PREDICTION OF PROSTATE CANCER GLEASON GRADES BASED ON BLOOD/URINE LEVELS OF PROSTATE SPECIFIC ANTIGEN (PSA) DECORATED WITH HIGH MANNOSE N-GLYCAN

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PURPOSE
To develop a modified PSA assay for prediction of prostate cancer Gleason grade based on levels of PSA decorated with high mannose N-glycans in blood or urine

Background

(A) A non-invasive assay for prediction of prostate cancer Gleason grade is needed to aid the treatment decision. The inability of using serum PSA levels to distinguish advanced from indolent prostate cancer has resulted in over-treatment of clinically insignificant disease, thus causing unnecessary suffering of many patients (1,2). Therefore, there is a pressing need to develop a non-invasive assay that can predict prostate cancer Gleason grade, especially one that can distinguish Gleason scores ≤6 from Gleason scores ≥3+4 (3).

(B) Scientific basis of this project: Recently, Dr. Cheng’s laboratory found that giantin, a Golgi matrix protein serving as a major targeting site for vesicles transporting glycosylation enzymes and their substrates from Endoplasmic Reticulum, lost its function as prostate cancer cells advanced from androgen-dependent to androgen-refractory stages. As a result, all but core 2 enzymes used GM130-GRASP65 site for Golgi targeting (4), causing alteration of mucin-O-glycosylation (3) and N-glycosylation (5). Figure 1 illustrates how shifting of Golgi localization of α-mannosidase IA (Man IA), a key enzyme involved in trimming Manα6→8GlcNAc down to Manα6GlcNAc, to enable synthesis of complex-type N-glycans, from giantin to GM130/GRASP65 (Fig. 2), resulting in a shift of Man IA localization from giantin to GM130/GRASP65 (Fig. 2), appearance of high Man N-glycans at cell surface (Fig. 3), and an increase in in vitro migration rate (Table 1).

(C) Localization of Man 1A at GM130/GRASP65 site and expression of cell surface high Man N-glycans correlate with aggressive phenotype of prostate cancer cells: After extended culture of androgen-dependent prostate cancer cells (LNCaP P8), some become androgen refractory (6) (LNCaP-P121-Clone 1), resulting in a shift of Man 1A localization from giantin to GM130/GRASP65 (Fig. 2), appearance of high Man N-glycans at cell surface (Fig. 3), and an increase in in vitro migration rate (Table 1).

(D) Man 1A is localized at Giantin site in normal prostate and stage II prostate tumors but at GM130/GRASP65 site in stages III and IV prostate tumors: (Fig. 5)

(E) High Man N-glycan was detected in PSA secreted from androgen-refractory prostate cancer cells (LNCaP P45, DU145 and PC3) but not androgen-dependent prostate cancer cells (LNCaP P6) (Fig. 6) and also in serum/plasma of prostate cancer patient but not benign prostate hyperplasia patient (Fig. 7)

AIMS
1. To show that PSA with high Man N-glycan is produced by aggressive prostate cancer cells
2. To validate that levels of PSA with high Man N-glycan in blood and urine correlate with Gleason ≤6, 3+4, 4+3, and ≥8 prostate cancer patients
3. To develop immuno and lectin combination Elisa assay of levels of PSA with high Man N-glycan in above mentioned specimens

APPRAOCH
After validate the concept that levels of PSA with high Man N-glycan in serum/urine can be used to predict prostate cancer Gleason grade, we will file a patent application and submit NIH RO1 or SBIR grant, DOD Idea award, or VA Merit.

NEXT STEPS/DELIVERABLES
The project described was supported by the National Institute of General Medical Sciences, 1UL5GM115458. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

REFERENCES

ACKNOWLEDGMENTS

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