Fat talks: a new role for adipose tissue in promoting prostate cancer in obesity

Matthew J. Watt, Renea A. Taylor

Department of Physiology, Metabolic Disease and Obesity Program, and Cancer Program of the Biomedical Discovery Institute, Monash University, Clayton, Victoria, Australia

Correspondence to: Matthew J. Watt, PhD; Renea A. Taylor, PhD. Department of Physiology, Monash University, Clayton, Victoria, 3800, Australia. Email: matthew.watt@monash.edu; renea.taylor@monash.edu.

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Why is it that obese men have more aggressive prostate cancer and die faster from their cancer compared with lean men? This question has remained largely unanswered, but a recent study by Laurent and colleagues (1) has provided one possible explanation: chemokine signals from prostate-associated fat cells directly communicate with cancer cells to promote local dissemination.

Obesity is a major health issue with approximately two in every three men in Westernized countries now classified as overweight or obese and obesity prevalence is increasing in all global regions (2). Obesity is a major risk factor for life-threatening diseases including cardiovascular disease, type 2 diabetes and many cancers, accounting for approximately one-third of cancer related deaths in 2012 (3). With respect to prostate cancer, obesity is not associated with evidence of increased incidence of disease but, importantly, is a significant risk factor for more aggressive prostate cancer with increased diagnosis of advanced, high-grade prostate cancer, increased biochemical recurrence after primary treatment, and increased prostate cancer-specific mortality in obese compared with lean men (4,5).

Intervention studies in mice have generally supported the view that obesity increases the risk of more aggressive disease. Feeding mice a high-fat diet recapitulates many of the metabolic and endocrine abnormalities of human obesity such as insulin resistance and hyperinsulinemia, dyslipidemia and low-grade inflammation. When mice are fed such high-fat diets for prolonged periods, there is clear evidence of increased tumour mass of xenografted human prostate cancer cells (6). Likewise, obesity accelerates progression in transgenic mice that are predisposed to prostate cancer (6).

Despite the well-documented association between these diseases, the biological mechanisms linking obesity and aggressive prostate cancer remain unresolved. Based on the understanding of tumorigenesis in other solid cancers (7), and a limited number of mechanistic murine studies (6), it has been proposed that both systemic and/or adipose tissue-derived factors promote prostate cancer progression. Systemic promoters are produced as a consequence of obesity co-morbidities and include altered circulating lipids resulting from dyslipidemia, insulin resistance and mild hyperinsulinemia resulting from the development of pre-diabetes, and alterations in several endocrine cascades including the growth hormone/insulin-like growth factor-1 axis, renin-angiotensin system and steroid hormones (*Figure 1*). Dramatic changes in adipose tissue morphology and function occur in obesity (8), and altered lipid metabolism, secretion of adipose tissue derived proteins called "adipokines", and the development of subclinical inflammation secondary to immune cell infiltration into adipose tissue have been postulated to drive cancer pathogenesis.

The prostate is covered anteriorly by the periprostatic adipose tissue (PPAT), which is prominently positioned to participate in bidirectional paracrine communication with prostatic cells (*Figure 1*). In this way, the aforementioned adipose-derived factors are postulated to perfuse the prostate gland to impact the tumour microenvironment and promote tumour growth, local invasion such as extracapsular extension into the PPAT, and possibly
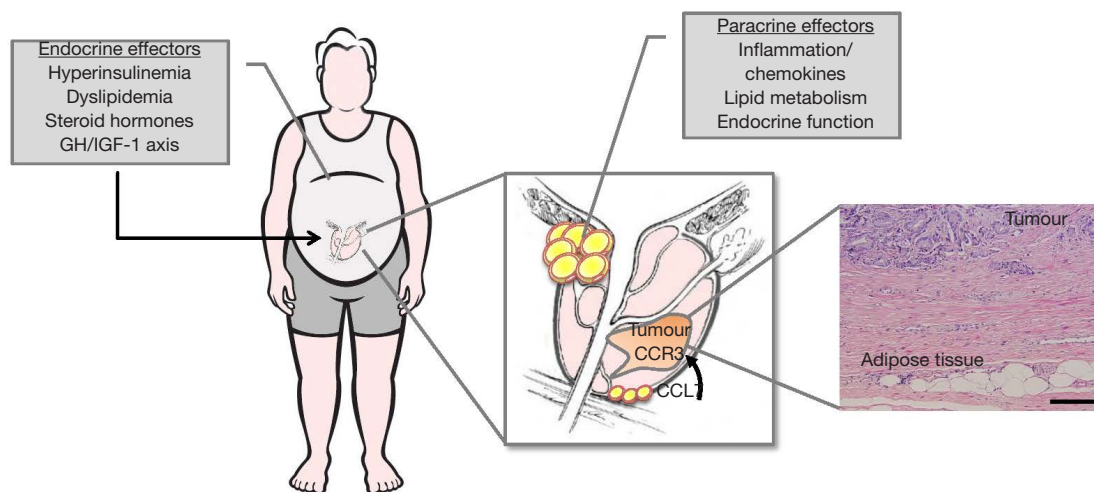
Figure 1 Factors secreted by distant and local adipose tissue influence prostate cancer progression. Left: schematic depicting the secretion of endocrine factors from visceral and subcutaneous adipose tissue depots that are postulated to increase tumourigenesis; center: the prominent periprostatic adipose tissue (PPAT) and possibly adipose tissue located near the peripheral zone secretes proinflammatory cytokines/chemokines (CCL7/CCR3 axis), proteins and lipids to influence cancer aggressiveness and potentially promote extracapsular extension; right: haematoxylin and eosin stained human prostate tissue showing adipose tissue adjacent to prostate cancer, separated by a fibromuscular pseudocapsule; adipocytes are rarely found in intra-prostatic tissue. Scale bar =200 µm.

distant metastases. The evidence that PPAT secretes pro-tumourigenic factors is underscored by studies in which cell culture medium enriched with PPAT secretions increased tumourigenesis in prostate cancer cells (9). Moreover, the PPAT secretions from obese men were more pathogenic to cultured cells than secretions from lean men (10), providing a plausible link between obesity and aggressive prostate cancer. In this regard, prospective diagnostic studies show that increasing thickness of the PPAT is associated with high-risk disease (11). Molecules implicated in driving this association are limited to IL-6 (12), matrix metalloproteinases 2 and 9 (9) and the fatty acid composition within adipocytes (10), although notably, none of these factors have been shown to be as causative.

In the most notable recent advance in the field, Laurant *et al.* (1) have employed an array of eloquent experiments to unravel a previously unidentified chemokine axis controlling prostate cancer migration. The focus on chemokine signaling was well justified based on the documented role of chemokines and their receptors in prostate cancer and other cancers (13), their known production and secretion from adipose tissue, which increases in obesity (14,15), and their ability to induce chemotaxis and cell migration. The authors identified the chemokine, C-X-C motif chemokine ligand 7 (CCL7), as a factor secreted from immortalized murine

adipocytes that promoted the migration of prostate cancer cells in a manner dependent on the receptor CC chemokine 3 (CCR3), thereby establishing the CCL7/CCR3 axis. CCL7 was shown to be secreted from adipocytes and not immune cells located within adipose tissue, and further studies showed that CCL7 was secreted by human PPAT, demonstrating relevance to human biology.

The authors next procured human PPAT and prostate tissue using serial punch biopsies along a continuous gradient and demonstrated progressive decreases in CCL7 expression from PPAT. This established the potential for PPAT secretion of CCL7 through the prostate capsule to signal to CCR3 expressing cancer cells, which are generally present in the peripheral zone of the prostate. The authors demonstrated potential relevance of the CCL7/CCR3 axis for prostate cancer severity by showing in two prospective cohorts that CCR3 is expressed in prostate cancer and that its expression was positively correlated with the occurrence of aggressive prostate cancer, including Gleason grade, T stage, lymphatic emboli, surgical failure and biochemical recurrence.

In a final proof-of-concept study, the investigators used short hairpin RNA technology to partially knockdown CCR3 in immortalized murine prostate cancer cells (TRAMP-C2). In contrast to the parental cells, CCR3 knockdown cells were refractory to migration upon the

addition of adipose tissue secreted factors to the cell culture medium. When these same cells were transplanted into mice, the tumour mass was reduced in the CCR3 knockdown cells compared with the parental TRAMP-C2 cells. Interestingly, the parental tumor cells growing adjacent to adipose tissue induced a reactive stromal phenotype where adipocytes disappear, fibroblast-like cells accumulate and a desmoplastic stroma ensues, indicating that bi-directional 'cross-talk' alters the adipose tissue phenotype and promotes the tumor's proliferative and invasive capacities.

The authors then provided the link between obesity and cancer aggressiveness by showing that CCL7 secretion was upregulated in obesity, that tumour growth of CCR3 deficient prostate cancer cells was completely attenuated in obese mice and that extraprostatic extension and local dissemination were increased in obese patients. Extraprostatic extension to PPAT is clinically significant as these so-called 'cancer-associated adipocytes' exhibit more aggressive behaviour characterized by increased proliferative and invasive capacities and, at a clinical level, this switch from a prostate-confined tumour to a locally disseminated cancer is also viewed as a crucial step in the progression of the disease (16).

The current study unravels a new pathway with therapeutic potential. Whilst the authors suggest that blocking CCR3 offers a new strategy to treat advanced prostate cancer, the chemokine-induced migration leading to extracapsular extension, and possibly metastasis, would have already occurred at this stage of disease progression. Hence, a more rational strategy might be to antagonize CCR3 in a preventative setting, when the disease is organ-confined. In addition, while the authors speculate that this treatment would be efficacious in obesity, it is likely to benefit all men in whom the CCL7/CRR3 axis and interactions with PPAT are present. CCR3 antagonists are currently being developed for other diseases, such as asthma, but their application to prostate cancer would be completely novel.

This work also raises broader issues with respect to understanding the anatomical location of adipose tissues and possible paracrine/endocrine communication with the prostate gland. An extensive pathological examination of prostatic specimens showed that unlike breast, the presence of intra-prostatic adipocytes is extremely rare (17) (*Figure 1*). The most prominent adipose tissue mass is the PPAT, which is located at the anterior surface of the prostate covering the central zone. There are also small depots of adipose tissue that lie along the periphery of the posterior surface of the prostate, in close proximity to the capsule of the peripheral zone where tumours are most commonly located. Laurent and colleagues suggest that factors from the PPAT can perfuse through the prostatic stroma to reach cancer cells (1); however, the evidence demonstrating direct portal circulation or even perfusion from the PPAT to prostate remains unclear. Others have suggested that adipocytes themselves may enter the tumor microenvironment to occupy the peritumoral space through the local vasculature or systemic circulation (18), but the chemo-physical properties of adipocytes makes transvascular transport highly unlikely and this hypothesis is devoid of direct experimental support. These are critical points that require clarification in order to interpret the current findings, but also in elucidating the broader relationship between local adipocytes, PPAT and prostate cancer cells.

In closing, the conceptual advance of this work is the demonstration that the CCL7/CCR3 axis links adiposity to cancer cell migration and predicts aggressive prostate cancer. While this provides important information on the biology of prostate cancer progression and a putative therapeutic target, we need to be cognisant that obesity is a complex disease and that a variety of factors are likely to impact on cancer pathogenesis, including both local and systemic influences (*Figure 1*). Future studies aimed at deciphering the complex mixture of factors derived from PPAT and their role in directing tumour progression will be required in formulating a broad spectrum of treatment modalities.

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Footnote

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