



The role of transglutaminases in the pathophysiology of prostate cancer

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Quantification of the enzymatic activity of macromolecules has been a longstanding adjunctive approach in the diagnosis and prognosis of a variety of diseases, including cancer. However, with a continuing role for enzymatic activity, there has been an increasing appreciation and high level of interest in the biologic functionality of enzymes at the cellular level.

One family of enzymes receiving increasing attention is the transglutaminases (TGases, EC 2.3.2.13¹). The TGases catalyze the posttranslational modification of proteins by the formation of epsilon-(gamma-glutamyl) lysine isopeptide bonds¹. With 9 isoenzymes having been identified², the TGases are implicated in a vast array of biologic functions, ranging from tissue remodeling and repair to intracellular signaling to apoptosis and such disease processes as inflammation, wound-healing, neurodegenerative disorders, and cancer².

Our group's independent and collaborative studies of TGases—plasma TGase [factor XIII (FXIII)], tissue TGase (TGase-2), and prostate TGase (TGase-4 or TGaseP)—have focused on the associations of these molecules with the pathophysiology of the prostate gland in health and disease, particularly cancer.

Attention to the possible role of TGases in the human prostate arose from initial observations of the presumptive³ and, subsequently, definitive⁴ identification of FXIII and TGase-2 as contributors to the immunoregulatory milieu of the microenvironment of the prostate⁵. Identified in normal and tumour-associated macrophages, and elsewhere in the normal and pathologic prostate and its secretions, FXIII and TGase-2 were observed to modulate the activity of select parameters of immune responsiveness, and in prostate cancer (compared with normal and benign conditions of the prostate), FXIII was found to be present in significantly increased concentrations⁶.

The close association of tumour-associated macrophages and FXIII suggest that FXIII is involved in the binding of host proteins to tumour cells, forming a stabilized intratumoral fibrin that facilitates tumour matrix generation, angiogenesis, and a barrier to mechanisms of host defense. The localization of FXIII

to prostatic histiocytes expressing monocyte and macrophage differentiation markers, providing a means for TGase to regulate antigen presentation and induce immune responses, portends to the permissive, if not direct, role of TGase in host regulation of tumour cell invasion and metastasis^{6,7}.

In addition to the role of TGases in prostate cancer *per se*, increased expression of TGase-2 has been observed in many inflammatory diseases². Prostatitis, with its acute and chronic inflammatory states (the latter suggested by one of our group as being associated with increased TGase-2⁸), possibly gives rise to prostate cancer. In this regard, recent observations of the role of TGase-2 in initiating inflammation by suppressing the anti-inflammatory peroxisome proliferation-activated receptor γ ⁸, localized in prostate cancer⁹, suggesting inhibition of TGase-2 as a therapeutic target, presents an attractive area for investigation.

Although FXIII and TGase-2 have been implicated in the role of the tumour microenvironment to tumorigenesis of the prostate^{5-7,a}, the subsequent identification of TGase-4, unique to the prostate, suggested that further investigation of TGase-4 would provide more specific information on the role of TGases in the pathophysiology of the prostate.

Studies of TGase-4 in prostate cancer have demonstrated it to be a key regulator of invasiveness¹⁰, cell migration, and cell-matrix adhesion¹¹ of prostate cancer cells, and of the interaction between prostate cancer cells and vascular endothelial cells¹². The latter action suggests a potential role of the Rho-associated kinase (ROCK) pathway in this interaction. The Rho-associated kinase is closely associated with tumour-cell migration and metastasis, thereby suggesting further investigation of TGase-4 and ROCK.

Of further note is the effect of TGase-4 on the epithelial-mesenchymal transition (EMT) of prostate cancer

^a Ablin RJ. Immunobiological implications of transglutaminases. Presented at Colloquium: Drug Designing Using Biological Active Peptides As Templates, fnrs-nfwo Contact Group, Brussels, Belgium; May 5-6, 1986)

cells¹³. An important biologic process during embryonic development, EMT is also a critical factor in the development and progression of cancer¹⁴. Overexpression of TGase-4 in prostate cancer cells has been observed to result in the loss of E-cadherin and the acquisition of N-cadherin—characteristics of the mesenchymal phenotype and of increased cellular motility¹³.

The foregoing properties of TGase-4—that is, increased adhesiveness, invasiveness, cell migration, and EMT—are in keeping with the characteristics of cancer cells associated with metastasis. In concert with the earlier observations related to FXIII and TGase-2, those properties suggest a very provocative role for these TGases in invasion and metastasis. In this regard, some observations, albeit preliminary, of the increased expression of TGase-4 in prostate cancer compared with normal prostate are interesting. Levels of TGase-4 marginally correlate with Gleason scores ($r = 0.293$, $p = 0.05$), with high levels of TGase-4 transcripts being seen in patients with high Gleason scores (>7)¹⁵.

Toward further defining the biologic role of TGase-4 in prostate cancer, colocalization of TGase-4 and the melanoma differentiation-associated gene-7 [MDA-7 (also known as interleukin-24)], the latter having growth-inhibiting properties, has been observed¹⁶. Therein, TGase-4 has been shown to have a direct impact on the response by prostate cancer cells to recombinant (rh) MDA-7, with cells not expressing TGase-4 responding well to rhMDA-7—that is, showing decreased cell adhesion, motility, and cell growth. However, cells expressing TGase-4 (naturally or forced) showed either no response or a marginal response to rhMDA-7¹⁶. Those observations point to significant implications of ongoing immunotherapy trials with the use of MDA-7, particularly in prostate cancer¹⁷.

The foregoing studies, pending further investigation, suggest that TGase-4 may be a prospective marker of disease progression and a possible target for therapy.

CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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