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PROSTATE CANCER

Fat attracts cancer cells

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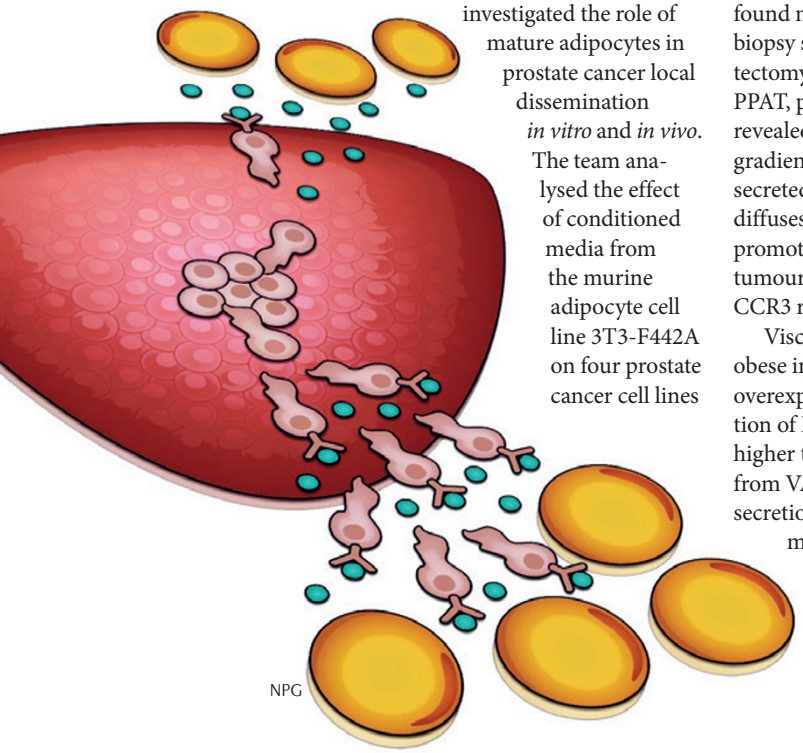
Obesity encourages the migration of prostate cancer cells away from the prostate gland, facilitating extraprostatic extension and increasing local dissemination, according to new research published in *Nature Communications*.

Mature adipocytes are now known to be endocrine cells, secreting hormones, growth factors, chemokines, proinflammatory molecules, and molecules known as 'adipokines'. Obesity leads to excess visceral adiposity, changes in the cellular composition of adipose tissue, and perturbs the normal balance of adipose tissue secretory proteins. Obesity is also associated with an increased risk of aggressive prostate cancer and a correlation exists between the abundance of periprostatic adipose tissue (PPAT) and tumour aggressiveness.

Laurent and colleagues investigated the role of mature adipocytes in prostate cancer local dissemination *in vitro* and *in vivo*. The team analysed the effect of conditioned media from the murine adipocyte cell line 3T3-F442A on four prostate cancer cell lines — LNCaP, C4-2B, DU145, and PC3 — and observed significant promotion of directed migration in all cell lines. Antagonizing various receptors revealed that inhibiting CCR3 had the strongest inhibitory effect on cell migration, an effect that was confirmed using blocking monoclonal antibodies, suggesting that CCR3 has an important regulatory role in prostate cancer cell migration.



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Proteomic analysis of the conditioned media to detect CCR3 ligands revealed six secreted chemokines, of which only CCL7 was a known ligand for CCR3. CCL7 was also discovered in conditioned media from mouse visceral adipose tissue and human PPAT. Recombinant CCL7 and conditioned media from human or mouse tissue caused chemotaxis of prostate cancer cells, which was inhibited by a CCL7 neutralizing antibody. Prostate cancer cells were found not to secrete CCL7. Punch biopsy samples of human prostatectomy specimens taken from the PPAT, prostate capsule, and prostate revealed a strong CCL7 expression gradient suggesting that CCL7 is secreted by PPAT and passively diffuses into the prostate, and might promote migration of invasive tumour cells that express the CCR3 receptor.

Visceral adipose tissue (VAT) of obese individuals and mice showed overexpression of *CCL7* and migration of PC3 cells was significantly higher towards conditioned media from VAT and isolated adipocyte secretions from obese mice than lean mice; this effect was totally abrogated by treatment with inhibitors or blocking antibodies directed against the CCR3–CCL7 axis. Orthotopic graft tumours expressing CCR3 were significantly larger in mice fed a high-fat diet than those fed a normal diet and depletion of CCR3 abolished the differences tumour in size observed. These data indicate that obesity promotes the directed migration of prostate cancer cells by modulating adipocyte secretions.

Tissue microarray analysis of human prostate tissue showed that CCR3 is expressed in cancer tissue but not normal epithelium. Expression correlated with Gleason score and levels of CCR3 were increased in Gleason 4 + 3 tumours compared with 3 + 4 tumours. CCR3 expression also correlated with local extension, biochemical recurrence, and surgical treatment failure, and significant overexpression was observed in tissue from obese patients.

Corresponding author Catherine Muller told *Nature Reviews Urology:* "Our main message is that PPAT chemoattracts cells in an obesity-dependent manner, which might be key to obesity's deleterious effects in prostate cancer. Once the tumour invades PPAT, a crosstalk is established with adipocytes, which is upregulated by obesity." She continues: "CCR3 represents a very interesting target in obese patients, and it is important to determine if CCR3 expression is linked to disease-free and overall survival."

"Testing the CCR3 inhibitors developed for the treatment of inflammatory diseases in these model systems would be very interesting."

Louise Stone

ORIGINAL ARTICLE Laurent, V. *et al.* Periprostatic adipocytes act as a driving force for prostate cancer progression in obesity. *Nat. Commun.* http://dx.doi.org/10.1038/ncomms10230 (2016).