Leukocyte complexity and the mutational spectrum of periampullary cancer: relationship with morphology and clinical outcome

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Introduction
Tumours arising in the periampullary region are diverse but share the common trait of having a poor prognosis. Anatomical origins for periampullary adenocarcinomas include the head of the pancreas, the duodenum, the common bile duct and the ampulla of Vater. For pancreatic cancer, the five-year overall survival rate is only 5%, with a median survival rate of 6 months. Approximately 85% of the patients are diagnosed in an advanced stage, thus not being eligible for curative resection. For patients with resectable disease, morphological subtype is an important prognostic factor, with intestinal-type (I-type) morphology being associated with a better outcome and pancreaticobiliary type (PB-type) morphology with a poorer outcome. Although the vast majority of pancreatic cancers contain somatic mutations, there is still a lack of “actionable” molecular targets. Adding to this, pancreatic cancer creates a non-immunogenic, or “cold”, tumour microenvironment, thus limiting the effects of immunotherapies. Therefore, standard of care treatment for these patients remains limited to conventional cytotoxic chemotherapy, and there is a great need to identify novel treatment strategies and predictive biomarkers for improved treatment. The overarching aim of this thesis project is to map the leukocyte complexity and mutational landscape of periampullary adenocarcinomas, with particular reference to their relationship with morphological type and clinical outcome.

Material and methods
The study cohort is a retrospective, consecutive cohort of all 175 patients who underwent surgical treatment for periampullary adenocarcinoma at Skåne University Hospital between 2001 and 2011, 110 of which were classified as PB-type and 65 as I-type. For paper I and II, immunohistochemistry was applied to assess the density of tumour infiltrating leukocytes, with emphasis of leukocytes in the innate immune system, i.e. natural killer (NK) cells
(CD56+), natural killer-like T cells (NKT, CD56+), macrophages (CD68+, CD163+, MARCO+) and dendritic cells (CD1a+). In paper III and IV, we will investigate the mutational landscape using next-generation sequencing of 102 tumours from the above-mentioned cohort. In paper V, we will use an *in vitro* model to assess NK cell functionality in pancreatic cancer.

**Results**

**Paper I**

In paper I we demonstrated, for the first time, that high infiltration of NK and NKT cells was associated with an improved prognosis, particularly in pancreatobiliary-type tumours. Moreover, a negative treatment interaction was found between high NK/NKT cell infiltration and adjuvant chemotherapy.

Related publication:

**Paper II**

In paper II we demonstrated, for the first time, that high infiltration of tolerogenic dendritic cells was an independent prognostic factor in periampullary adenocarcinoma. Additionally, high infiltration of CD68+ and CD163+ macrophages was associated with poor prognosis in the entire cohort, whereas high infiltration of MARCO+ macrophages was an independent prognostic factor in intestinal type tumours.

Related publication:

**Preliminary data from paper III**

High mutational burden was shown to be associated with poor patient outcome. Mutated *KRAS* was associated with poor overall survival in intestinal type but not in pancreatobiliary type tumours, and mutated *ERBB3* was associated with an improved prognosis in the entire cohort, but not in strata according to morphology. In addition, mutated *SMARCA4* was a negative predictor of adjuvant chemotherapy response.

**Significance**

Periampullary adenocarcinoma is a disease with utterly poor prognosis and few available treatment options. By performing a thorough mapping of the immune as well as molecular landscape in periampullary adenocarcinoma, we hope to gain further insight into the potential heterogeneity regarding response to targeted therapies of these tumours, so as to enable improved tailored treatment for individual patients.