PODXL - an independent biomarker of poor prognosis in cancer

Cancer
Cancer is a major health problem throughout the world. In 2008, there were an estimated 12.7 million new cancer cases worldwide, and 7.6 million deaths that could be attributed to cancer. Due to a world population with an increased life expectancy, there is no reason to expect a decline in cancer incidence in the near future.

Cancer, though often denoted as a singular disease, is truly a multitude of diseases. This understanding has evolved over the years, but still many patients are not receiving optimal treatment for their disease. For cancer patients to receive a more individualized treatment, there is a need for new and better ways to stratify patients. The classical, pathology based prognostic factors such as stage and grade of the tumor are insufficient for a correct estimation of patient prognosis. Additional information from immunopathology biomarkers promise to substantially improve this estimation, ultimately leading to a more individualized treatment, thus avoiding both under- and over-treatment of patients.

PODXL
Podocalyxin (PODXL) is a transmembrane protein that is involved in cell-cell interaction. In normal tissue, the protein is expressed in the kidney glomerular podocytes, where it plays an important part in maintaining filtration pathways, and in endothelial cells in blood vessels. PODXL is overexpressed in several types of cancer, e.g. breast, prostate, and testicular cancer. The PODXL protein was identified on the Human Protein Atlas (proteinatlas.org) as a potentially interesting testicular cancer biomarker, and has later been found to be a prognostic biomarker in both colorectal and urothelial cancer.

PODXL in colorectal cancer
Colorectal cancer is one of the most common types of cancer. Each year, approximately one million new cases are detected, and approximately 600,000 deaths can be contributed to this disease worldwide. Today, surgery is the only curative treatment for colorectal cancer, but adjuvant treatment may significantly improve patient survival. For adjuvant treatment to be successful, however, it is important to correctly identify patients that will benefit from treatment. Adjuvant treatment is currently recommended for patients with stage III and high-risk stage II disease. For patients with stage II colorectal cancer, it is thus of utmost importance to find biomarkers that can separate high-risk disease from low-risk disease.

PODXL protein expression has been analyzed by immunohistochemistry (IHC) in three different colorectal cancer patient cohorts. High membranous PODXL expression in the tumor was shown to be an independent predictor of poor prognosis in all three patient cohorts. In Figure 1, IHC stainings of membranous versus no or non-membranous positivity using a monoclonal Anti-PODXL antibody are presented. There was no association between PODXL expression and age at diagnosis, gender, or tumor location in any of the cohorts studied.

Figure 2A shows survival of colorectal cancer patients according to membranous PODXL expression in the tumors. A high membranous PODXL expression correlated with a reduced survival in all cohorts. Patients with tumors expressing high membranous levels of PODXL that were treated with adjuvant chemotherapy (CT) had similar colorectal cancer-specific survival (CCSS) to patients with PODXL-low tumors. Untreated patients with PODXL-high tumors had shorter CCSS than all the other patient groups (Figure 2B).

These results suggest that patients with tumors expressing high membranous levels of PODXL would benefit from adjuvant chemotherapy.
PODXL in urothelial cancer

A major clinical problem in urothelial cancer is the identification of high-risk patients among those diagnosed with T1 disease (where the tumor has invaded connective tissue but not yet muscle). For these stage T1-patients, the prognosis is generally good, but nearly one third will still eventually require cystectomy after failure of other therapies. To identify these patients at an early stage would mean a great improvement for patients as well as society. Due to high recurrence rates, and need for invasive monitoring of the disease, the health care cost per patient is high for urothelial cancer. For patients with muscle-invasive disease, prognostic markers that could guide in the choice of treatment and/or treatment intensity would also mean an improvement in patient care.

The association between membranous PODXL expression and reduced survival was confirmed in both Cox univariable analysis and multivariable analysis adjusted for age, gender, T-stage and grade. When analyzing membranous PODXL expression in the subgroup of patients with stage Ta (non-invasive) and T1 tumors, it was found that membranous PODXL expression was associated with increased risk of disease progression as well as increased risk of death from disease in this group of patients. Figure 3 shows an example of membranous PODXL expression from a urothelial carcinoma sample using immunohistochemistry.

PODXL protein expression has been analyzed by IHC in two different urothelial cancer patient cohorts (Cohort I, n=110 and Cohort II, n=344 respectively). Compared to no or non-membranous expression, membranous PODXL expression in the tumor was shown to be associated with a reduced 5-year overall survival in both patient cohorts (Figure 4A and B).

![Figure 3](image3.png)

**Figure 3**  
Membranous PODXL expression in urothelial cancer obtained by IHC analysis using the Anti-PODXL antibody AMAb90643.

![Figure 4](image4.png)

**Figure 4**  
Kaplan–Meier estimates of 5-year Overall Survival (OS) according to PODXL expression in (A) Cohort I and (B) Cohort II.

Summary

- There is a great need today for novel biomarkers capable of distinguishing between different types, stages, and forms of both colorectal and urothelial cancer.

- PODXL has been found to be a prognostic biomarker in colorectal and urothelial cancer, with high membranous PODXL expression being an independent predictor of poor prognosis.

- Analyzing PODXL expression could stratify colorectal cancer patients into those that should receive chemotherapy and those that may be spared adjuvant treatment.

References:


