Abstract

Aging population, stressfully transforming lifestyle and perturbed urological physiology is contributing to the recent anxious rise of incidence of prostate cancer (PCa) across the globe, including India. Despite of advancing knowledge in both medical diagnostic technology and curative interventions; and decades of applied urological research, the existing insights are insufficient to curb the menace. This very situation intrigued us to investigate and identify the differential and clinically relevant prognostic serum based biomarkers in induced animal model of PCa with an intention to contribute an insight in early and accurate detection and additive avenues for effective clinical case management.

We employed 2-DE and peptide mass fingerprinting based on MALDI-TOF-MS techniques adopting proteomics approach, tissue diagnosis for pathophysiological characterization and disease differentiation were assessed by histopathology and to corroborate the sustainable evidences of proteomics observations and to ascertain the functional association and regulation of corresponding genes; transcriptional genomics were performed using qRT-PCR.

We distinctly observed SRCIN1, DCAF6, PTP4A2 and MRPL15; novel and under investigated serum markers in protein profiling and time dependent differentially expressed patterns of respective genes in Wistar rat PCa tissues. We found
significantly upregulated expression of MRPL15 and quite early pronounced shift (4.9 fold), suggesting specificity and efficiently early tumour inducer candidate marker; whereas DCAF6, though showed overall upregulation, but pronounced and noticeable shift (7.8 fold) was observed quite late; suggesting time dependent sensitivity as marker’s characterization of late tumour inducer candidate. Further, SRCIN1 were down regulated irrespective of time course, whereas PTP4A2 were also down regulated but quite late and marginally showed non-significant upregulation (<0.5 fold); suggesting specificity of SRCIN1 and PTP4A2, as tumour suppressor marker. However, PTP4A2 may have dichotomic potential as quite late phase tumour inducer marker candidate as well.

In normal and abnormal prostate growth, the prostate specific gene has different roles, and it plays a crucial role in the early and specific diagnosis and treatment of prostate cancer. In the present study, a robust homology model of Human Prostate Specific Gene-1 protein (HPG-1) was modeled to forecast interaction phenomenon with inhibitory molecules using a structure-based drug designing strategy. Docking calculation using anticancer and TOSLab compounds revealed key active site residues such as Asp87, Arg115 and Lys117 for ligand binding. A molecular dynamics (MD) simulation of ethyl 5-[(4-{[4-(ethoxycarbonyl)-1,2,3-thiadiazol-5-yl] amino} butyl) amino]-1,2,3-thiadiazole-4-carboxylate and ethyl 5-[(3-{[4-(ethoxycarbonyl)-1,2,3-thiadiazol-5-yl] amino} propyl)amino]-1,2,3-thiadiazole-4-
carboxylate with a modeled structure exhibited the importance of hydrogen bonding with active site residues and solvent molecules, which may be crucial for successful development of drug candidates. Moreover, MD simulation analysis revealed that both protein ligand complexes depicted a decreasing order of gyration radii, which suggests their shape and size were becoming compact. Fascinatingly, as compared to complex I (-59.3), complex II showed higher negative binding free energy (-69.2). As evidenced from MD stability parameters, complex II was found to be more stable than complex I where van der Waals energy contributed significantly towards higher binding energy. The cation Pi interaction also played a vital role for the stable molecular conformation within the receptor macromolecule. Overall, the present study is believed to provide valuable information to design a new compound with improved anti HPG-1 activity.

In conclusion, by developing a well-established Wistar rat prostate cancer model, we analyzed the differential protein expression pattern of treated group or induced group in comparison to control group and identified novel set of proteins at very early stages of prostate carcinogenesis by proteome analysis using 2-DE and MS techniques. To the best of our knowledge, the proteins reported in our study have not been previously reported to be differentially expressed during very early stages of prostate carcinogenesis. These proteins may therefore possess a potential candidature in improving PCa diagnosis in its early stage. Further functional and
clinical validation studies of these cancer-associated proteins are necessary to elucidate their precise role in the process of prostate carcinogenesis. Moreover, the results from our study may provide useful addition to the growing knowledge in the pathogenesis of prostate cancer. Ultimately, such proteins (biomarkers) would aid clinicians in diagnosing PCa during the early stages and preventing from unnecessary biopsy and overtreatment.