volume or adiposity of periprostatic adipose tissue (PPAT) is significantly associated with Gleason score and other pathological markers of prostate cancer aggressiveness (11-14). Furthermore, when examined by microarray and

RNA sequencing, PPAT was found to express significantly distinct sets of genes in patients with prostate cancers of different clinical severities with several genes associated with inflammation, including *CXCL2*, *SELE*, and *SOCS3*, found to be upregulated (15,16). In further examining the interaction between PPAT and prostate cancer it has been shown that adipokines secreted from PPAT can directly influence cancer growth and aggressiveness. As early as 2009, Finley *et al.* cultured PPAT from radical prostatectomy specimens and demonstrated that PPAT from cancers with a Gleason score ≥8 secreted significantly higher levels of interleukin-6 (IL-6) than PPAT from low Gleason score cancers (17). The higher levels of IL-6 also correlated with increased STAT3 phosphorylation in these tissues, which is linked to cell cycle progression, invasion, and immune evasion and is known to be aberrantly regulated in prostate cancer (18). Leptin, another adipokine, also stimulates prostate cancer growth and proliferation and is known to be secreted by PPAT and upregulated in obesity reinforcing the idea that PPAT can influence prostate cancer outcomes (19,20).

To extend these findings, Dahran *et al.* investigated the association of PPAT expression of the inflammatory adipokine tumour necrosis factor alpha (TNFα) and the angiogenic adipokine vascular endothelial growth factor (VEGF) with prostate cancer Gleason score and pathological tumour (pT) staging. First the authors examined immunohistochemical (IHC) staining for TNFα, VEGF and androgen receptor (AR) in the PPAT from 69 radical prostatectomy patients with localised prostate cancer. TNFα and VEGF were both present at significantly higher levels in cancers of Gleason score ≥7 than in their Gleason 6 or below counterparts (P=0.001 and P=0.004, respectively). TNFα was also significantly associated with pT stage, with patients with pT3 cancers having significantly more TNFα in their PPAT than patients with pT2 cancers (P=0.047). This active role of PPAT adipokines in prostate cancer outcomes confirms observations that access to PPAT is a more important determinant of cancer outcome than an invasive phenotype (21). This role is also supported by a study from Ribeiro *et al.* that found that co-culturing PPAT with prostate carcinoma cultured media induced the secretion of adipokines associated with cancer progression including osteopontin, TNFα and IL-6, indicating both the important role of adipokines in prostate cancer and also the communication across the microenvironment (22).

PPAT has also previously been investigated in search of an accurate prognostic marker to determine whether patients are at risk of prostate cancer mortality at the time of diagnosis. In one study, Mangiola *et al.* were able to generate a gene signature from PPAT that was able to determine prostate cancer severity on a cohort of localised disease with a sensitivity of 0.72 (15). Dahran *et al.* also examined the predictive ability of PPAT VEGF and TNFα levels using a ROC curve analysis. TNFα provided a sensitivity and specificity of 74.6% and 100% and VEGF detected at 85.7% and 100% respectively. Interestingly among patients that were classified as Gleason ≤6 at biopsy 70% were found to have Gleason ≥7 cancer at prostatectomy. Comparison of these 20 patients that had presented as Gleason ≤6 at biopsy found that the 14 patients that were subsequently upgraded to Gleason ≥7 had significantly higher levels of VEGF in PPAT than those that had been correctly categorised (P=0.013). TNFα mirrored this trend but did not reach statistical significance. This suggests that detecting high levels of VEGF or TNFα in biopsy specimens may indicate the presence of Gleason ≥7 disease and may have prognostic applications.

Dahran *et al.* have confirmed that adipocyte mediated TNFα expression is associated with prostate cancer aggressiveness, and have also indicated the importance of PPAT secreted VEGF for the first time. However, like similar studies, their data suffers from small sample size, with only 6 patients in their Gleason ≤6 cohort, which suggests the need to confirm these observations in a larger cohort to ensure these observations are robust across the pathological spectrum of prostate cancer. Additionally, the separation of the cohorts into Gleason ≤6 and Gleason ≥7 fails to account for well-characterised differences in disease outcomes observed between Gleason 7 and Gleason ≥8 cancers, perhaps reducing the prognostic power of these data. Even when the high-grade cohort was divided into Gleason 3+4 and Gleason ≥4+3 there was significant overlap in the levels of TNFα and VEGF between the two cohorts which brings into question whether a threshold to separate these groups could be defined. A further challenge to developing a prognostic assay can be seen in the anatomical location of fat tissue sampled by Dahran *et al.* Although not explicitly stated, PPAT used for this analysis appears to be immediately adjacent to the posterolateral prostate surface. This PPAT would be difficult to accurately biopsy, and it is unclear what impact increased distance between tumour and biopsied PPAT would have on the signal of a prognostic assay. In this case, biopsy of the anterior fat pad is probably more feasible and whether PPAT from this location displays the same metabolic activity would need to be confirmed in a

further study.

In conclusion, understanding the interactions between cancers and their microenvironments is still a relatively new area of study, especially the contribution of adipocytes and cancer-adjacent adipose tissue. That PPAT is contributing to prostate cancer outcomes is clear from many existing clinical studies and yet the exact role of adipose cells in prostate cancer progression is still unknown. Here, Dahran *et al*. contribute to the growing evidence that secreted factors from PPAT are directly influencing prostate cancer development. Due to the continued need for accurate prostate cancer prognostics these data highlight the increasing signs that PPAT is a valuable resource for predicting prostate cancer outcomes.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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