SUMMARY

Gastric cancer is the second leading cause of cancer death worldwide, both in men and women. In India, it is one of the leading cancers in males. Tumorigenesis is asymptomatic and patients with gastric cancer are diagnosed at an advanced stage. There is a dire need to identify molecular markers for early detection of gastric cancer. Discovery of genes that are aberrantly expressed in cancer as compared to normal would lead to the development of biomarkers for clinical diagnosis and prognosis. In order to achieve this, two different approaches were used. In the first approach, a genome wide gene expression analysis was carried out to identify differentially expressed genes in gastric adenocarcinoma tissues as compared to adjacent normal tissues. Agilent’s whole human genome oligonucleotide microarray platform representing ~41,000 transcripts was used to carry out gene expression analysis. Through this approach, several previously known candidate genes along with a number of novel candidate genes were identified in gastric cancer. Testican-1 (SPOCK1) was one among the novel candidates that was found to be 10-fold upregulated in tumors. Using tissue microarrays, the expression of testican-1 was validated by immunohistochemical staining. It was overexpressed in 56% (160/282) of the cases tested. Secondly, mass spectrometry-based quantitative proteomic analysis was carried out to identify genes that were differentially expressed at protein level. In particular, the proteins that were specifically secreted from gastric cancer were studied using gastric cancer cell lines. Stable isotope labeling with amino acids in cell culture (SILAC) was employed to identify differentially secreted proteins. This study led to the identification of several markers. PCSK9, LMAN2, LGALS4 and PDAP1 were four novel candidates chosen for validation by immunohistochemical analysis. Through this study, a robust pipeline to discover biomarkers has been established. The first phase includes discovery of biomarkers using DNA microarrays and mass spectrometry-based platforms followed by large scale validation using tissue microarrays. The candidate markers identified in this study should be tested in larger cohort of patients if they were to be used routinely in the clinic.