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Editorial for Increased Expression of Tumour Associated Trypsin Inhibitor, TATI in Prostate Cancer and in Androgen-Independent 22Rv1 Cells.

Do Trypsinogens And TATIs Have A Role To Play In Prostate Cancer Progression.

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It was originally believed that Trypsinogens and pancreatic secretory trypsin inhibitor also known as Tumour Associated Trypsin Inhibitor (TATI) were only expressed in the pancreas [1]. The function of Trypsinogens once activated are to aid digestion by degrading proteins derived from food and activating proenzymes also necessary for digestion [2]. TATI inhibit the trypsinogens from digesting the pancreas itself, maintaining the balance between these two proteins is necessary for a healthy pancreas, as inappropriate activation of trypsinogens is one of the initial steps underlying development of pancreatitis [2].

Over the past 30 years it has been widely accepted that trypsinogens and TATI are also expressed out with the pancreas, in particular in the ovaries and gastrointestinal tract [3]. Tumours require proteolytic activity for invasion, and trypsin is a potent activator of MMPs associated with tissue remodelling and invasion, it is therefore not completely surprising that various tumours e.g. ovarian [4], lung [5] and gastric [6] are reported to express trypsinogens and TATI [7]. More recently however it has been reported that trypsinogens are expressed in human seminal fluid suggesting one possible source could be the prostate gland [7]. Trypsin has been demonstrated to be expressed in the human prostate gland and indeed be involved both with activation of proPSA and degradation of PSA in the seminal plasma [7]. Trypsinogens may

therefore play a role in reproduction, however if trypsinogens do have a physiological function in the prostate, their expression could also contribute to invasion and metastasis of prostate cancer. In deed trypsinogens are highly expressed in high grade prostate cancers, and not only by the luminal secretory cells but also by malignant cells, suggesting that trypsinogenes may be involved in promoting tumour growth and invasion [3]. As trypsinogen and TATI have been reported to be co-expressed in a variety of tumours including colorectal [8], ovarian [9] and bladder cancer [10,11] and it had previously been reported that expression of trypsinogens was associated with prostate cancer it seemed logical to investigate the role of TATI in prostate tumours. A paper in this edition by Paju et al. report that TATI is weakly expressed in benign prostatic epithelium and expressed with increasing intensity in prostate cancers, the intensity of staining in the prostate tumours correlates with Gleason grade. It is hypothesised that as the TATI are expressed in the basal epithelial cells and the physiological function of the TATI in the prostate is to inhibit trypsin that have leaked from the luminal epithelial cells into the extracellular fluid. However, it remains unclear if TATI co-expressed with trypsinogens in the malignant cells, as is observed in other tumour types; the authors suggest that they are expressed in the same tumours as both trypsinogens and TATI correlate with increasing Gleason grade. Dual stain experiments would be useful to formally assess this. Interestingly, TATI was found to be secreted by the androgen independent cell line 22Rv1, but not in the androgen sensitive LNCaP cell lines, suggesting TATI might be associated with a more aggressive phenotype cancer. It is worth noting that not only is TATI expression in the tumour associated with Gleason, but serum levels also correlated with PSA and tumour stage. The series of studies from this group has demonstrated that trypsinogens and TATI may be involved in prostate cancer invasion and may also

be of prognostic significance. However further work is required to establish the exact role these proteins play in progression, and also if they are associated with patient survival. This is an area of research that requires further investigation and should be watched with interest.

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